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Scope

The Atlas of Genetics and Cytogenetics in Oncology and Haematology is a peer reviewed on-line journal in open access, devoted to genes, cytogenetics, and clinical entities in cancer, and cancer-prone diseases. It presents structured review articles ("cards") on genes, leukaemias, solid tumours, cancer-prone diseases, more traditional review articles on these and also on surrounding topics ("deep insights"), case reports in haematology, and educational items in the various related topics for students in Medicine and in Sciences.

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Unbalanced rearrangement, der(9;18)(p10;q10) in a patient with myeloproliferative neoplasm.
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CTCF (CCCTC-binding factor (zinc finger protein))

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Identity
HGNC (Hugo): CTCF
Location: 16q22.1
Local order: AGRP, FAM65A, CTCF, RLTPR, ACD, PAR6A.

DNA/RNA

Note
See figure 1.

Description
76776 bp gene (Ensembl).

Transcription
Ubiquitously highly expressed gene (GeneCards), 12 exons, 11 introns with at least 5 differentially spliced transcripts (Ensembl).

Pseudogene
No.

Figure 1. Schematic representation of CTCF location on chromosome 16, gene structure and transcripts. Chromosome 16 is represented with the characteristic banding pattern. The region surrounding the CTCF gene is enlarged. Genes are represented by arrows pointing in the direction of transcription. Transcripts are represented with exons as vertical bars and introns as lines. Distances are in kilo bases (NCBI Map Viewer).
CTCF (CCCTC-binding factor (zinc finger protein))

Protein Description

CTCF was originally described as a c-myc activator (Klenova et al., 1993). It is a 727 aa protein with a MW of 82.8 kD, a charge of 8.5 and an iso electric point of 6.95 (Ensembl). The central domain with 11 zinc fingers of the C2H2 type is highly conserved.

Expression

CTCF is an abundant and ubiquitously expressed protein, yet absent in primary spermatocytes (Loukinov et al., 2002). It is downregulated during differentiation of human myeloid leukemia cells (Delgado et al., 1999; Torrano et al., 2005). Post-translational modifications include acetylation (Choudhary et al., 2009), sumoylation (Kitchen et al., 2010; MacPherson et al., 2009), phosphorylation, in particular ser604-612 by CKII (El-Kady et al., 2005; Klenova et al., 2001), and poly(ADPribosylation) (see figure 2). The latter modification is lost or decreased in proliferating cells and in BT (Docquier et al., 2009) (for sites and role see Farrar et al., 2010 and Yu et al., 2004). CTCF is a downstream target protein of growth factor-induced pathways and is regulated by EGF and insulin through activation of ERK and AKT signaling cascades (Gao et al., 2007). It was recently shown to be regulated by NF-kB (Lu et al., 2010).

Localisation

CTCF is localized in the nucleoplasm of proliferating cells with exclusion from the nucleolus. It was detected at the centrosomes and midbody during mitosis (Zhang et al., 2004). It is associated with the nuclear matrix (Dunn et al., 2003; Yusufzai et al., 2004a) and the Lamina (Guelen et al., 2008; Ottaviani et al., 2009). Nucleolar translocation after growth arrest is accompanied by inhibition of nucleolar transcription (Torrano et al., 2006). Cytoplasmic expression was described in sporadic breast tumors (Rakha et al., 2004).

Function

CTCF is an essential protein, since KO mice die before ED 9.5 (Heath et al., 2008) (reviewed in Filippova, 2008 and Phillips et al., 2009). It interacts with up to 39609 genomic sites (in ES cells) (Chen et al., 2003; Bao et al., 2007; Barski et al., 2007; Kim et al., 2007). The 11 Zn fingers would provide flexibility in DNA recognition (Filippova et al., 1996), the central 4 bind to a consensus DNA sequence (Filippova et al., 1996; Filippova et al., 1996), the central 4 bind to a consensus DNA sequence (Filippova et al., 1996, 1997). Multiple interacting proteins were described including RNA polymerase II (Chernukhin et al., 2007), cohesin (Parelho et al., 2008; Rubio et al., 2008; Wendt et al., 2008), Suv12 (Li et al., 2008), CHD8 (Ishihara et al., 2006), YY1 (Donohoe et al., 2007), nucleophosmin (Yusufzai et al., 2004b), Kaiso (Defossez et al., 2005) and Sin3A (Lutz et al., 2000).
Mediating DNA looping (Splinter et al., 2006) could be at the basis of most functions of CTCF. Long range interactions are cell type specific (Hou et al., 2010) and would depend on the chromosomal environment of the CTCF-binding sites, in particular its interaction with other factors (see concept of modular insulators in Weth et al., 2010). One thoroughly studied factor is the thyroid receptor (Awad et al., 1999; Lutz et al., 2003). Its chromosomal environment could also explain the multiple (not necessarily exclusive) functions that were described for CTCF, including chromatin barrier (Cuddapah et al., 2008; Witcher et al., 2009), promoter insulation from enhancer (Bell et al., 1999) or silencer (Hou et al., 2008), transcriptional activation (Gombert et al., 2009) (for instance of the tumour suppressor genes INK4A/ARF (Rodriguez et al., 2010) and p53 (Soto-Reyes et al., 2010)), repression (for instance hTERT (Renaud et al., 2005)), nucleosome positioning (Fu et al., 2008b), protection from DNA methylation (Mukhopadhyay et al., 2004; Schoenherr et al., 2003; Guastafierro et al., 2008), preservation of triplet-repeat stability (Cho et al., 2007), X chromosome inactivation (Chao et al., 2002), chromosome “kissing” (Ling et al., 2006), transvection (Liu et al., 2008), death signaling (Docquier et al., 2005; Gomes et al., 2010; Li et al., 2007), replication timing (Bergstrom et al., 2007), mitotic bookmarking (Burke et al., 2005) or MHC class II gene expression (Majumder et al., 2008).

**Homology**

49 orthologues were described including D. melanogaster (Smith et al., 2009) and C. elegans proteins (Moon et al., 2005), 3 paralogues: CTCFL or BORIS, originating from a gene duplication in reptiles (Hore et al., 2008; Loukinov et al., 2002), and possibly ZFP64 (Mack et al., 1997) and the Histone H4 transcription factor HINF-P (van Wijnen et al., 1991).

**Mutations**

**Note**

SNP at AA 630/K/E 90/D/G 447 fR (NCBI).

**Germinal**

Non-coding mutations only.

**Somatic**

Mutations are rare and include point mutations of Zn-fingers in breast (BT) (Aulmann et al., 2003), prostate (PT) and Wilms tumor (WT) (Filippova et al., 2002) and insertion in BT (Aulmann et al., 2003) (see figure 2).

**Implicated in**

**Various cancers**

**Note**

LOH of CTCF was described in many cancers together with potential tumor suppressor genes (TSG), including E-Cad, since it is part of a larger deletion (Cancer Chromosomes; Sanger institute). In addition to WT (Yeh et al., 2002; Mummert et al., 2005), BT (Rakha et al., 2004), PT (Filippova et al., 1998), LOH was found in laryngeal squamous cell carcinoma (Grbesa et al., 2008), however, there is no evidence that CTCF is the TSG at 16q22.1 (Rakha et al., 2005), except possibly in lobular carcinoma in situ of the breast (Green et al., 2009). CTCF was also described to be overexpressed in BT (Docquier et al., 2005). An indirect role of CTCF in tumor progression is mainly suggested by mutation or aberrant methylation of its bindings sites (reviewed by Recillas-Targa et al., 2006). Interestingly, a causal link between LOH of CTCF and hypermethylation was proposed by Mummert et al. in 2005, although no real correlation was found by Yeh et al. in 2002. Methylation of CTCF sites was first described in the IGF2 imprinting control region in WT (Cui et al., 2001). Aberrant methylation of this region was also found in PT (Fu et al., 2008a; Paradowska et al., 2009), HNSCC (De Castro Valente Esteves et al., 2006; Esteves et al., 2005), colorectal cancer (Nakagawa et al., 2001), osteosarcoma (Ulaner et al., 2003), ovarian carcinoma (Dammann et al., 2010) and laryngeal squamous cell carcinoma (Grbesa et al., 2008). Hypomethylation was described in bladder cancer (Takai et al., 2001). Microdeletions were described in Beckwith-Wiedemann syndrome and WT (Prawitt et al., 2005; Sparago et al., 2007). Other methylated CTCF targets were found in the genes AWT1 or WT1-AS in WT (Hancock et al., 2007), Bcl6 in B cell lymphomas (Lai et al., 2010), p53, pRb (De La Rosa-Velazquez et al., 2007), ARF (Tam et al., 2003; Rodriguez et al., 2010), INK4B, BRCA1 (Butcher et al., 2004; Butcher et al., 2007; Xu et al., 2010) and Rasgrf1 (Yoon et al., 2005).

We describe below the rare cases of point mutations affecting the CTCF protein.

**Invasive ductal breast carcinoma, grade 2**

**Note**

G2 grade tumor, no protein detected (Aulmann et al., 2003).

**Cytogenetics**

14 bp insertion at AA D91, see figure 2.

**Invasive ductal breast carcinoma, grade 3**

**Note**

G3 grade tumor (Aulmann et al., 2003).

**Cytogenetics**

LOH and Q72H, figure 2.
**Breast cancer**

**Note**
Zinc finger mutation (Filippova et al., 2002).

**Cytogenetics**
LOH and K343E, figure 2.

**Prostate cancer**

**Note**
Zinc finger mutation (Filippova et al., 2002).

**Cytogenetics**
LOH and H344E, figure 2.

**Wilms tumor**

**Note**
Zinc finger mutation (Filippova et al., 2002).

**Cytogenetics**
LOH and R339W or R448Q, figure 2.

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This article should be referenced as such:

Gene Section

Review

EPS8 (epidermal growth factor receptor pathway substrate 8)

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Identity

HGNC (Hugo): EPS8
Location: 12p12.3

DNA/RNA

Description
The EPS8 gene can be found on chromosome 12 at 12p12.3, starting at position 15664342 bp and ending at 15833601 bp from pter on the reverse strand. It contains 21 exons.

Transcription
The transcript consists of 4.1 kb and translates to a 822 residue protein.

Protein

Description
822 amino acids; contains pleckstrin homology (PH) domain at amino acids 69-129 and 381-414; contains Src homology (SH3) domain at amino acids 531-590; intertwined dimer.

Expression
Ubiquitous in adult; temporal expression in developing mouse embryo, in frontonasal neural crest cells, branchial arches, liver primordium, central nervous system and submandibular glands.

Localisation
Plasma membrane; cytoplasm; perinuclear; possibly nuclear.

Function
Scaffolding protein; participates in signal transduction downstream of receptor tyrosine kinases (incl. EGFR, CSF1R, PDGFR); receptor endocytosis; cell motility; actin reorganization.

Homology
45 orthologues identified (Ensembl).
3 paralogues: EPS8L1; EPS8L2; EPS8L3.

Implicated in Cancer

Note
Eps8 is reported to be expressed at elevated levels in a range of human malignancies, including breast cancer, pancreatic cancer, colon cancer and head and neck squamous cell carcinoma.

Oncogenesis
Overexpression of EPS8 has been reported to be sufficient to transform non-tumorigenic human cells to a tumorigenic phenotype. In a model system using murine fibroblasts, EPS8 overexpression led to enhanced mitogenic signaling and growth factor-dependent cellular transformation. Constitutive tyrosine phosphorylation of EPS8 has been documented in human tumor cell lines, although the significance of this for tumorigenesis remains to be established.

Breast cancer
Oncogenesis
EPS8 overexpression has been shown via integrated cDNA array comparative genomic hybridization and serial analyses of gene expression in a number of human breast cancer cell lines such as ductal carcinoma in situ cell lines, invasive ductal carcinomas and lymph node metastases, as novel candidate breast cancer oncogenes.

Pancreatic cancer
Oncogenesis
EPS8 was found to be overexpressed in multiple pancreatic tumors, with elevated levels primarily found in pancreatic ductal cells, cell lines derived from malignancies and ascites compared to lower levels in primary tumors and normal pancreatic tissues. EPS8 was reported to localize to the tips of F-actin filaments, filopodia, and the leading edge of the cells, and was therefore correlated with the migratory potential of tumor cells.

Colon cancer
Oncogenesis
EPS8 was found to be overexpressed in the majority of colorectal tumors compared to their normal counterparts. It was also found to modulate FAK expression and together, EPS8 and FAK were found to play an important role in cell locomotion.

Head and neck squamous cell carcinoma
Oncogenesis
Greater expression of EPS8 was found in malignant head and neck squamous cell carcinoma cell lines (HN12) compared to the primary tumor derived cells (HN4) from the same patient. Ectopic overexpression of EPS8 in HN4 cells led to increased cell proliferation and migration in vitro and tumorigenicity in vivo.

Signaling processes involving EPS8. Dashed lines, direct protein interactions; blue circles, effector proteins.
Knockdown of EPS8 in HN12 cells led to reduced migration in vitro and reduced tumorigenicity in vivo. EPS8 was found to mediate alphavbeta6 and alpha5beta1 integrin dependent activation of Rac1 and resulting cell migration. Suppression of either EPS8 or Rac1 resulted in reduced cell motility of the same tumor cells, however constitutive expression of Rac1 rescued reduced cell migration in EPS8 knockdown cells. Therefore EPS8 and Rac1 likely modulate integrin-dependent tumor cell motility. FOXM1, a cell cycle related transcription factor, was found to be upregulated in tumor cells with elevated EPS8. Further studies showed cell proliferation and migration due to EPS8 occurs in part by FOXM1 deregulation and induction of CXC-chemokine expression, which is mediated by PI3K and AKT-dependent mechanisms.

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FAM107A (family with sequence similarity 107, member A)

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Identity

Other names: DRR1; FLJ30158; FLJ45473; TU3A
HGNC (Hugo): FAM107A
Location: 3p14.3
Note: The FAM107A protein is encoded by FAM107A gene.

DNA/RNA

Description
FAM107A DNA contains 17742 bps (genomic size), on negative strand.

Transcription
FAM107A has two transcript variants. FAM107A transcript variant 1 mRNA contains 3465 bps and 5 exons. FAM107A transcript variant 2 mRNA contains 3367 bps and 4 exons. These two transcript variants encode for the same protein.

Protein

Description
144 amino acids, 17.5 kDa.
FAM107A protein includes a nuclear localization signal (NLS) and a coiled domain (Yamato et al., 1999; Wang et al., 2000).

Expression
FAM107A protein is expressed in a wide variety of normal tissues. High expression is found in the brain and heart (Wang et al., 2000; Zhao et al., 2007).

Localisation
Nucleus and cytoplasm (Wang et al., 2000; Zhao et al., 2007; Le et al., 2010).

Function
FAM107A is a candidate tumor suppressor gene. FAM107A protein is downregulated in several tumor cell lines and primary tumors. Overexpression of FAM107A can suppress tumor cell growth (Yamato et al., 1999; Wang et al., 2000; Kholodnyuk et al., 2006; van den Boom et al., 2006; Liu et al., 2009; Asano et al., 2010; Le et al., 2010).
FAM107A protein is also involved in neuronal cell survival. Downregulation of FAM107A protein in primary cultured cortical neurons decrease cell number (Asano et al., 2010).
FAM107A protein probably plays important roles in embryo development (Zhao et al., 2007).
FAM107A protein is a cytoskeletal crosslinker that regulates FA dynamics and cell movement. FAM107A protein is an important molecular in cell invasion (Le et al., 2010).

Homology
No proteins with significant homology with FAM107A protein were found (Wang et al., 2000).
Mutations

Note
Up to now, no point mutations were identified.

Implicated in

Renal cell carcinoma
Disease
Loss of FAM107A gene was found on 3p21.1 in renal cell carcinoma. Reduced expression was found in renal cell carcinoma cell lines and primary renal cell carcinomas. Overexpression of FAM107A in renal cell carcinoma cell line resulted in growth suppression of these cells (Yamato et al., 1999; Wang et al., 2000). Also, FAM107A hypermethylation was detected in renal cell carcinomas and significantly associated with advanced tumor stage (Awakura et al., 2008).

Astrocytomas
Disease
FAM107A was expressed at significantly lower levels in secondary glioblastomas as compared to diffuse astrocytomas (Van den Boom et al., 2006).

Lung cancer
Disease
Loss of expression of FAM107A was found in non-small cell lung cancer and primary lung cancers. Overexpression of FAM107A in non-small cell lung cancer cell line reduced cell proliferation activity and induced apoptosis (Liu et al., 2009).

Neuroblastoma
Disease
FAM107A protein was detected in the normal ganglions and the ganglions exhibiting neuroblast hyperplasia from 2 weeks hemizygote MYCN transgenic mice. However, the expression of FAM107A completely disappeared in the tumors from 8 weeks hemizygote MYCN transgenic mice (Asano et al., 2010).

Brain tumor
Disease
FAM107A is not expressed in normal glial cells, it is highly expressed in the invasive component of gliomas. It was found that FAM107A associates with and organizes the actin and microtubular cytoskeletons. FAM107A regulates focal adhesion disassembly and cell invasion (Le et al., 2010).

Embryo development
Note
The expression level of FAM107A gene increases gradually with embryo development in the early stages (Zhao et al., 2007).

Schizophrenia and bipolar disorder
Note
High expression level of FAM107A was found in the dorsolateral prefrontal cortex from schizophrenia and bipolar disorder patient (Shao et al., 2007).

Neuronal cell survival
Note
FAM107A protein was mainly localized in the neurites of the primary culture of cerebral cortical neurons. Downregulation of FAM107A expression with siRNA decreased neuron cell number. These data suggest that FAM107A plays a critical role in neuronal cell survival (Asano et al., 2010).

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This article should be referenced as such:
**GAST (gastrin)**

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**Identity**

**Other names:** GAS  
**HGNC (Hugo):** GAST  
**Location:** 17q21.2

**DNA/RNA**

**Note**  
The 4.3 kb gene for human gastrin contains two introns and 3 exons that encode preprogastrin, the gastrin precursor. It is located on chromosome 17(q21), and consists of three exons that contain the code sequence for a prepropeptide of 101 amino acid residues with a calculated molecular mass of 11.4 kDa (see diagram below). The primary structure of human preprogastrin protein consists of an N-terminal 21-amino acid signal sequence followed by a spacer peptide, a bioactive domain, and finally a hexapeptide C-terminal flanking peptide (CTFP). Upon initiation of translation, the signal sequence facilitates the translocation of the elongating polypeptide into the endoplasmic reticulum (ER), where it is subsequently removed by a membrane-bound signal peptidase that cleaves the growing polypeptide chain between alanine residue 21 and serine 22 to generate the 80 amino acid peptide, progastrin. Progastrin is further processed (see protein section below) into the two principal C-terminal alpha-amidated forms of circulating gastrin generated from the proteolytic cleavage of progastrin are gastrin-17 (G17) and gastrin-34 (G34).

**Protein**

**Note**  
It should be noted that the numbering system of critical amino acid residues involved in peptide cleavage and post-translational modifications of gastrin varies within the scientific literature. This is due to the fact that the numbering system of some authors is based on the sequence of preprogastrin, which includes the 21 amino acids of the signal peptide sequence, whereas the numbering system of others is based on the sequence of progastrin. Our description of prohormone processing will be based on the 80 amino acid peptide sequence of progastrin.

After signal peptide cleavage, progastrin undergoes additional post-translational modifications as it transits from the ER through the Golgi to the trans-Golgi network before it is sorted into immature secretory vesicles of the regulated exocytosis (secretory) pathway. The modifications include O-sulfation at tyrosine residue 66 of the propeptide by tyrosylprotein sulfotransferases and/or phosphorylation at serine 75 by a calcium-dependent casein-like kinase. Although O-sulfation is thought to occur primarily in the trans-Golgi network, a recent study provides evidence suggesting that it may continue through later compartments of the regulated secretory pathway.
Schematic representation of the preprogastrin gene, its mRNA, and the peptide precursor preprogastrin. The gene is transcribed as a 303 nucleotide RNA transcript and the mRNA is processed into a 101 amino acid (aa) preprohormone. The preprogastrin peptide consists of a 21-aa signal sequence, which is co-translationally cleaved, a N-terminal spacer, the active peptide and the C-terminal flanking peptide (CTFP). Progastrin is formed after removal of the signal peptide.

The extent of gastrin O-sulfation varies with species and cellular localization of peptide synthesis within the GI tract as well as the developmental stage of the tissues. For example, in adult humans, approximately half of the gastrin peptide synthesized in G cells of the antrum and duodenum, and released into the circulation are sulfated, whereas all of the gastrin peptide produced by the fetal pancreas appears to be sulfated. Functionally, sulfation of gastrin enhances endoproteolytic processing of progastrin, and may promote protein-protein interactions and peptide sorting between secretory pathways. However, unlike sulfation of the related peptide, cholecystokinin (CCK), sulfation of gastrin does not significantly affect its affinity for its physiologic receptor.

Phosphorylation of serine 75 of progastrin may promote proteolytic processing at the upstream arginine residues at positions 73 and 74 (arginine 73-arginine 74) releasing the C-terminal flanking peptide, and may affect the conversion of glycine-extended gastrin intermediates to mature C-terminal alpha-amidated peptides. However, since phosphorylation is not essential for progastrin processing, its biological significance remains an enigma.

Following sulfation and/or phosphorylation, progastrin exits the trans-Golgi network and enters immature granules of the regulated secretory pathway. The major proteolytic processing of progastrin to its biologically active peptides occurs in the maturing dense core secretory granules of the regulated pathway. Progastrin is cleaved by two types of proteases: endo- and exopeptidases. Endopeptidases, also known as prohormone convertases (PC), typically cleave polypeptides downstream of two adjacent basic amino-acid residues at the general motif (lysine/arginine)-(X)n-(lysine/arginine), where n=0, 2, 4, or 6 and X is any amino acid, but usually not a Cysteine. PC1/3 and PC2 are involved in progastrin processing. The two principal biologically active forms of circulating gastrin are gastrin-17 (G17) and gastrin-34 (G34). In rodent and human G cells of antrum and proximal duodenum, approximately 95% of the progastrin is processed to partially sulfated G17 (85%) and G34 (10%). Although G17 is the predominant product, G34 is the major circulating form of gastrin due to its slower rate of clearance. In both humans, the half-life of circulating G34 is approximately five times longer than that of G17. The proteolytic processing of progastrin involves convertase-specific cleavage at three dibasic consensus sites. PC1/3 is active early in the secretory pathway in granules with a neutral pH (i.e., pH ≈ 7) and cleaves the prohormone after the arginine 36-arginine 37 and arginine 73-arginine 74 sequences, releasing the C-terminal flanking peptide, and generating G34. The post-cleavage residual basic residues are then removed by carboxypeptidase E, generating what are commonly referred to as the glycine-extended gastrins (i.e., G34-Glycine). In contrast to PC1/3, PC2 is mainly active in mature granules at an acidic pH (i.e., pH ≈ 5). Cleavage of G34-glycine by PC2 after the dibasic amino acid sequence lysine 53-lysine 54 produces G17-glycine. These glycine-extended peptides are substrates for the peptidyl-glycine alpha-amidating monoxygenase (PAM) that utilizes the glycyl residue as an amide donor to alpha-amidate the carboxyl group of the C-terminus of the peptide. The ratio of amidated gastrins to processing intermediates varies considerably across tissues and cell types. Processing intermediates are quite scarce in the gastric antrum, making up only about 1-5% of gastrin gene products, while in the duodenum the value has been reported to be as high as 15-20%.
Processing of gastrin. The numbering system of critical amino acid residues involved in peptide cleavage and post-translational modifications of gastrin varies within the scientific literature. This is due to the fact that the numbering system of some authors is based on the sequence of preprogastrin, which includes the 21 amino acids of the signal peptide sequence, whereas the numbering system of others is based on the sequence of progastrin. The numbers at the top of the diagram represents the amino acid (aa) sequence for preprogastrin; the numbers at the bottom of the diagram represents the aa sequence for progastrin. The signal peptide is cleaved co-translationally in the rough ER by signal peptidase. In the Trans-Golgi-Network (TGN), progastrin is modified by sulfation at Tyr 66 and phosphorylation of Ser 75 by a casein-like kinase. Prohormone convertases (PC) and carboxypeptidase E (CPE) sequentially convert the prohormone to the glycine-extended forms (G71-Gly, G34-Gly, G17-Gly). Abbreviations: CTFP: C-terminal flanking peptide, TPST: tyrosyl-protein sulfotransferase, PAM: peptidyl-alpha-amidating-monooxygenase.

as 20%. Carboxyl-terminus alpha-amidation is a prerequisite for high affinity binding of gastrin to its cognate receptor, CCK2 receptor.

Mutations

Note
There are no known mutations in the gastrin gene causing a pathologic entity. Overexpression of gastrin, or aberrant expression of gastrin, have both been associated with gastric, colorectal, esophageal and pancreatic cancers.

Implicated in

Gastrinomas

Note
Gastrinomas are neuroendocrine tumors that can arise from the stomach, duodenum or pancreas. Patients with multiple endocrine neoplasia type 1 (MEN1) have a mutation in the menin gene and are at very high risk for developing gastrinomas. In patients with hypergastrinemia due to pernicious anemia or MEN1, tissue and plasma levels of PAI-2 are elevated. Gastrin directly regulates PAI-2 expression in CCK2 receptor-positive cells, and in neighboring receptor-negative cells, by way of paracrine mediators released from the CCK2 receptor-expressing cells. Direct regulation involves cell autonomous activation of CRE and AP-1 transcription factors via a PKC, Ras, Raf, RhoA, and the NFkappaB signaling pathways in CCK2 receptor-expressing cells by gastrin. The CRE and AP-1 transcription factors, in turn, regulate expression of the genes for IL-8 and COX2. IL-8 acts through a GACAGA site via the activating signal cointegrator 1 (ASC-1) complex, whereas prostaglandins, resulting from the activation of COX2, target the Myc-associated zinc finger protein (MAZ site via the small GTPase RhoA to stimulate PAI-2 expression in adjacent CCK2 receptor-negative cells.

Inflammation-associated carcinomas

Note
In a rat intestinal epithelial cell model, MAPKs mediate CCK2 receptor regulation of cyclooxygenase 2 (COX-2). COX-2 is an inducible enzyme catalyzing the rate-limiting step in prostaglandin synthesis, converting arachidonic acid to prostaglandin H2. A large body of genetic and biochemical evidence support the important role of
COX-2 and the subsequent synthesis of prostaglandins in the regulation of inflammation and promotion of tumorigenesis. Gastrin has been shown to increase COX-2 expression in colorectal, gastric, and esophageal cancers.

**Gastric cancer**

**Note**

Gastric carcinogenesis is a multistep process that arises from superficial gastritis, chronic atrophic gastritis, progressing to intestinal metaplasia, dysplasia, and finally carcinoma. H. pylori is the most common known cause of chronic gastritis in humans, secretes urease, which converts urea to ammonia, and neutralizes the acid in the stomach. H. pylori initiates a host inflammatory response that is associated with the recruitment of mononuclear and polymorphonuclear leukocytes, and bone marrow-derived cells. Specific inflammatory cytokines from immune cells are required for the initiation and promotion of carcinogenesis. In addition to local inflammation, H. pylori induces the systemic elevation of serum gastrin (hypergastrinemia). The combination of achlorhydria and hypergastrinemia, induced by H. pylori infection, results in gastric bacterial overgrowth, lack of parietal cell differentiation, development of gastric metaplasia, and eventual progression to gastric carcinoma.

**Colorectal cancer**

**Note**

Gastrin and gastrin-like peptides are upregulated locally in 78% of premalignant adenomatous polyps, before the appearance of invasive carcinoma, and gastrin expression has been linked to key mutations in the initiation of colorectal carcinogenesis. When the APC<sup>min/t</sup> mouse was crossed with a gastrin gene knockout mouse, the hybrid developed fewer intestinal polyps. Gastrin transcription is linked to the Wnt/beta-catenin pathway by a binding site for the transcription factor TCF4 in the gastrin promoter. Induction of the wild-type APC decreased gastrin mRNA expression, while transfection of constitutively active beta-catenin increased gastrin promoter activity.

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This article should be referenced as such:

PAK2 (p21 protein (Cdc42/Rac)-activated kinase 2)

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Identity

Other names: PAK65; PAKgamma
HGNC (Hugo): PAK2
Location: 3q29

DNA/RNA

Description
Pak2 gene at 193763319 to 193859670 bp from pter contains 96352 bases and 34 exons. Pak2 gene at the alternative location starts at 196466728 and ends at 196559518 bp from pter. The PAK2 gene in this location contains 20 exons.

Protein

Description
Pak2 has an N-terminal regulatory domain and a C-terminal catalytic domain. In the regulatory domain, Pak2 have several conserved regions, including an autoinhibitory domain (AID), a p21-binding domain (PBD), dimerization domain, proline-rich regions, and an acidic region. The schematic structure of Pak2 is shown in figure above. The catalytic domain of Pak is a conserved bilobal structure in most of the protein kinases.

Expression
Pak2 is 58.8 kDa (524 residues) and expressed ubiquitously in mammalian cells.

Function
PAK activation is through disruption of autoinhibition, followed by autophosphorylation. In the inactive state, the AID interacts with the catalytic domain to inhibit its kinase activity. GTP-bound Cdc42 can disrupt autoinhibition, which, in turn, leads to autophosphorylation and activation of PAK. Pak2's basal autophosphorylation activity is observed and Pak2 is autophosphorylated at 5 sites, serines 19, 20, 55, 192 and 197. Additional three phosphorylation sites (serines 141 and 165 and threonine 402) are autophosphorylated in the presence of Cdc42(GTP) and ATP. Autophosphorylation of Thr402 in the activation loop is required for the kinase activity of Pak2. Pak2 can be activated in response to a lot of stresses. Moderate stresses, like hyperosmolarity, ionizing radiation, DNA-damaging agents and serum-deprivation, induce Pak2 activation in cells and lead to cell cycle arrest at G2/M. Activated Pak2 inhibits translation by phosphorylation of various substrates. Pak2 has specific protein substrates, e.g. histone 4, myosin light chain (MLC), prolactin, c-Abl, eukaryote translation initiation factor 3 (eIF3), eIF4B, eIF4G, and Mnk1. Pak2 recognizes the consensus sequence (K/RRXS).

Pak2 is the only member of the PAK family that is directly activated by caspase 3. When Pak2 is cleaved and activated by caspase 3, Pak2 promotes the morphological and biochemical changes of apoptosis. The pro-apoptosis protease, caspase 3 cleaves Pak2 after Asp 212, and thus produces a p27 fragment containing primarily the regulatory domain, and a p34 fragment containing a small piece of the regulatory domain and the entire catalytic domain. Autophosphorylation results in a constitutively active p34 kinase domain.
The nuclear import signal (245-251) is required for nuclear localization. Disruption of the region (197-246), containing nuclear export signal results in the nuclear localization of the Pak2 p34 fragment.

**Homology**

Pak1, Pak2 and Pak3 are highly homologous. The primary sequence of human Pak2 is 72% identical to Pak1 and 71% identical to Pak3.

**Mutations**

*Note*

None is reported.

**Implicated in**

**Tumors**

**Prognosis**

Huang (2004) showed Pak2 is a negative regulator of Myc and suggested Pak2 may be the product of a tumor suppressor gene. Coniglio (2008) reported Pak2 mediates tumor invasion in breast carcinoma cells. Inhibition of RhoA in Pak2-depleted cells decreases MLC phosphorylation and restores cell invasion. Also, the NF2 tumor suppressor Merlin is a substrate of Pak2. Wilkes (2009) showed that Erbin regulates the function of Merlin through Pak2 binding to Merlin.

**Immunodeficiency**

*Note*

Human immunodeficiency virus type 1 HIV-1.

**Prognosis**

Human immunodeficiency virus type 1 Nef associates with a active Pak2 independently of binding to Nck or PIX. Nef recruits the GEF Vav1 to plasma membrane to associate with Pak2.

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This article should be referenced as such:

Gene Section
Mini Review

TGFBRAP1 (transforming growth factor, beta receptor associated protein 1)

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Identity

Other names: TRAP-1; TRAP1
HGNC (Hugo): TGFBRAP1
Location: 2q12.1

DNA/RNA

Description
Encoded on the minus strand. 12 exons, exon number 1 is not depicted in the diagram and appears to undergo differential splicing, according to recent NCBI-AceView (accessed 17 Apr 2011).

Transcription
Work by the Wurthner lab in 2003-2005 identified an 860 aa protein that could be matched with genomic sequences. Recently predicted proteins from mRNA variants describe translation products of 896, 952, 161 and 30 aminino acids (NCBI AceView, accessed 17 April 2011).

Protein

Description
A fragment of TGFBRAP1 was initially identified in a Yeast-2-Hybrid screen as a TGF-beta type I receptor interacting protein (Chang et al., 2002). Further work by Wurthner et al. demonstrated binding of the full-length molecule exclusively to either TGF-beta receptor I and TGF-beta receptor II, or to Smad4, suggesting TGFBRAP1 to be a Smad4 chaperone (Wurthner et al., 2001). Furthermore, receptor activated Smads were shown to compete for binding of TRAP1 with Smad4, suggesting only a transient association between TRAP1 and Smad4. In addition, an interaction of TRAP1 with 5-lipoxygenase in a yeast two-hybrid system was described by a different group (Provost et al., 1999). Gene inactivation of TGFBRAP1 through conventional targeting leads to early developmental arrest of murine embryos around day E 6.5 (Messler et al., 2010).
Expression
Ubiquitous.

Localisation
Punctate pattern suggestive of endosomal localisation.

Function
Chaperone for Smad4 in the TGF-beta signal transduction cascade (Wurthner et al., 2001). Endosomal trafficking (circumstantial evidence: domain structure and early embryonic lethality; Messler et al., 2010).

Homology
hVPS39 (hVam6, hTrap-like-Protein).

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This article should be referenced as such:
AXIN1 (axin 1)
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Identity
Other names: AXIN; MGC52315
HGNC (Hugo): AXIN1
Location: 16p13.3

Note
According to Entrez gene and Ensembl the isoform a starts at 337440 and ends at 402464 bp with the total length of 65025 bp. The isoform b starts at 338122 and ends at 397025 with the total length of 58904 bp. Zeng et al. (1997) renamed the gene that was originally termed Fu to Axin in order to avoid confusion with the unrelated Drosophila gene fused.

DNA/RNA

Description
Axin 1 consists of 11 exons (isoform a). Full gene transcript product length is 3675 bp. Isoform b lacks an in-frame exon in the 3’ coding region and is shorter with sequence length of 3567 bp (Salahshor and Woodgett, 2005) (Figure 1).

Transcription
There are two transcript variants. Variant 1 (encoding for isoform a) represents the longer transcript (NM 003502.3). Variant 2 (encoding for isoform b) is shorter compared to variant 1 (NM 181050.2). According to Ensembl there are six transcripts of AXIN1 of which first two are well known isoforms a and b and the remaining 4 are still in research.

Protein

Note
Protein name: Axin 1, Axin, Axis inhibitor, Axis inhibitor protein 1.

Description
At least two isoforms of protein axin are expressed. Longer isoform has all eleven exons translated and consists of 862 aminoacids while shorter has 826 aminoacids translated from ten exons. Axin 1 protein can be recognized primarily by two domains, the N-terminal RGS domain (regulators of G-protein signaling) and the C-terminal DIX domain (dishevelled and axin) (Luo et al., 2005; Shibata et al., 2007). RGS domain is needed for APC binding while DIX domain for homodimerization and heterodimerization (Ehebauer and Arias, 2009; Noutsou et al., 2011). There is also a central region of the protein that binds GSK3beta and beta-catenin. Axin protein has nuclear localization (NLS) and nuclear export (NES) sequences as well. It is well known that axin is a scaffold protein that can shuttle between the cytoplasm and the nucleus.

Figure 1. Genomic structure of Axin 1. Axin 1 is composed of 10 exons and they encode isoform a, while in isoform b exon 8 is spliced out.
Nucleo-cytoplasmatic shuttling under normal circumstances suggests existence of possible "salvage pathway" that would be activated by axin translocation to the nucleus in order to reduce beta-catenin oncogenic activity by exporting nuclear beta-catenin and degrading it in the cytoplasm (Wiechens et al., 2004). Axin can also undergo posttranslational modifications. Phosphorilation by casein kinase 1 (CK1) enhances binding of GSK3beta and AXIN1. For activation of JNK pathway axin needs to be SUMOylated (Kim et al., 2008) (Figure 2).

**Figure 2.** Two crystallized domains of the Axin 1 protein are shown: (A) RGS and (B) DIX.

**Expression**

Axin is expressed ubiquitously.

**Localisation**

Axin is predominantly expressed in the cytoplasm, but periplasmic and nuclear localization are also observed depending on the stimulation of the cells (Cong and Varmus, 2004; Luo and Lin, 2004). In nonstimulated cells, axin colocalizes with Smad3. The subcellular location of axin is not well defined in the literature. It has been reported that physiological concentrations of axin is low in Xenopus egg cells. It has also been shown that it is located in cytoplasmic puncta in living mammalian cells. Wang et al. (2009) report that axin 1 is highly co-localized with beta-catenin in the cytoplasm of human cumulus cells and that this localization denotes intact wnt signaling. Pecina-Slaus et al. (2011) showed the subcellular location of axin in normal brain white matter and glioblastoma tissue. The majority of glioblastomas (69.04%) had axin localized in the cytoplasm. Nevertheless, 9.5% of glioblastomas samples had axin localized in the nucleus (Figure 3). Distribution of axin was reported previously by Anderson et al. (2002) in neoplastic colon. Altered nuclear expression of axin seen in colon polyps and carcinomas may be a consequence of the loss of full-length APC and the advent of nuclear beta-catenin.

**Figure 3.** Glioblastoma samples immunohistochemically stained for protein expression of axin. (A) Cytoplasmic localization of axin and (B) nuclear localization of axin.

**Function**

Tumor suppressor protein Axin 1 is an inhibitor of the Wnt signaling pathway (Polakis, 2000; Salahshor and Woodgett, 2005). As a scaffold protein, its main role is binding multiple members of Wnt signaling and formation of the beta-catenin destruction complex. It down-regulates beta-catenin, wnt pathway’s main effector signaling molecule, by facilitating its phosphorylation by GSK3-beta (Hart et al., 1998). It binds directly to APC (adenomatous polyposis coli), beta-catenin, GSK3-beta and dishevelled forming a so called "beta-catenin destruction complex" in which phosphorylated beta-catenin is targeted for quick ubiquitinilation and degradation in the 26S proteosome (Yamamoto et al., 1999; Logan and Nusse, 2004). In response to wnt signaling, or under the circumstances of mutated axin or APC, beta-catenin is stabilized, accumulates in the
cytoplasm and enters the nucleus, where it finds a partner, a member of the DNA binding protein family LEF/TCF. Together they stimulate the expression of target genes including c-myc, c-jun, fra-1 and cyclin D1. In development Axin controls dorsoventral polarity axis formation (Zeng et al., 1997; Wodarz and Nusse, 1998) by two independent mechanisms: downregulation of beta-catenin, but also by activation of Wnt-independent stem cells differentiation (Reya et al., 2003) and transforming growth factor beta signaling (Furuhashi et al., 2001). Reports indicate that beta-catenin and axin regulate critical developmental processes of normal CNS development (Pecina-Slaus, 2010).

Axin interacts with a number of proteins including: APC, Axam, Axin, beta-catenin, Cdc1, CKI, DAXX, DCAP, Diversin, Dvl, gamma-tubulin, GSK3beta, HIPK2, I-mfa, LRP5/6, MDFIC, MEKK1, MEKK4, P53, PIAS, Pirh2, PP2A, Rnf11, Zbed3, Tip60, Smad3, Smad6, and Smad7 (Cliffe et al., 2003; Chen et al., 2009; Fumoto et al., 2009; Li et al., 2009; Choi et al., 2010; Kim and Jho, 2010).

**Homology**

Homologs are found in: Pan troglodytes, Canis lupus familiaris, Bos taurus, Mus musculus, Rattus norvegicus, Gallus gallus, Danio rerio.

**Mutations**

**Note**

According to HGMD there are 3 missense mutations reported for AXIN 1 in colorectal carcinoma. Nikuseva Martic et al. (2010) identified gross deletions (Loss of Heterozygosity) of AXIN 1 in 6.3% of glioblastomas, in one neuroepithelial dyssembrioplastic tumor and in one medulloblastoma. In a primary hepatocellular carcinoma 13 somatic events were reported by OMIM, a 33-bp deletion in exon 3 of the AXIN1 gene, and 12 missense mutations. OMIM also reports on hypermethylation of AXIN 1 promotor region in caudal duplication anomaly.

**Implicated in**

**Hepatocellular carcinoma**

**Note**

In a primary hepatocellular carcinoma (HCC), Satoh et al. (2000) found a 33-bp deletion in exon 3 of the AXIN1 gene, involving 2 glycogen synthase kinase-3-beta phosphorylation sites. In addition to this deletion they found 12 missense mutations, of which 9 occurred in codons encoding serine or threonine residues. They confirmed that all 13 mutations found in primary HCCs occurred as somatic events. Taniguchi et al. (2002) found AXIN1 mutations in seven (9.6%) HCCs. The AXIN1 mutations included seven missense mutations, a 1 bp deletion, and a 12 bp insertion. Loss of heterozygosity at the AXIN1 locus was present in four of five informative HCCs with AXIN1 mutations, suggesting a tumor suppressor function of this gene. Park et al. (2005) showed that mutations of AXIN 1 are late events in hepatocellular carcinogenesis.

**Medulloblastoma**

**Note**

To find out if Axin is also involved in the pathogenesis of sporadic medulloblastomas, Dahmen et al. (2001) analyzed 86 cases and 11 medulloblastoma cell lines for mutations in the AXIN1 gene. Using single-strand conformation polymorphism analysis, screening for large deletions by reverse transcription-PCR, and sequencing analysis, a single somatic point mutation in exon 1 (Pro255Ser) and seven large deletions (12%) of AXIN1 were detected. Baeza et al. (2003) screened 39 sporadic cerebellar medulloblastomas for alterations in the AXIN1 gene. The authors found missense AXIN1 mutations in two tumours, CCC-->TCC at codon 255 (exon 1, Pro-->Ser) and TCT-->TGT at codon 263 (exon 1, Ser-->Cys). Furthermore, the A allele at the G/A polymorphism at nucleotide 16 in intron 4 was significantly over-represented in medulloblastomas (39 cases; G 0.76 vs-A 0.24) compared to healthy individuals (86 cases; G 0.91 vs A 0.09; P=0.0027). Yokota et al. (2002) showed another AXIN1 mutation in exon 3, corresponding to GSK-3beta binding site.

**Colorectal carcinoma**

**Note**

Hart et al. (1998) report on overexpression of Axin1 in connection to the downregulation of wild-type beta-catenin in colon cancer cells. In addition, Axin1 dramatically facilitated the phosphorylation of APC and beta-catenin by GSK3 beta in vitro. Another group (Jin et al., 2003) analyzed 54 colorectal cancer tissues for mutations in AXIN1 gene. They found 3 silent mutations, 6 missense point mutations in different functionally important regions. The missense mutation rate was hence 11%, suggesting that Axin 1 deficiency may contribute to the onset of colorectal tumorigenesis. Segditsas and Tomlinson (2006) report on mutations in AXIN1 in microsatellite-unstable colon cancers. Three AXIN1 missense variants P312T, R398H, and L445M were detected in 1 of 124 patients with multiple colorectal adenomas. Three other missense mutations, D545E, G700S, and R891Q, were found. The overall frequency of the rare variants was significantly higher in the patients as compared with the controls (Fearnhead et al., 2004).
**Brain tumors**

**Note**
A sample of 72 neuroepithelial brain tumors was investigated for AXIN-1 gene changes by Nikuseva Martic et al. (2010). Polymorphic marker for AXIN-1, showed loss of heterozygosity in 11.1% of tumors. Down regulation of axin expression and up regulation of beta-catenin were detected. Axin was observed in the cytoplasm in 68.8% of samples, in 28.1% in both the cytoplasm and nucleus and 3.1% had no expression. Comparison of mean values of relative increase of axin and beta-catenin showed that they were significantly reversely proportional (P=0.014) in a set of neuroepithelial brain tumors. Pecina-Slaus et al. (2011) also explored axin's existence at the subcellular level in glioblastomas and showed that the highest relative quantity of axin was measured when the protein was in the nucleus and the lowest relative quantity of axin when the protein was localized in the cytoplasm.

**Ovarian endometroid adenocarcinomas**

**Note**
Wu et al. (2001) report on a nonsense mutation in one ovarian endometroid adenocarcinoma (OEa). They also found another missense AXIN1 sequence alteration in OEA-derived cell lines.

**Lung cancer**

**Note**
In 105 lung SCC and adenocarcinoma tissue samples, the cytoplasmic expression of Axin was significantly lower than in normal lung tissues. Western blot analysis also demonstrated that the relative expression quantity of Axin was significantly reduced in lung cancer tissues compared with normal lung tissues. Nuclear expression of Axin was observed in 21 cases (20%) of lung cancers (Xu et al., 2011).

**Oesophageal squamous cell carcinoma**

**Note**
Nakajima et al. (2003) found reduced expression of Axin1 in oesophageal squamous cell carcinoma. Several mutations have also been reported in oesophageal squamous cell carcinoma.

**Cervical cancer**

**Note**
Su et al. (2003) examined AXIN1 in cervical cancer. Among the 30 tested cervical cancers mutation analysis of AXIN1 revealed that one specimen had a heterozygous mutation at codon 740. Six polymorphisms were also found. Immunohistochemistry showed no relationship between the protein expression patterns and mutation of AXIN1.

**Prostate cancer**

**Note**
Yardy et al. (2009) reported on AXIN1 mutations in advanced prostate cancer. They found 7 mutations in prostate cancer cases and 4 polymorphisms in prostate cancer cell lines.

**Caudal duplication anomaly**

**Note**
Hypermethylation of the AXIN1 promoter is associated with the caudal duplication anomalies. Oates et al. (2006) examined methylation at the promoter region of the AXIN1 gene in monozygotic twins. The promoter region of the AXIN1 gene was significantly more methylated in the twin with the caudal duplication than in the unaffected twin.

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This article should be referenced as such:

Gene Section
Mini Review

CCR2 (chemokine (C-C motif) receptor 2)

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Identity

Other names: CC-CKR-2; CCR2A; CCR2B; CD192; CR2; CKR2A; CKR2B; CMKBR2; FLJ78302; MCP-1-R; MGC103828; MGC111760; MGC168006
HGNC (Hugo): CCR2
Location: 3p21.31

DNA/RNA

Note
CCR2 is a member of the beta chemokine receptor family. CCR2 is a seven transmembrane protein similar to G protein-coupled receptors. This gene encodes two isoforms of a receptor for monocyte chemoattractant protein-1, a chemokine which specifically mediates monocyte chemotaxis. Monocyte chemoattractant protein-1 is involved in monocyte infiltration in inflammatory diseases such as rheumatoid arthritis as well as in the inflammatory response against tumors. The receptors encoded by this gene mediate agonist-dependent calcium mobilization and inhibition of adenyl cyclase. This gene is located in the chemokine receptor gene cluster region including CCR1, CCR12, CCR3, CCR5 and CCXCR1 on chromosome 3p.

Description
Size: 7195 bases.

2 isoforms:
- C-C chemokine receptor type 2 isoform A. CCDS43078.1
- C-C chemokine receptor type 2 isoform B. CCDS46813.1

Transcription
Homo sapiens chemokine (C-C motif) receptor 2 (CCR2), transcript variant A, mRNA: 2689 bp.
Homo sapiens chemokine (C-C motif) receptor 2 (CCR2), transcript variant B, mRNA: 2335 bp.

Pseudogene
No pseudogenes have been reported for CCR2.

Protein

Note
Chemokine receptors are cytokine receptors found on the surface of cells, which interact with a type of cytokine called a chemokine. They have a 7 transmembrane structure and couple to G-protein for signal transduction within a cell, making them members of a large protein family of G protein-coupled receptors. Following interaction with their specific chemokine ligands, chemokine receptors trigger a flux in intracellular calcium (Ca²⁺) ions (calcium signaling). This causes cell responses, including the onset of a process known as chemotaxis that traffics the cell to a desired location within the organism.
Chemokine receptors share many common structural features; they are composed of about 350 amino acids that are divided into a short and acidic N-terminal end, seven helical transmembrane domains with three intracellular and three extracellular hydrophilic loops, and an intracellular C-terminus containing serine and threonine residues that act as phosphorylation sites during receptor regulation. The first two extracellular loops of chemokine receptors are linked together by disulfide bonding between two conserved cysteine residues. The N-terminal end of a chemokine receptor binds to chemokine(s) and is important for ligand specificity. G-proteins couple to the C-terminal end, which is important for receptor signaling following ligand binding.

**Description**
374 amino acids; 41915 Da.

**Expression**
Peripheral blood monocytes, activated T cells, B cells and immature dendritic cells.

**Localisation**
Cell membrane; multi-pass membrane protein.

**Function**
Receptor for the MCP-1/CCL2, MCP-3/CCL7 and MCP-4/CCL13 chemokines. Transduces a signal by increasing the intracellular calcium ions level. Alternative coreceptor with CD4 for HIV-1 infection.

**Homology**
CCR2 proteins contains amino acid sequence homology to other C-C chemokines. CCR1 (56%), CCR5 (71%), CCR3 (78%), CCR4 (75%).

**Implicated in**

**Multiple myeloma**

**Prognosis**
In a cohort of 80 patients with Multiple Myeloma (MM), patients with active disease showed significant lower expression of CCR1, CCR2 and CXCR4 than patients with non-active disease.

**Oncogenesis**
CCR1 and CCR2 are overexpressed in myeloma cells compared to normal B cells. Osteoclasts express genes coding for CCR2 chemokines specifically (CCL2, CCL7, CCL8, and CCL13) and high CCR2 gene expression in myeloma cells is associated with increased bone lesions in MM patients. CCR2 is significantly overexpressed in MM cells compared to normal bone marrow plasma cells. Osteoclasts can directly recruit MMC by CCR2 chemokines production, promote MMC survival, growth, and drug resistance by producing various growth factors. MMC will promote osteoclast progenitor recruitment and differentiation producing CCL3, MIP-1beta, and CXCL12 chemokines, IGF-1, and increasing RANKL production by stromal cells. Osteoclasts are the main cells in the BM environment that produce...
various CCR2 chemokines enabling malignant plasma cells attraction.

**Neuroblastoma**

**Oncogenesis**

98 untreated primary neuroblastosmas from patients with metastatic disease were analyzed for tumor-infiltrating iNKTs (Valpha24-Jalpha18-invariant natural killer T cells) using RT-PCR and immunofluorescent microscopy. 53% of tumors contained iNKTs. CCR2 is more frequently expressed by iNKT compared to T cells and natural killer cells from blood. iNKTs migrate toward neuroblastoma cells in a CCL2-dependent manner, preferentially infiltrating MYCN nonamplified proto-oncogene tumors that express CCL2.

**Melanoma**

**Oncogenesis**

MCP-1 may play a role in tumor angiogenesis and early tumor growth of human malignant melanoma by inducing VEGF and inflammatory cytokines production (IL-1alpha and TNFalpha by the tumor-associated macrophages (TAM)) and autocrine/paracrine effects on melanoma cells in a mouse model.

**Prostate cancer**

**Prognosis**

The pleiotropic roles of CCL2 in the development of prostate cancer are mediated through its receptor, CCR2. An association between prostate cancer progression and CCR2 expression was demonstrated on tissue microarray specimens of patients. CCR2 mRNA and protein were significantly overexpressed within prostate cancer metastatic tissues compared to localized prostate cancer and benign prostate tissue. CCR2 overexpression was also associated with higher Gleason score and higher clinical pathological stages.

**Oncogenesis**

CCL2 support prostate cancer cell survival via PI3K/AKT in vitro. CCL2 derived from human bone marrow endothelial cells induces PC-3 cell line transendothelial cell migration via activation of the small GTPase Rac. In a cell co-culture system, prostate cancer cell-conditioned medium induces CCL2 overexpression in endothelial cells and osteoblasts. In osteoblasts, this secretion is mediated in part by parathyroid hormone-related protein.

In mouse model, neutralizing antibody against CCL2 inhibits prostate cancer PC-3 and VCaP growth in bone. Same results were obtained with CCL2 knockdown. CCL2 induces surviving expression in prostate cancer cells and protect them from autophagic death.

**Breast cancer**

**Prognosis**

Overexpression of the chemokine CCL2 is frequently associated with advanced tumor stage and metastatic relapse in breast cancer.

**Oncogenesis**

Overexpression of CCL2 promotes breast cancer metastasis to both lung and bone in mice. Blocking CCL2 with a neutralizing antibody reduced lung and bone metastases. The enhancement of lung metastases by CCL2 was associated with increased macrophage infiltration. In bone, it was associated with osteoclast differentiation. CCL2 produced by breast tumor cells activates CCR2 positive stromal cells of monocytic origin (including macrophages and preosteoclasts) leading to metastases in lung and bone.

**Esophageal carcinoma**

**Oncogenesis**

CCL2 is expressed by tumor cells of esophageal squamous cell carcinoma. CCL2 produced by tumor cell and CCR2 expressed on vascular endothelial cells may participate in esophageal carcinoma tumor angiogenesis.

**Gastric cancer**

**Oncogenesis**

CCL2 produced by human gastric carcinoma cells is involved in angiogenesis via macrophage recruitment and activation via CCR2. CCL2 produced by gastric carcinoma cells induces tumor growth in ectopic xenografts and increased tumorigenicity and induced lymph node metastases and ascities in orthotopic xenografts.

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Zhang J, Patel L, Pienta KJ. CC chemokine ligand 2 (CCL2) promotes prostate cancer tumorigenesis and metastasis. Cytokine Growth Factor Rev. 2010 Feb;21(1):41-8


This article should be referenced as such:

DDC (dopa decarboxylase (aromatic L-amino acid decarboxylase))

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Identity

Other names: AADC
HGNC (Hugo): DDC
Location: 7p12.1
Local order: Centromere to telomere.

DNA/RNA

Note
The complete nucleotide structure of the human DDC gene has been determined from tissues of neural and non-neural origin (Sumi-Ichinose et al., 1992; Ichinose et al., 1992). The full DDC cDNA sequence has been cloned from human cells, such as pheochromocytoma (Ichinose et al., 1989), liver (Ichinose et al., 1992), hepatoma cells (Scherer et al., 1992), placenta (Siaterli et al., 2003), peripheral leukocytes (Kokkinou et al., 2009b), as well as from several human cell lines, such as, U937 macrophage cells (Kokkinou et al., 2009a), SH-SY5Y, HTB-14 and HeLa cells (Chalatsa et al., 2011).

Description
The human DDC gene exists as a single-copy in the haploid genome. It is composed of 15 exons and 14 introns, spanning for more than 85 kbs (Sumi-Ichinose et al., 1992). The size of the exons was found to range from 20 to 406 bps (Sumi-Ichinose et al., 1992), whereas the size of the introns ranged from 927 to 24077 bps (Sumi-Ichinose et al., 1992; Yu et al., 2006). The DDC gene is located in close proximity to the epidermal growth factor (EGF) gene (Craig et al., 1992).

Transcription
Alternative splicing events are responsible for the production of two distinct DDC mRNAs, termed neural and non-neural, which differ in their 5' untranslated region (UTR). The neural-type transcript includes exon N1 (83 bps) that is located 17.8 kbs upstream of exon two. The non-neural type DDC mRNA bears exon L1 (200 bps), which is located 4.2 kbs upstream to the location of exon N1. The second exon contains the translation start site and is located 22 kbs downstream from the non-neural (L1) exon (Ichinose et al., 1992). The transcription of the gene starts at position -111 (Sumi-Ichinose et al., 1992).

It has been reported that the two alternative DDC transcripts share identical coding regions and that their production is a result of alternative splicing and alternative promoter usage (Ichinose et al., 1992; Sumi-Ichinose et al., 1995). Neural and non-neural promoters have been identified 5' to the flanking region of the respective exon 1 (Le Van Thai et al., 1993; Sumi-Ichinose et al., 1995; Chatelin et al., 2001; Dugast-Darzacq et al., 2004).

An alternative splicing event has been described within the coding region of DDC mRNA, leading to the formation of a shorter transcript lacking exon 3 (O'Malley et al., 1995; Chang et al., 1996).
It must be noted that the above authors did not specify the nature, neural or non-neural, of this shorter transcript. Recent evidence have revealed the neural nature of this alternative transcript in humans (Kokkinou et al., 2009a; Kokkinou et al., 2009b; Chalatsa et al., 2011).

A novel DDC mRNA coding region splice-variant, resulting in the formation of a truncated DDC mRNA has been also identified. This human DDC mRNA (1.8 kbs), termed as Alt-DDC, lacks exons 10-15 of the full-length transcript, but includes an alternative exon 10 (Vassilacopoulou et al., 2004). The Alt-DDC exon 10 (358 bps) was found within intron 9 of the DDC gene. Although Alt-DDC mRNA was detected in human placenta, high expression levels of this alternative transcript were found in human kidney (Vassilacopoulou et al., 2004). The notion that transcription of the human DDC gene leads to the production of multiple mRNA isoforms, which are expressed in a non-mutually exclusive and tissue-specific manner, underlines the complexity of the expression patterns of this gene (table 1).

**Pseudogene**
None has been identified yet.

**Protein**
Although, it was initially suggested that the DDC gene encoded for a single protein product (Sumi-Ichinose et al., 1992), evidence that demonstrated the expression of additional DDC protein isoforms in humans, argue against it (OMalley et al., 1995; Chang et al., 1996; Vassilacopoulou et al., 2004).

Expression of the DDC gene, in humans, results in the production of additional protein isoforms (OMalley et al., 1995; Chang et al., 1996; Vassilacopoulou et al., 2004). O'Malley et al. (1995) identified of a new DDC protein isoform (OMalley et al., 1995). The truncated DDC protein isoform (Mr; 50 kDa) consists of 442 amino acid residues (DDC<sub>442</sub>). This isoform was found to be inactive towards the decarboxylation of both L-Dopa to Dopamine and 5-Hydroxytryptophan (5-HTP) to serotonin (O'Malley et al., 1995). As mentioned above, the translation of Alt-DDC mRNA resulted in the synthesis of a truncated 338 amino acid long polypeptide, termed as Alt-DDC (Mr; 37 kDa). This isoform was identical to the full-length DDC protein up to amino acid residue 315. The remaining 23 amino acids of the C-terminal sequence are encoded by the alternative DDC exon 10 and are not incorporated in the full-length DDC protein sequence (Vassilacopoulou et al., 2004).

Although previous data had suggested that DDC was a rather unregulated molecule, several findings have indicated that DDC activity can be modulated by many factors, such as D1, DA receptor antagonists (Rossetti et al., 1990), α<sub>2</sub>-adrenergic receptor antagonists (Rossetti et al., 1989), D1, D2 receptor antagonists (Zhu et al., 1992; Hadjiconstantinou et al., 1993), DA receptor
agonists (Zhu et al., 1993), PK-A and PK-C mediated pathways (Young et al., 1993; Young et al., 1994) and by endogenous inhibitors isolated from human serum (Vassiliou et al., 2005) and placenta (Vassiliou et al., 2009).

**Expression**

DDC has been detected throughout the length of the gastrointestinal tract (Eisenhofer et al., 1997) and in blood plasma (Boomsma et al., 1986). DDC is expressed in normal human kidney and placenta (Mappouras et al., 1990; Siaterli et al., 2003). DDC expression was observed in normal peripheral leukocytes and T-lymphocytes (Kokkinou et al., 2009b). Furthermore, DDC is expressed in the human cancer cell lines U937 (Kokkinou et al., 2009a), SH-SY5Y, HeLa and HTB-14 (Chalatsa et al., 2011). Interestingly, the expression of the alternative DDC isoform (Alt-DDC) was also demonstrated in peripheral leukocytes (Kokkinou et al., 2009b), U937 (Kokkinou et al., 2009a), SH-SY5Y and HeLa cell lines (Chalatsa et al., 2011).

In the central nervous system, increased DDC enzymatic activity is detected in the hypothalamus, epiphysis, striatum, locus ceruleus, olfactory bulb and retina (Park et al., 1986). Elevated enzymatic DDC activity is also detected in peripheral organs such as liver, pancreas, kidney, lungs, spleen, stomach, salivary glands, as well as in the endothelial cells of blood vessels (Lovenberg et al., 1962; Rahman et al., 1981; Lindström and Sehlin, 1983).

**Localisation**

DDC was considered to be a cytosolic molecule (Lovenberg et al., 1962; Sims et al., 1973). Nevertheless, additional experimental findings have demonstrated that a population of enzymatically active DDC molecules is associated with the cellular membrane fraction in the mammalian CNS (Poulakikos et al., 2001). Membrane-associated, enzymatically active DDC subpopulations were detected in the highly hydrophobic fractions of normal human leukocytes and U937 cancer cells (Kokkinou et al., 2009a; Kokkinou et al., 2009b).

**Function**

In terms of substrate specificity, the DDC molecule purified from insects demonstrated a remarkably high affinity towards the decarboxylation of L-Dopa to dopamine (Fragoulis and Sekeris, 1975; Mappouras and Fragoulis, 1988; Bossinakou and Fragoulis, 1996). However, work by Mappouras et al. (1990) in the normal human kidney has suggested that the enzyme is capable of also decarboxylating L-5-Hydroxytryptophan to serotonin, although the decarboxylation activity towards L-5-Hydroxytryptophan was found to be considerably lower than the one observed for L-Dopa (Mappouras et al., 1990). Since DDC expression results in the production of multiple protein isoforms, it is conceivable that these different protein molecules could be responsible for the decarboxylation of other aromatic L-amino acids.

**Homology**

Comparison of the amino acid sequence of DDC from different species, suggested that the enzyme is an evolutionarily conserved molecule. The amino acid sequence around the coenzyme binding lysine is also evolutionarily conserved (Bossa et al., 1977; Ichinose et al., 1989). The conserved amino acids are residues 267-317, which surround the PLP-binding site (Ichinose et al., 1989), as well as, the extended regions of amino acids 64-155 and 182-204, which according to Maras et al. (1991) are important for the enzyme’s catalytic function (Maras et al., 1991). Table 2 shows the percentage of human DDC amino acid identity to other species (Maras et al., 1991; Mantzouridis et al., 1997).

**Mutations**

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Amino acid change</th>
<th>Exon number</th>
</tr>
</thead>
<tbody>
<tr>
<td>122C&gt;A</td>
<td>L108I</td>
<td>13</td>
</tr>
<tr>
<td>19C&gt;T</td>
<td>E7X</td>
<td>2</td>
</tr>
<tr>
<td>140C&gt;A</td>
<td>P47H</td>
<td>2</td>
</tr>
<tr>
<td>194G&gt;A</td>
<td>R347Q</td>
<td>11</td>
</tr>
<tr>
<td>749C&gt;T</td>
<td>S250F</td>
<td>7</td>
</tr>
<tr>
<td>304G&gt;A</td>
<td>G102S</td>
<td>3</td>
</tr>
<tr>
<td>925T&gt;C</td>
<td>F309L</td>
<td>9</td>
</tr>
<tr>
<td>439A&gt;C</td>
<td>S147R</td>
<td>5</td>
</tr>
<tr>
<td>272C&gt;T</td>
<td>A91V</td>
<td>3</td>
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<tr>
<td>823G&gt;A</td>
<td>A275T</td>
<td>8</td>
</tr>
<tr>
<td>833C&gt;T</td>
<td>R283W</td>
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<tr>
<td>1303C&gt;T</td>
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<td>13</td>
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<tr>
<td>c387G&gt;A</td>
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</tr>
<tr>
<td>127dC</td>
<td>P43fsX20</td>
<td>2</td>
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<td>IVS6+1A&gt;T</td>
<td>M239fsX230</td>
<td>6 and 7</td>
</tr>
</tbody>
</table>

Table 3. The mutations of the DDC gene in the AADC disorder.

**Germinal**

Such mutations have not been identified so far.

**Somatic**

Aromatic L-amino acid decarboxylase (AADC) deficiency, a rare autosomal-recessive inherited defect, is associated with mutations of the DDC gene. This disorder leads to profound modifications in the homeostasis of central and peripheral nervous system (Hyland et al., 1992). In their majority, such mutations are missense and are listed above (table 3). Other mutations of the human DDC gene that are related to AADC-deficiency are also included (Fiunara et al., 2002; Chang et al., 2004; Pons et al., 2004; Tay et al., 2007; Lee et al., 2009).

**Implicated in**

**Prostate cancer**

**Note**

Neuroendocrine differentiation features have been identified in prostatic adenocarcinoma. Aggressiveness of the disease is increased as the cells reach the androgen-independent phase (Speights et al., 1997; Nelson et al., 2002). L-Dopa decarboxylase has been identified as a novel androgen receptor (AR) coactivator protein (Wafa et al., 2003). Recent evidence have shown that the expression of DDC mRNA could serve as a potential novel biomarker in prostate cancer (Avgeris et al., 2008). Wafa et al. (2007) have indicated by immunohistochemistry that DDC was found to be a putative neuroendocrine marker for prostate cancer. In certain NE tumor cells of the prostate gland, DDC was found to co-expressed with AR. DDC expression was increased after hormone-ablation therapy, as well as, in metastatic tumors that have progressed to the androgen-independent phenotypes (Wafa et al., 2007).

**Disease**

Increased DDC mRNA and/or elevated protein expression levels were detected in the LnCaP cell line following synthetic androgen treatment. DDC protein was found to be enzymatically active in the androgen-treated LnCaP cells as compared to the untreated controls. In treated LnCaP cells, DDC was up-regulated during AR-activation, while DDC expression was down-regulated following AR-inhibition. These findings support a coactivator role for DDC in AR activation (Shao et al., 2007). DDC over-expression affects the gene expression profile of the androgen-dependent prostate cancer cell line, LnCaP, as revealed by microarray analysis (Margiotti et al., 2007).

**Prognosis**

Statistically significant elevated DDC mRNA levels were observed in prostate cancer tissue specimens when compared to benign hyperplasia human samples. Multivariate survival analysis indicated that the expression of the DDC gene could be used as an independent marker for the differential diagnosis between prostate cancer and benign hyperplasia patients, using tissue biopsies. DDC mRNA expression was also shown to be associated with advanced tumor stage and higher Gleason score. This finding suggested an unfavorable prognostic value for DDC expression in patients with tumors in their prostate glands (Avgeris et al., 2008).

**Colorectal carcinoma**

**Note**

High L-Dopa decarboxylase activity has been detected in almost half of the original colorectal carcinomas examined, as well as, in the majority of cultured cell lines, established from human primary and metastatic tumors (Park et al., 1987). Other data have shown that most solid colorectal tumors exhibited DDC activity at lower levels when compared to the enzymatic DDC activity displayed by the NE tumors (Gazdar et al., 1988). DDC mRNA expression was found to be elevated in well-differentiated (grade I) intestinal adenocarcinomas as compared to more aggressive tumors (Kontos et al., 2010).

**Prognosis**

Increased DDC mRNA levels were observed in grade I colorectal adenocarcinomas. Survival analysis revealed a significantly lower risk of disease recurrence and longer overall survival for patients with DDC-positive colorectal neoplasms. These results indicate that DDC mRNA expression might represent a possible future biomarker for the prognosis of colorectal cancer patients (Kontos et al., 2010).

**Gastric cancer**

**Note**

Advanced gastric cancer is characterized by peritoneal dissemination, the most common disease relapse, which is caused by the dispersal of free gastric cancer cells into the peritoneal cavity (Baba et al., 1989; Abe et al., 1995).

**Disease**

It has been proposed that increased DDC mRNA expression could be an accurate tool for the detection of gastric cancer micrometastases in the peritoneal cavity. According to Sakakura et al. (2004), DDC expression levels were equivalent to the degree of dissemination potential of gastric cancer cells.

**Pheochromocytomas**

**Note**

Pheochromocytomas are characterized by over-production of catecholamines (Eisenhofer et al., 2001).
Lung carcinomas

Note
Elevated DDC enzymatic activity was observed in small-cell lung carcinoma (SCLC) as compared to normal lung epithelia (Nagatsu et al., 1985). The majority of non-SCLC (NSCLC) exhibited low levels or no DDC enzyme activity (Gazdar et al., 1981; Bepler et al., 1988). It is noted that in some NSCLC cases, high DDC activity values have been reported (Baylin et al., 1980), although in these lung lesions the detection of DDC activity was restricted to large-cell carcinomas and adenocarcinomas, while squamous cell carcinomas did not exhibit any enzymatic activity (Gazdar et al., 1988).

Disease
DDC activity appears to be a valuable neuroendocrine marker for identifying SCLC tumor cells in culture (Baylin et al., 1980). DDC enzymatic activity is highest during the exponential cellular growth phase and/or when the cells are during the transition from G2 to the M phase of the cell cycle (Francis et al., 1983). DDC activity has been also used as a useful biomarker for the distinction of SCLC from NSCLC. Furthermore, DDC activity has been used for the differentiation between the classical SCLC cell lines (SCLC-C), which express high DDC activity levels, from the variant subtype of the SCLC (SCLC-V), which does not express the enzyme (Carney et al., 1985; Gazdar et al., 1985).

Prognosis
The elevated DDC enzymatic activity, which is observed in patients harboring SCLC tumors, seems to be associated with disease differentiation grade. High DDC activity has been associated with better prognosis and patient's outcome (Bepler et al., 1987).

Medullary thyroid carcinoma

Note
The expression of L-Dopa decarboxylase has been detected in medullary carcinoma of the thyroid gland (Pearse, 1969; Atkins et al., 1973).

Disease
Medullary thyroid carcinoma (MTC) originates from the calcitonin (CT)-secreting thyroid C cells and is a unique malignancy of endocrine origin (Tashjian and Melvin, 1968). Malignancy progression could be monitored, in patients with the virulent phenotype of the disease, using the simultaneous increased levels of DDC and histaminase (Trump et al., 1979; Lippman et al., 1982). It has been proposed that increased DDC enzymatic activity might represent an early differentiation marker in the virulent form of this neoplasm (Berger et al., 1984).
Neuroendocrine tumors (NETs): bronchial, liver and ileal carcinoids, gastric / pancreatic / pulmonary tumors

Note
DDC enzymatic activity constitutes an excellent cellular marker for identifying tumors of the neuroendocrine (NE) origin. The majority of NE tumors tested were found to express relatively high DDC enzymatic activity (Gazdar et al., 1988). DDC expression and/or activity have been reported in NETs, particularly in SCLC. For these reasons, DDC has been considered as a general endocrine marker (Gazdar et al., 1988; Jensen et al., 1990).

Disease
Strikingly higher DDC mRNA expression levels were revealed in all bronchial carcinoids and pulmonary NETs when compared to their normal corresponding types of tissues. Immunohistochemical data have confirmed DDC protein expression in all of these tumors. In the gastroenteropancreatic NETs examined, the detected DDC mRNA levels were comparable to those of normal gastric, ileal and pancreatic tissues. About half of the pancreatic and stomach NETs and all ileal carcinoids were found to be DDC immunoreactive (Uccella et al., 2006). Interestingly, hepatic carcinoid tumors demonstrated a 20-fold increase in DDC activity as compared with normal surrounding liver tissues (Gilbert et al., 1995).

Hybrid/Mutated gene
Not yet discovered.

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溴化腺苷酸 (aromatic L-amino acid decarboxylase)


DDC (dopa decarboxylase (aromatic L-amino acid decarboxylase))


This article should be referenced as such:
Gene Section

Review

DDR1 (discoidin domain receptor tyrosine kinase 1)

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Identity

Other names: CAK; CD167; DDR; EDDR1; HGK2; MCK10; NEP; NTRK4; PTK3; PTK3A; RTK6; TRKE

HGNC (Hugo): DDR1

Location: 6p21.33

DNA/RNA

Description

The DDR1 gene comprises 17 exons and spans 12 kb of the genomic sequence on chromosome 6 (from position 30851861 bp to 30867933 bp in the positive strand orientation).

Transcription

The 3840-bp mRNA is transcribed in a centromeric to telomeric orientation. Alternative splicing can occur, and 5 named isoforms (DDR1a-e) are recognised.

Pseudogene

No pseudogene has been described.
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**Protein**

![Schematic diagram of the DDR1 protein and localization of the DDR1 Tyrosine phosphorylated sites at intracellular domain.]

**Description**

DDR1 belongs to the DDRs subfamily of tyrosine kinase receptors. This subfamily is composed of only two members, DDR1 and DDR2, and it is distinguished by an extracellular domain that is homologous to the carbohydrate-binding lectin discoidin-I in Dictyostelium discoideum. The Discoidin domain is essential for the ability of DDRs to bind ligands. To-date, collagen is the only unique DDR1 ligand that has been identified. Five isoforms of DDR1 that are generated by alternative splicing have been described. The longest DDR1 transcript codes for the full-length receptor (DDR1c isoform) and is composed of 919 amino acids. DDR1a and DDR1b isoforms lack 37 amino acids in the juxtamembrane domain or 6 amino acids in the kinase domain. DDR1d and DDR1e isoforms are C-terminally truncated receptors. DDR1d lacks exons 11 and 12 causing a frame-shift mutation that generates a stop codon and premature termination of transcription. Finally, DDR1e lacks exons 11 and 12 as well as the first half of exon 10 (Alves et al., 1995).

**Expression**

DDR1 is ubiquitously expressed in a variety of epithelial tissues (Alves et al., 1995; Curat and Vogel, 2002; Ferri et al., 2004; Hou et al., 2001; Mohan et al., 2001; Sakamoto et al., 2001; Tanaka et al., 1998). DDR1 is also expressed in endothelial blood capillary cells and oligodendrocytes in the human brain (Franco-Pons et al., 2009; Roig et al., 2010). DDR1 is significantly overexpressed in several human cancers (Barker et al., 1995; Colas et al., 2011; Ford et al., 2007; Hajdu et al., 2010; Heinzelmann-Schwarz et al., 2004; Laval et al., 1994; Nemoto et al., 1997; Park et al., 2007; Tun et al., 2011; Weiner et al., 1996; Weiner et al., 2000; Yamanaka et al., 2006; Yoshida et al., 2007) and carcinoma cell lines (Alves et al., 1995; Gu et al., 2011; Park et al., 2007; Sakuma et al., 1996).

**Localisation**

Transmembrane.

**Function**

Receptor tyrosine kinases are key components of several signal transduction pathways. These kinases control multiple cellular processes, including motility, proliferation, differentiation, metabolism and survival. DDR1 is actively involved in tumorigenesis and promotes the proliferation of neoplastic cells. The interaction of DDR1 and Notch1 displays a prosurvival effect (Kim et al., 2011). DDR1 participates in the collective migration of cancer cells by coordinating the cell polarity regulators Par3 and Par6 (Hidalgo-Carcedo et al., 2011).

**Homology**

- *P. troglodytes*, discoidin domain receptor tyrosine kinase 1, DDR1
- *C. lupus*, discoidin domain receptor tyrosine kinase 1, DDR1
- *M. musculus*, discoidin domain receptor family member 1, Ddr1
- *R. norvegicus*, discoidin domain receptor tyrosine kinase 1
- *D. rerio*, discoidin domain receptor family member 1

**Mutations**

**Note**

Few somatic mutations have been described. Four mutations (G1486T, A496S, CC2469/2470TT, R824W) have been identified in a cohort of 26 primary lung neoplasms (Davies et al., 2005). One somatic mutation (A803V) was found in 4 acute myeloid leukaemia patients (Tomasson et al., 2008).
Implicated in

Breast cancer

Note
DDR1 overexpression was observed in human primary breast tumours samples compared to that in normal breast tissues (Barker et al., 1995). In addition, invasive ductal and lobular carcinomas showed differential expression of DDR1. DDR1 was downregulated in lobular carcinomas (Turashvili et al., 2007a; Turashvili et al., 2007b).

Osteosarcoma

Note
The DDR1 promoter presents a potential p53 binding-site. A previous study has shown that p53 expression upregulated the mRNA expression levels of DDR1 in human osteosarcoma cells (Sakuma et al., 1996).

Oesophageal cancer

Note
The overexpression of DDR1 was reported in 12 carcinomatous oesophageal tissues compared to that in normal tissues. Furthermore, a positive correlation was identified between DDR1 mRNA expression and the proliferative activity of the tumoural cells (Nemoto et al., 1997).

Ovarian cancer

Note
DDR1 was highly expressed in 158 histological subtypes of primary epithelial ovarian cancers (EOC) compared to that in normal ovarian surface epithelium samples (Heinzelmann-Schwarz et al., 2004).

Endometrial cancer

Note
DDR1 has been implicated as a potential molecular marker of endometrial cancer (Colas et al., 2011; Domenyuk et al., 2007). A gene expression screening of 52 carcinomas samples showed differential expression of several genes, including the DDR1 gene. These data were also demonstrated in 50 tumoural and non-tumoural uterine aspirates (Colas et al., 2011).

Brain tumours

Note
DDR1 was originally isolated in malignant childhood brain tumours, which overexpressed DDR1 (Weiner et al., 1996). Replicable findings were found in metastatic brain neoplasms and glioma cells (Yamanaka et al., 2006; Weiner et al., 2000). In glioma cells, DDR1 was involved in cell proliferation and invasion via cell interactions with the extracellular matrix (Ram et al., 2005; Yamanaka et al., 2006). Moreover, a study on DDR1a and DDR1b isoforms overexpression in glioma cells has identified distinct roles for each DDR1 isoforms in the cell attachment process, which is mediated by collagen I (Ram et al., 2005). The analysis of the expression profile in mice that had PDGF-induced glioma showed overexpression of DDR1 (Johansson et al., 2005).

Primary central nervous system lymphoma (PCNSL)

Note
A PCNSL pathway analysis revealed upregulation of DDR1 expression in the extracellular matrix and the adhesion-related pathways (Tun et al., 2011).

Pituitary adenoma

Note
In different subtypes of pituitary adenoma, DDR1 expression was related to the hormonal background. DDR1 was more highly expressed in macroadenomas, compared to microadenomas, and in PRL- and GH-producing adenomas (Yoshida et al., 2007).

Lung cancer

Note
DDR1 was upregulated in tumour lung tissue compared to that in normal tissue and was an independent favourable predictor for prognosis (Ford et al., 2007). Similarly, DDR1 was highly phosphorylated in non-small cell lung cancer (NSCLC) (Rikova et al., 2007).
One study described the presence of DDR1 somatic mutations in lung cancer (Davies et al., 2005). However, no mutations were detected in another lung cancer study (Ford et al., 2007).

**Liver cancer**

**Note**

DDR1a and DDR1b isoforms were overexpressed in hepatocellular carcinoma cell lines HLE and Huh-7. DDR1 isoform overexpression enhanced the migration and invasion of the hepatocellular carcinoma cell lines in association with the matrix metalloproteinases MMP2 and MMP9 (Park et al., 2007).

The downregulation of miR-199a-5p, which is a direct target of DDR1, deregulated DDR1 functionality and increased cell invasion in human hepatocellular carcinoma (HCC) (Shen et al., 2010). Finally, a profiling study on receptor tyrosine kinase phosphorylation in cholangiocarcinoma patients showed high levels of phosphorylation of DDR1 and other tyrosine kinases in tumour tissues in comparison to para-tumour tissues (Gu et al., 2011).

**Mesenchymal neoplasm**

**Note**

Solitary fibrous tumour (SFT) expression profiling of 23 samples showed an over-expression of several receptor tyrosine kinase genes, including DDR1. However, no mutations were identified using cDNA sequencing (Hajdu et al., 2010).

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Gene Section
Review

ERBB2 (v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian))

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Identity

Other names: CD340; HER2; HER-2; HER-2/neu; MLN 19; NEU; NGL; TKR1
Location: 17q12

Note
Tyrosine-kinase receptor (RTK). The HER family of RTKs consists of four receptors: epidermal growth factor receptor (EGFR, also called HER-1 or erbB-1), HER-2 (also called erbB-2 or Neu), HER-3 and HER-4 (also called erbB-3 and erbB-4, respectively).

DNA/RNA

Description
Sequence length: 40522; CDS: 3678. 30 exons, 26 coding exons; total exon length: 4816, max exon length: 969, min exon length: 48. Number of SNPs: 17.

Polymorphisms: allelic variations at amino acid positions 654 and 655 of isoform (a) (positions 624 and 625 of isoform (b)) have been reported, with the most common allele B1 (Ile-654/Ile-655); allele B2 (Ile-654/Val-655); allele B3 (Val-654/Val-655). This nucleotide polymorphism could be associated with development of gastric carcinoma and with breast cancer risk, particularly among younger women.

Transcription
Alternative splicing results in several additional transcript variants, some encoding different isoforms and others that have not been fully characterized.
- mRNA transcript variant: this variant (1) represents the shorter transcript but encodes the longer isoform (a) (protein: erbB-2 isoform (a)).
- mRNA transcript variant: this variant (2) (protein: erbB-2 isoform (b)) contains additional exons at its 5’ end and lacks an alternate 5’ noncoding exon, compared to variant (1). These differences result in translation initiation at an in-frame, downstream AUG and an isoform (b) with a shorter N-terminus compared to isoform (a).
- mRNA transcript variant: herstatin HER2-ECD 1300 bp alternative erbB-2 transcript that retains intron 8. This alternative transcript specifies 340 residues identical to subdomains I and II from the extracellular domain of p185erbB-2 followed by a unique C-terminal sequence of 79 aa encoded by
intron 8. The herstatin mRNA is expressed in normal human fetal kidney and liver, but is at reduced levels relative to p185erbB-2 mRNA in carcinoma cells that contain an amplified erbB-2 gene.

- mRNA transcript variant: an alternative transcript form of the human homologous gene erbB-2, containing an in-frame deletion encompassing exon 19, has been detected in human breast carcinomas.

- mRNA transcript variant: an alternative transcript form of the human homologous gene erbB-2, called HER2Δ16, has been detected in human breast carcinomas. This splicing variant, contains an in-frame deletion and encodes a receptor lacking exon 16, which immediately precedes the transmembrane domain containing two cysteines. The loss of these cysteine residues might induce a change in the conformation of HER2 receptor extracellular domain that promotes intermolecular disulfide bonding and, in turn, homodimers capable of transforming cells. Ectopic expression of HER2Δ16 promotes receptor dimerization, cell invasion, and trastuzumab resistant tumor cell lines. The potential metastatic and oncogenic properties of HER2Δ16 were mediated through direct coupling of HER2Δ16 to Src kinase.

Protein

Description

erbB2 encodes a 185-kDa, 1255 amino acids, orphan receptor tyrosine kinase, and displays potent oncogenic activity when overexpressed. The proto- oncogene consists of three domains: a single transmembrane domain that separates an intracellular kinase domain from an extracellular ligand-binding domain. An aberrant form of HER2, missing the extracellular domain, so-called HER2p95, has been found in some breast cancers. HER2p95 is constitutively active because the external domain of these receptors acts as an inhibitor until they are bound by ligand. This isoform can cause resistance to trastuzumab, an antibody that works by binding to a domain in the external domain of HER2. HER2p95 fragments arise through at least 2 different mechanisms: proteolytic shedding of the extracellular domain of the full-length receptor and translation of the mRNA encoding HER2 from internal initiation codons. Shedding of the ectodomain of HER2 generates a 95- to 100-kDa HER2 p95 membrane-anchored fragment. Translation of the mRNA encoding HER2 can be initiated from the AUG codon that gives rise to the full-length protein of 1255 amino acids or, alternatively, from 2 internal initiation codons at positions 611 and 678, located upstream and downstream of the transmembrane domain, respectively.

Expression

HER2 protein is expressed in several human organs and tissues: normal epithelium, endometrium and ovarian epithelium and at neuromuscular level; prostate, pancreas, lung, kidney, liver, heart, hematopoietic cells. HER2 expression is low in mononuclear cells from bone marrow, peripheral blood (PB) and mobilized PB. The higher expression has been found in cord blood-derived cells. Quiescent CD34+ progenitor cells from all blood sources and resting lymphocytes are HER2 negative, but the expression of this receptor is up-regulated during cell-cycle recruitment of progenitor cells. Similarly, it increases in mature, hematopoietic proliferating cells, underlying the correlation between HER2 and the proliferating status of hematopoietic cells.

Localisation

Plasma membrane.
ERBB2 (v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian))

Function
Activation and interactions
For the other member of the HER family, ligand binding induces receptor homo- or heterodimerization, which is essential for TKs activation and subsequent recruitment of target proteins, in turn initiating a complex signaling cascade that leads into distinct transcriptional programs. There are several HER-specific ligands. HER2, which apparently has no direct or specific ligand, plays a major coordinating role in the HER network because of its ability to enhance and stabilize the dimerization: each receptor with a specific ligand appears in fact to prefer HER-2 as its heterodimeric partner. HER-2-containing heterodimers are characterized by extremely high signaling potency because HER-2 dramatically reduces the rate of ligand dissociation, allowing strong and prolonged activation of downstream signaling pathways.

Signaling and cellular
The most important intracellular pathways activated by HER2 are those involving mitogen activated protein kinase (MAPK) and phosphatidylinositol-3 kinase (PI3K). HER2 expression in cancer, besides its role in proliferation, enhances and prolongs survivals signals, associating up-regulation of this receptor to the malignant phenotype. At the same time, and depending on cellular status, the role of this receptor in controlling cell fate can also lead to differentiation and apoptosis.

Physiological
Role in development and differentiation:
- HER2 has several non-oncogenic roles in regulating growth, differentiation, apoptosis and/or remodeling in normal mammary glands. Dominant-negative forms of HER2 have significant defects in mammary development and lactation.
- HER2 has an important role in development and function of heart. Cre-Lox technology to mutate erbB-2 specifically in ventricular cardiomyocytes leads to a severe cardiomyopathy. This is inferred also by the adverse cardiac side effects observed in breast cancer patients treated with the monoclonal anti-HER2 Ab Trastuzumab.
- HER2 has a role in control of Schwann cell myelination and it has been demonstrated that HER2 signaling is also critical for oligodendrocyte differentiation in vivo.
- HER2 has a dual role in both muscle spindle maintenance and survival of myoblasts. Muscle-specific HER2 KO results in fact in viable mice with a progressive defect in proprioception due to loss of muscles spindles.

Homolog
Homolog to avian erythroblastic leukemia viral (v-erb-b) oncogen 2.

Mutations
Somatic
The Cancer Genome Project and Collaborative Group sequenced the erbB-2 gene from 120 primary lung tumors and identified 4% that had mutations within the kinase domain; in the adenocarcinoma subtype of lung cancer, 10% of cases had mutations.
In non small cell lung cancer (adenocarcinoma) the following erbB-2 mutations were found: insertion/duplication of GCATACGTGATG at nucleotide 2322 of the erbB-2 gene, resulting in a 4-amino acid insertion (AYVM) at codon 774. Insertion of CTGTTGAGCT at nucleotide 2335 of the erbB-2 gene, resulting in a 3-amino acid insertion (VGS) starting at codon 779; a 2-bp substitution in the erbB-2 gene, TT-CC at nucleotides 2263 and 2264, resulting in a leu755-to-pro (L755P) substitution.
In lung cancer a C44645G transition in the erbB-2 gene that caused a pro1170-to-ala substitution (P1170A).
In a glioblastoma a 2740G-A transition in the erbB-2 gene that caused a glu914-to-lys substitution (E914K).
In a gastric tumor a 2326G-A transition in the erbB-2 gene that caused a gly776-to-ser (G776S) substitution.
In an ovarian tumor, a 2570A-G transition in the erbB-2 gene that caused an asn857-to-ser (N857S) substitution.

Implicated in
Hematological malignancies
Disease
HER2 expression can be detected in blast cells from patients with hematological malignancies including acute lymphoblastic leukemia (ALL). It could be used as a potential target for the application of HER2-directed treatment strategies in ALL including vaccination approaches.

Bladder cancer
Prognosis
HER2 is overexpressed in 25% to 40% of several human tumors and associated with the malignancy of the disease, high mitotic index and a shorter survival time for the patient. Overexpression of ErbB-2 is also associated with transitional cell carcinoma of the bladder. HER2 overexpression occurs in muscle-invasive urothelial carcinomas of the bladder and is associated with worse survival; amplifications of erbB-2 gene are also frequently linked to alterations of the TOP2A gene in bladder cancer. Furthermore, HER2 overexpression and amplification in urothelial carcinoma of the bladder is found associated with MYC co-amplification.
**Breast carcinoma**

**Prognosis**

Normal tissues have a low content of HER2 membrane protein. Overexpression of HER2 is seen in 20% of breast and it confers worse biological behavior and clinical aggressiveness in breast cancer. Breast cancers can have up to 25 to 50 copies of the HER2 gene and up to a 40- to 100-fold increase in HER2 protein resulting in 2 million receptors expressed at the tumor cell surface. The differential HER2 expression between normal tissues and tumors helps to define HER2 as an ideal treatment target. Trastuzumab, the first treatment targeting HER2, is well tolerated in patients and has little toxicity because its effects are relatively specific for cancer cells overexpressing HER2. HER2 amplification is a relatively early event in human breast tumorigenesis, occurring in almost 50% of in situ carcinomas. HER2 status is maintained during progression to invasive disease and to nodal and distant metastasis. The fact that only 20% of invasive breast cancers are HER2 amplified suggests that many HER2-amplified in situ cancers never progress to the invasive stage. HER2 amplification defines a subtype of breast cancer with a unique signature of genes and this is maintained during progression. Some tumors lose HER2 expression following treatment with trastuzumab, presumably by selection of a HER2-negative clone not killed by treatment. Conversely, HER2 may become positive in some initially negative tumors over time, especially after endocrine therapy targeting ER. Indeed, estrogen receptor has been shown to downregulate HER2 and, conversely, HER2 is able to downregulate ER expression. Therefore, it is not surprising that blocking ER might upregulate HER2 and that blocking HER2 might upregulate ER. HER2-amplified breast cancers have unique biological and clinical characteristics. They have increased sensitivity to certain cytotoxic agents such as doxorubicin, relative resistance to hormonal agents, and propensity to metastasize to the brain and viscera. HER2-amplified tumors have an increased sensitivity to doxorubicin possibly due to coamplification of the topoisomerase-2 gene, which is near the HER2 locus on chromosome 17 and is the target of the drug. Half of HER2-positive breast cancers are ER positive but they generally have lower ER levels, and many have p53 alterations. These tumors have higher proliferation rates and more aneuploidy and are associated with poorer patient prognosis. The poor outcome is dramatically improved with appropriate chemotherapy combined with the HER2-targeting drug trastuzumab. Overexpression of the erbB-2 gene is associated with tumor aggressiveness, and with patient responsiveness to doxorubicin, cyclophosphamide, methotrexate, fluorouracil (CMF), and to paclitaxel, whereas tamoxifen was found to be ineffective and even detrimental in patients with HER2-positive tumors. In Paget's disease of breast, HER2 protein overexpression is caused by amplification of the erbB-2 gene. HER2 has a role in this disease of the breast, where the epidermis of the nipple is infiltrated by large neoplastic cells of glandular origin. It seems that binding of heregulin-alpha to the receptor complex on Paget cells results in chemotaxis of these breast cancer cells. The isoforms HER2p95 and HER2Δ16 are found in some breast cancers and the expression of these hyperactive forms of HER2 may contribute to the malignant progression.

**Cervical cancer**

**Prognosis**

HER2 may be activated in the early stage of pathogenesis of cervical carcinoma in geriatric patients and is frequently amplified in squamous cell carcinoma of the uterine cervix.

**Childhood medulloblastoma**

**Prognosis**

Overexpression of HER2 in medulloblastoma is associated with poor prognosis and metastasis and HER2-HER4 receptor heterodimerization is of particular biological significance in this disease.

**Colorectal cancer**

**Prognosis**

Overexpression of HER2 occurs in a significant number of colorectal cancers. It was significantly associated with poor survival and related to tumor progression in colorectal cancer.

**Oral squamous cell carcinoma**

**Prognosis**

E6/E7 proteins of HPV type 16 and HER2 cooperate to induce neoplastic transformation of primary normal oral epithelial cells. Overexpression of HER2 receptor is a frequent event in oral squamous cell carcinoma and is correlated with poor survival.

**Gastric cancer**

**Prognosis**

HER2 amplification/overexpression does not seem to play a role in the molecular pathogenesis of most gastrinomas. However, mild gene amplification occurs in a subset of them, and overexpression of this receptor is associated with aggressiveness of the disease. HER2 overexpression in patients with gastric cancer, and it has been solidly correlated to poor outcomes and a more aggressive disease. The overall HER2 positive rate is about 22%. HER2 overexpression rate in gastric cancer varies according to the site of the tumor. A higher overexpression rate (36%) was shown in gastroesophageal junction (GEJ) tumors in comparison to 21% in gastric tumors.
**Germ-cell testicular tumor**

**Prognosis**
A significant correlation was observed between HER2 overexpression and clinical outcome in germ-cell testicular tumors.

**Cholangiocarcinoma**

**Prognosis**
Data are still controversial about HER2 role in this carcinoma. Increased HER2 expression contributes to the development of cholangiocarcinogenesis into an advanced stage associated with tumor metastasis. In addition, overexpression of HER2 and COX-2 correlated directly with tumor differentiation. However, other studies report that HER2 expression is associated with more favorable clinical features, such as a polypoid macroscopic type and absence of other organ involvement, and has been reported that the proportion of HER2-positive cases in papillary adenocarcinoma is higher than in other histological types and is associated with an early disease stage. HER2 is preferentially expressed in well differentiated component, and it is also expressed in dedifferentiated components in progressive cases.

**Lung cancer**

**Prognosis**
HER2 is overexpressed in less than 20% of patients with non-small cell lung cancer (NSCLC) and studies have shown that overexpression of this receptor is correlated with a poor prognosis in both resected and advanced NSCLC. HER2 overexpression has an important function in the biology of NSCLC and may have a prognostic value for patients with metastatic NSCLC.

**Osteosarcoma**

**Prognosis**
Higher frequency of HER2 expression has been observed in samples from patients with metastatic disease at presentation and at the time of relapse, and it correlates with worse histologic response and decreased event-free survival. HER2 could be an effective target for the immunotherapy of osteosarcoma, especially the type with high metastatic potential.

**Ovarian cancer**

**Prognosis**
HER2 overexpression varies from 9% to 32% of all cases of ovarian cancer and its overexpression is more frequent in advanced stage of ovarian cancer. Overexpression of HER2 in ovarian cancer cells leads to faster cell growth, higher abilities in DNA repair and colony formation. A cross-talk between HER2 and estrogen receptor (ER) was identified in ovarian cancer cells. Estrogen has been proven to induce the phosphorylation of HER2, and initiate the HER2's signaling pathway.

**Pancreatic adenocarcinoma**

**Prognosis**
Overexpression of HER-2 in pancreatic adenocarcinoma seems to be a result of increased transcription rather than gene amplification. The coexpression of HER2 oncogene protein, epidermal growth factor receptor, and TGF-beta1 in pancreatic ductal adenocarcinoma is related to the histopathological grades and clinical stages of tumors. The blockade of HER2 inhibits the growth of pancreatic cancer cells in vitro. HER2 overexpression was reported to accumulate in well differentiated pancreas adenocarcinomas whereas it is only infrequently found in poorly differentiated or undifferentiated tumors, in vivo and in vitro analyses have suggested that targeting HER2 might increase treatment effects of conventional chemotherapies of pancreas adenocarcinoma. However, unlike in breast cancer, the application of antibodies directed against HER2 has not yet become an established therapy for pancreas adenocarcinoma.

**Prostate cancer**

**Prognosis**
HER2 plays pivotal roles in prostate cancer. Studies have shown that 25% of untreated primary tumors, 59% of localized tumors after neoadjuvant hormone therapy, and 78% of metastatic tumors overexpressed HER2. Several lines of evidence have implicated HER2 as a key mediator in the recurrence of prostate cancer to a hormone-refractory, androgen-independent tumor, which is the hallmark of prostate cancer progress. The driving force for prostate cancer recurrence is the reactivation of androgen receptor (AR), which is a type of nuclear receptors, activated by steroid hormone but ablated in hormonal therapy. Phosphorylation and reactivation of AR stimulate cancer cell growth and trigger tumor progression. It has been observed that overexpression of HER2 kinase enhanced AR function and hormone-independent growth in prostate tumor cells. HER2 activated AR through the MAPK pathway. Additionally, the HER2/HER3 dimer increases AR protein stability and promotes the binding of AR to the promoter region of its target genes, resulting in AR activation in an androgen-depleted environment.

**Salivary gland tumor**

**Prognosis**
Several results demonstrated significant positive staining of HER2 in the salivary tumorigenic tissue but not in the surrounding non-tumorigenic tissue, pointing to a biological role in the tumorigenic process. HER2 amplification is present predominantly in tumors with high HER2 expression and seems to be the dominant
mechanism for HER2 overexpression in this tumor type.

To be noted

Note
Possible therapeutic strategies: 1) growth inhibitory antibodies (like Trastuzumab), used alone or in combination with standard chemotherapeutics; 2) tyrosin kinase inhibitors (TKI); 3) active immunotherapy, because HER2 oncoprotein is immunogenic in some breast carcinoma patients; 4) dimerization inhibitor antibodies, like Pertuzumab: its binding to HER2 inhibits the dimerization of HER2 with other HER receptors.

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KIAA0101 (KIAA0101)

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Identity

Other names: FLJ58702; NS5ATP9; OEATC-1; OEATC1; PAF; p15(PAF); p15PAF
HGNC (Hugo): KIAA0101
Location: 15q22.31

DNA/RNA

Note
Murine gene embryonic expression shows highly restricted expression of KIAA0101 in facial prominences, limbs, somites, brain, spinal cord and hair follicles. It has a suggested role in embryonic development (van Beuren et al., 2007).

Description
The gene is composed of 4 exons.

Transcription
One transcript. RNA was expressed as a 1.1 kb message in liver, pancreas and placenta at high levels (Yu et al., 2001). RNA profiling shows it is highly expressed in a number of tumors, specifically in esophageal tumors, anaplastic thyroid carcinomas, pancreatic cancer and non-small-cell lung cancer lines (Yu et al., 2001; Hosokawa et al., 2007). KIAA0101 was also reported to be down-regulated in colon cancer cells (Simpson et al., 2006) and human hepatocellular carcinoma (Guo et al., 2006). Nuclear protein NF-kappaB (p50) (Li et al., 2008), the Hepatitis C virus protein non-structural protein 5A (NS5A) (Shi et al., 2008) and ATF3 (Turchi et al., 2009) bind to the promoter region upstream of the KIAA0101 transcription initiation site promoting transcription in response to DNA damage.

Pseudogene
None.

Protein

Note
NS5ATP9, Hepatitis C virus NS5A-transactivated protein 9, HCV NS5A-transactivated protein 9, Overexpressed in anaplastic thyroid carcinoma-1, OEATC-1, OEATC1, p15(PAF), L5.

Description
The KIAA0101 gene encodes for a 111 amino acid 15 kDa protein. It contains a conserved proliferating cell nuclear antigen (PCNA)-binding motif (Yu et al., 2001).

DNA diagram. KIAA0101 9768 chr: 62444265-62460755. One transcript, 4 exons.
Protein diagram. 111 aa in length, single transcript, mutation I-A at position 65 and mutation F-A at position 68 results in loss of PCNA binding.

Expression
Predominant expression in liver, pancreas and brain. Not detected in heart or liver (Yu et al., 2001). The KIAA0101 protein was down-regulated in human hepatocellular carcinoma (Guo et al., 2006; Yuan et al., 2007). Increased protein levels have been detected in pancreatic cancer cells (Hosokawa et al., 2007).

Localisation
Nucleus, mitochondrion (Yu et al., 2001; Guo et al., 2006; Simpson et al., 2006; Yuan et al., 2007).

Function
The KIAA0101 protein binds to PCNA through a conserved PCNA binding domain. PCNA is required for DNA replication or repair as a supplementary factor for DNA polymerase (Paunesku et al., 2001). Proteins bound to PCNA can prevent its binding to DNA polymerase, in turn leading to inhibition of DNA synthesis, cell cycle progression and G1 cell cycle arrest (Yuan et al., 2007). PCNA binding proteins also interact with each other to modulate this regulation. For example, KIAA0101 also interacts in a complex with p33ING1 isoform 2, another PCNA binding protein which is a potential tumor suppressor and regulator of p53 (Simpson et al., 2006). UV irradiation caused increased association of KIAA0101 with PCNA suggesting that this association occurs in response to DNA damage. KIAA0101 also competes with p21WAF for binding to PCNA (Yu et al., 2001). KIAA0101 most recently been shown to act in concert with ATF3 to control genomic integrity after UV stress (Turchi et al., 2009). KIAA0101 expression levels are also regulated by NF-κappaB, this protein family having significant roles in apoptosis, cell cycle regulation and onogenesis (Hosokawa et al., 2007; Li et al., 2008). Together this data suggests a likely role for KIAA0101 in DNA repair and in protection from UV-induced cell death.

Mutations
Note
Experimentally mutation I-A at position 65 and F-A at position 68 result in loss of PCNA binding (Yu et al., 2001). No other mutations have been described. Screening of colon tumour samples identified a polymorphism in the intronic region just prior to the start of exon 2 (982-15deIT) (Simpson et al., 2006).

Implicated in

Hepatocellular carcinoma
Disease
KIAA0101 expression was proposed to promote growth advantage and hypoxic insult resistance and be associated with promoting cell proliferation (Yuan et al., 2007). KIAA0101 overexpression was associated with concomitant p53 mutation and vascular invasion (Yuan et al., 2007). This study suggested that high expression in hepatocellular carcinoma was indicative of tumour recurrence, metastatic potential and poor prognosis (Yuan et al., 2007). KIAA0101 was also reported to be downregulated in hepatocellular carcinoma (Guo et al., 2006). This study suggested that KIAA0101 had a growth inhibitory effect.

Astrocytommas
Disease
Grade IV (glioblastoma multiforme) astrocytommas had 5 times higher expression levels when compared to Grade I (pilocytic) astrocytommas suggesting that KIAA0101 abundance correlates with malignancy grade in human astrocytes (Marie et al., 2008).

Pancreatic cancer
Disease
Pancreatic cells overexpress KIAA0101 both at cDNA and protein level. Knock down of KIAA0101 by siRNA attenuated proliferation and DNA replication whereas overexpression enhanced cell growth in pancreatic cancer cell lines (Hosokawa et al., 2007).

Anaplastic thyroid carcinoma
Disease
Anaplastic thyroid carcinoma cell lines had significant overexpression of KIAA0101. Cell growth was inhibited by silencing KIAA0101 expression using siRNA. KIAA0101 may be oncogenic or cell growth-promoting but the mechanism for this is not understood (Mizutani et al., 2005).

Follicular lymphoma
Disease
High expression of KIAA0101 (along with CCNB1 (cyclin B1), CDC2, CDKN3A, CKS1B, ANP32E) was associated with better survival/response rate in a univariate analysis following CHOP (cyclophosphamide, vincristine, doxorubicin, prednisone) chemotherapy for follicular lymphoma treatment. Identification of these proteins aims to develop a follicular lymphoma international prognostic index to aid in informing a successful treatment strategy (Bjorck et al., 2005).
Onogenesis
This gene is thought to be oncogenic through modulation of DNA repair pathways via interaction with PCNA.

References


This article should be referenced as such:
PPP1R8 (protein phosphatase 1, regulatory (inhibitor) subunit 8)

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Identity

Other names: ARD-1; ARD1; NIPP-1; NIPP1; PRO2047
HGNC (Hugo): PPP1R8
Location: 1p35.3

DNA/RNA

Note
ARD1 is a frequently used alias for NIPP1, however, this name actually corresponds to an alternative transcript (NIPP1gamma), which encodes a truncated form of NIPP1 encompassing residues 225-351 only. This transcript has been shown to restore endoribonuclease activity to E. coli rne gene mutants (Wang and Cohen, 1994; Claverie-Martin et al., 1997; Chang et al., 1999; Jin et al., 1999; Van Eynde et al., 1999). Moreover, note that the name ARD1 is also used for a completely unrelated protein, TRIM23 (Mishima et al., 1993).

Description
The entire PPP1R8 gene spans 20.9 kb on the forward strand of the long arm on chromosome 1. The gene contains 7 exons of which exon 1 has 5' alternative splice sites.

Transcription
The PPP1R8 gene contains 7 exons which give rise to 5 alternative splice products (see diagram above).

Genomic organization of the PPP1R8 gene and the alternative splice variants with their corresponding coding sequences (black line). Exons and alternative splice sites are indicated by different colors.
When speaking about NIPP1, one usually refers to the NIPP1alpha isoform (39 kDa, 351 residues) which is by far the most abundant isoform in all examined mammalian tissues. When visualized by immunoblotting with C-terminal antibodies (which recognize all isoforms except NIPP1epsilon), also smaller polypeptides are visualized albeit at a much lower intensity as compared to the alpha isoform. However, it is not clear yet whether these represent some of the other NIPP1 isoforms or simply degradation products of NIPP1alpha (Van Eynde et al., 1999; Chang et al., 1999; Fardilha et al., 2004).

**Pseudogene**
A processed pseudogene, termed PPP1R8P, has been mapped to chromosome 1p33-32 (48790762-48791795 bp from pter according to hg19-Feb 2009). Consistent with this notion, it is only 1034 bp in size, contains no introns and encodes an incomplete NIPP1 transcript due to the presence of various premature stop codons (Van Eynde et al., 1999).

**Protein**

**Note**
Nuclear Inhibitor of PP1 (NIPP1) was first identified in bovine thymus nuclei as a potent inhibitor of the protein Ser/Thr phosphatase PP1 (Beullens et al., 1992; Beullens et al., 1993). Later on, it became clear that NIPP1 exerts various functions in the eukaryotic cell by serving as a kind of scaffold protein onto which a variety of proteins can bind. These interaction partners range from protein kinase MELK, protein phosphatase PP1 (PPP1C-a/PPP1C-b/PPP1C-c), the pre-mRNA splicing factors SAP155 (SF3B1) and CDC5SL to the chromatin modifiers EED and EZH2.

**Description**
NIPP1 consists of 351 amino acids and has a molecular mass of 39 kDa. However, it migrates at a size of about 45 kDa on SDS-PAGE. NIPP1 contains an N-terminal ForkHead Associated (FHA) domain. Via this established phosphothreonine-binding domain, NIPP1 interacts with protein kinase MELK, the splicing factors SAP155 and CDC5L and the histone methyltransferase EZH2. Moreover, it was shown that the NIPP1 FHA-domain binds to its ligands via phosphorylated TP-dipeptide motifs, present in the interacting proteins (Boudrez et al., 2000; Boudrez et al., 2002; Vulteke et al., 2004; Nuytten et al., 2008).

Two additional interactors, PP1 and EED, have two separate binding sites on NIPP1: one in the central domain and the other at the C-terminus. In the central domain, the binding of NIPP1 to PP1 is mediated by a so called RVXF-motif, which is present in about two thirds of all known PP1 interacting proteins (Beullens et al., 1999; Beullens et al., 2000; Hendrickx et al., 2009). In addition, the C-terminal 22 residues can interact with nucleic acids (Jin et al., 1999).

**Expression**
NIPP1 is ubiquitously expressed (Van Eynde et al., 1995).

**Localisation**
NIPP1 is a nuclear protein and is enriched in splicing factor storage sites called speckles (Trinkle-Mulcahy et al., 1999; Jagiello et al., 2000). Although largely nuclear, some data suggest that there also exists a cytoplasmic pool of NIPP1 (Boudrez et al., 1999; Jagiello et al., 1997).

**Function**
NIPP1 is a scaffold protein and exerts its functions via its interacting proteins. NIPP1 was discovered as a potent inhibitor and a major nuclear interactor of the phosphatase PP1 (Beullens et al., 1999). PP1 functions as a holoenzyme in which the interacting proteins confine substrate specificity, activity and/or localization of PP1 (Beullens et al., 2010). For NIPP1, it has been shown that it acts as a physiological PP1 inhibitor for some substrates, while functioning as an activator towards other substrates (Parker et al., 2002; Lesage et al., 2004; Comerford et al., 2006; Shi and Manley, 2007).

A schematic representation of the domain structure of NIPP1 and its interactor binding sites. The FHA-domain (red) binds the indicated interactors via a phosphorylated TP dipeptide motif. NIPP1 binds PP1 via the indicated RVXF-motif and via a C-terminal binding site (green). EED and RNA binding sites are colored blue and orange, respectively. Known phosphorylation sites are indicated in black (in vivo validated) or grey (in vitro data).
Also, the interaction between NIPP1 and PP1 can be regulated by phosphorylation (Beullens et al., 1993; Van Eynde et al., 1994; Jagiello et al., 1995; Vulsteke et al., 1997; Beullens et al., 1999). NIPP1 is also involved in 3 other major cellular processes: splicing, transcription and development. Firstly, NIPP1 is associated with splicosomes and splicing factor storage sites called “speckles”, probably mediated by its interaction with the splicing factors CDC5L, and SAP155 (Boudrez et al., 2000; Deckert et al., 2006). Pre-mRNA splicing assays showed that NIPP1 is required for late stage spliceosome formation (Beullens and Bollen, 2002). Recently it was published that NIPP1 directs associated PP1 to dephosphorylate SAP155 (Tanuma et al., 2008).

Secondly, NIPP1 is a transcriptional repressor via its interaction with EED and EZH2 (Jin et al., 2003; Roy et al., 2007), two core components of the Polycomb repressive complex 2 (PRC2). Through its interaction with PRC2, NIPP1 directs it to a subset of Polycomb target genes, where the methyltransferase EZH2 will mark genes prone for silencing by trimethylating histone 3 on lysine 27 (Nuytten et al., 2008). In 2010, Van Dessel et al. showed that this targeting function of NIPP1 is dependent on associated PP1. Finally, NIPP1 is essential for embryonic development as a NIPP1 knock out mouse is embryonically lethal at the onset of gastrulation (Van Eynde et al., 2004).

The splice variant NIPP1gamma or ARD1 displays a site-specific Mg2+-dependent endoribonuclease activity, in contrast to the NIPP1alpha isoform, which does not possess this function (Wang and Cohen, 1994; Claverie-Martin et al., 1997; Chang et al., 1999; Jin et al., 1999; Van Eynde et al., 1999).

**Homology**

NIPP1 is highly conserved in all multicellular organisms.

**Implicated in**

**Hepatoma**

**Disease**

Cancer.

**Prognosis**

An increase in NIPP1 mRNA is correlated with a malignant phenotype in rats (Kim et al., 2000).

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Beullens M, Bollen M. The protein phosphatase-1 regulator NIPP1 is also a splicing factor involved in a late step of spliceosome assembly. J Biol Chem. 2002 May 31;277(22):19855-60


This article should be referenced as such:

SMYD2 (SET and MYND domain containing 2)

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Identity

Other names: HSKM-B; KMT3C; MGC119305; ZMYND14
HGNC (Hugo): SMYD2
Location: 1q32.3

DNA/RNA

Description
55913 bp, 12 exons.

Transcription
1689 bp mRNA.

Protein

Description
433 amino acids. The protein contains SET domain, MYND domain/zinc-finger motif, and cysteine-rich post-SET domain. The SET domain is split into two segments by a MYND domain.

Expression
Wide, highly expressed in heart, brain, liver, kidney, thymus, ovary, embryonic tissues (heart, hypothalamus) (Brown et al., 2006).

Localisation
Cytoplasmic and nucleus (Brown et al., 2006).

Function
Regulation of transcription as a lysine methyltransferase for histone 3, lysine 36 (H3K36) and inhibition of p53’s transactivation activity as a lysine methyltransferase for lysine 370 (K370) of p53 through the SET domain (Brown et al., 2006; Huang et al., 2006). Possibly promotion of cell proliferation and/or differentiation through its overexpression/activation-induced inhibition of p53’s transactivation activity. Methylation of retinoblastoma (RB) tumor suppressor at lysine 860, that is regulated during cell cycle progression, cellular differentiation, and in response to DNA damage (Saddic et al., 2010). RB monomethylation at lysine 860 provides a direct binding site for the transcription repressor L3MBTL1. Through interaction with HSP90alpha, SMYD2 histone methyltransferase activity and specificity for histone H3 at lysine 4 (H3K4) are enhanced in vitro (Abu-Farha et al., 2008). SMYD2 gain of function is correlated with the upregulation of 37 and down regulation of 4 genes, the majority of which are involved in the cell cycle, chromatin remodelling, and transcriptional regulation (Abu-Farha et al., 2008).
**Homology**

Xenopus laevis, Zebrafish, Chicken, Gray short-tailed opossum, Mouse, Rat, Rabbit, Pig, Horse, Cattle, Dog, White-tufted-ear marmoset, Rhesus monkey, Sumatran orangutan, Chimpanzee.

**Mutations**

*Note*

Not found.

**Implicated in**

**Esophageal squamous cell carcinoma (ESCC)**

*Note*

Frequent overexpression of SMYD2 mRNA and protein was observed in KYSE150 cells with remarkable amplification at 1q32-q41.1 and other ESCC cell lines (11/43 lines, 25.6%). Overexpression of SMYD2 protein was frequently detected in primary tumor samples of ESCC (117/153 cases, 76.5%) as well and significantly correlated with gender, venous invasion, the pT category in the tumor-lymph node-metastasis classification and status of recurrence. Patients with SMYD2-overexpressing tumors had a worse overall rate of survival than those with non-expressing tumors. Knockdown of SMYD2 expression inhibited and ectopic overexpression of SMYD2 promoted the proliferation of ESCC cells in a TP53 mutation-independent but SMYD2 expression dependent manner (Komatsu et al., 2009).

**Thyroid carcinoma and benign thyroid nodule**

*Note*

Using differential display-polymerase chain reaction method, the gene expression differences between benign thyroid nodules (BTNs) and follicular and classic variants of papillary thyroid carcinoma (PTC) were evaluated in a group of 42 patients (15 BTNs, 14 follicular variant of PTC and 13 classic variant of PTC). SMYD2 had lower expression in both carcinoma groups than in BTNs (Igci et al., 2011).

**Breast cancer**

*Note*

Expression of a group of three genes (MTSS1, RPL37, and SMYD2) evaluated by real-time PCR was shown to be a potential candidate to predict response to neoadjuvant chemotherapy (4 cycles of doxorubicin and cyclophosphamide) in breast cancer patients (Barros Filho et al., 2010).

**References**


This article should be referenced as such:

Leukaemia Section
Mini Review

**t(1;9)(p34;q34)**

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**Clinics and pathology**

**Disease**

B cell progenitor acute lymphoid leukemia (B-ALL)

**Epidemiology**

Only one case to date, a 22-year-old male patient (Hidalgo-Curtis et al., 2008).

**Prognosis**

Complete remission was obtained, a relapse occurred. The patient was in complete remission 6 years after diagnosis.

**Cytogenetics**

**Cytogenetics morphological**

The translocation was found solely in the main clone, and a subclone also showed a +21.

**Genes involved and proteins**

**SFPQ**

**Location**

1p34.3

**Protein**

DNA- and RNA binding protein; pre-mRNA splicing factor; binds specifically to intronic polypyrimidine tracts.

Role in transcription and RNA splicing: SFPQ, often called PSF, is a coactivator of Fox proteins, which bind the RNA element UGCAUG and regulate alternative pre-mRNA splicing. SFPQ and NONO are part of a large complex with all the snRNPs. SFPQ is phosphorylated by GSK3, which prevents SFPQ from binding PTPRC (CD45 antigen) pre-mRNA. The association of HNRNPL and SFPQ drives the change in PTPRC (CD45) splicing (CD45 undergoes alternative splicing in response to T-cell activation).

DNA damage: DNA double-strand breaks are repaired via nonhomologous DNA end joining and homologous recombination. The SFPQ/NONO heterodimer enhances DNA strand break rejoining. SFPQ has homologous recombination and non-homologous end joining activities. SFPQ is associated with the RAD51 protein complex.

Role in transcriptional regulation: SFPQ and PTK6 (protein tyrosine kinase 6, also called BRK) play a role downstream of the EGF receptor (EGFR). SFPQ and NONO form complexes with the androgen receptor (AR) and modulate its transcriptional activity (Huret, 2011).

**ABL1**

**Location**

9q34

**Protein**

ABL1, when localized in the nucleus, induces apoptosis after DNA damage. Cytoplasmic ABL1 has a possible function in adhesion signalling (Turhan, 2008).

**Result of the chromosomal anomaly**

**Hybrid gene**

**Description**

Break in the 3' of SFPQ exon 10 and reunion with ABL1 intron 3; a further mRNA splicing gives rise
to a chimeric SFPQ exons 1 to 9 (nucleotide 2072) fused to ABL1 exon 4 to end.

**Fusion protein**

**Description**

1609 amino acids fusion protein of 174 kDa; retains most of SFPQ, including the RNA recognition motifs and the coiled-coil domain (dimerization domain), fused to the SH2 domain of ABL1; the fusion protein also includes the SH1 domain (tyrosine kinase activity), the nuclear localization domain, and the actin binding domain of ABL1.

**Oncogenesis**

Constitutive tyrosine kinase activation is likely, through dimerization of the fusion protein.

**References**


Hidalgo-Curtis C, Chase A, Drachenberg M, Roberts MW, Finkelstein JZ, Mould S, Oscier D, Cross NC, Grand FH.. The t(1;9)(p34;q34) and t(8;12)(p11;q15) fuse pre-mRNA processing proteins SFPQ (PSF) and CPSF6 to ABL and FGFR1. Genes Chromosomes Cancer. 2008 May;47(5):379-85.


This article should be referenced as such:

Understanding the structure and function of ASH2L

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Introduction

ASH2L (Absent, Small, or Homeotic-Like) encodes the protein ASH2L which was named after the Drosophila protein Ash2 a known regulator of HOX genes (Ikegawa et al., 1999). ASH2L is known to be a component of histone H3 lysine 4 (H3K4) methyltransferase complexes and H3K4 methylation is commonly associated with active gene transcription (Ikegawa et al., 1999; Hughes et al., 2004; Dou et al., 2006; Steward et al., 2006; Cho et al., 2007). Previous studies have shown that disruption of ASH2L leads to a decrease in H3K4 trimethylation, which negatively affects gene expression (Dou et al., 2006; Steward et al., 2006). Furthermore, disruption of ASH2L or the methyltransferases involved in H3K4 methylation can lead to oncogenesis mostly through the regulation of HOX gene expression (Hughes et al., 2004; Lüscher-Firzlaff et al., 2008). Interestingly, overexpression of ASH2L leads to tumor proliferation and knock-down of ASH2L inhibits tumorigenesis, which is the reason why ASH2L is thought to be an oncoprotein (Lüscher-Firzlaff et al., 2008). Understanding the role that ASH2L plays in facilitating proper H3K4 methylation may provide insight into how disruption of ASH2L can lead to abnormal cell proliferation and oncogenesis.

ASH2L function

Genetic information and sequence alignments identified ASH2L to be homologous to the transcriptional activator Drosophila Ash2 (Wang et al., 2001; Ikegawa et al., 1999). Drosophila Ash2 (Absent, small, and homeotic discs) is a member of the Trithorax family, known regulators of developmental homeotic genes (LaJeunesse and Shearn, 1995). Mammalian ASH2L is known to be important for development because ASH2L-null mice exhibit an embryonic lethal phenotype (Stoller et al., 2010). Work has established ASH2L as a core component of the H3K4 methyltransferase complexes MLL1-4 and SET1A and SET1B. Furthermore, ASH2L containing methyltransferase complexes are shown to be important for the maintenance of HOX gene expression by binding to HOX gene promoters and by adding H3K4 di- and trimethylation (Fig. 1) (Hughes et al., 2004; Tan et al., 2008; Yates et al., 2010). HOX gene expression is important for proper development and differentiation, and disruption in H3K4 methylation leads to defects in HOX gene expression and the development of cancer (Tan et al., 2008; Hess, 2006; Rampalli et al., 2007; MacConaill et al., 2006; Hughes et al., 2004). Biochemical data has shown that ASH2L is found in a methyltransferase core complex composed of ASH2L, RBBP5, DPF30, WDR5, and the catalytic SET domain containing protein (Fig. 1). This core complex is highly conserved and similar to the budding yeast Set1 complex that consists of Set1 (MLL/SET1), Bre2 (ASH2L), Swd1 (RBBP5), Swd3 (WDR5), Swd2 (WDR82), Sdc1 (DPY-30), Spp1 (CFP1/CGBP). ASH2L is also known to associate with numerous additional factors listed in Table 1. Many of these additional factors are thought to associate with ASH2L and the H3K4 methyltransferase complexes to target the complex to specific sites within the genome (Stoller et al., 2010; Cho et al., 2007; Steward et al., 2006; Dou et al., 2006; Hughes et al., 2004).
Figure 1. ASH2L functions in a histone methyltransferase complex. The role of ASH2L within the MLL histone H3K4 methyltransferase complex. ASH2L interacts with RBBP5 and DPY-30 increasing the activity of the MLL complex. Histone H3K4 methylation in mammals peaks at the start sight of open reading frames and is important in active transcription. Knock-down of ASH2L in mammalian cells results in a decrease in H3K4 trimethylation and changes in gene expression.

<table>
<thead>
<tr>
<th>ASH2L interacting protein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLL1-4/ SET1 A and B</td>
<td>Catalytic core; Histone methyltransferase (HMT)</td>
</tr>
<tr>
<td>RBBP5</td>
<td>Component of HMT complex</td>
</tr>
<tr>
<td>DPY-30</td>
<td>Component of HMT complex</td>
</tr>
<tr>
<td>WDR5</td>
<td>Component of HMT complex</td>
</tr>
<tr>
<td>CXXC1</td>
<td>Component of HMT complex</td>
</tr>
<tr>
<td>C16orf53/PA1</td>
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</tr>
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</tr>
<tr>
<td>E2F6</td>
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<td>Host cell factor</td>
</tr>
<tr>
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<tr>
<td>KDM6A</td>
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<td>MCRS1</td>
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</tr>
<tr>
<td>MEN1</td>
<td>Tumor suppressor</td>
</tr>
<tr>
<td>MYST1/MOF</td>
<td>Histone acetyltransferase</td>
</tr>
<tr>
<td>NCOA6</td>
<td>Transcriptional co-activator</td>
</tr>
<tr>
<td>PAXIPI1/PTIP</td>
<td>Transcription factor</td>
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<td>Transcription factor</td>
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<tr>
<td>PRP31</td>
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</tr>
<tr>
<td>SENP3</td>
<td>Sumo-specific protease</td>
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<td>TATA-box binding proteins</td>
</tr>
<tr>
<td>TEX10</td>
<td>Unknown</td>
</tr>
<tr>
<td>TBX1</td>
<td>Transcription factor</td>
</tr>
</tbody>
</table>

Table 1.
ASH2L and BRE2 subunits are important for proper histone methylation. Studies done in yeast show that deletion of the ASH2L homolog BRE2 leads to a complete loss of H3K4 trimethylation and reductions in mono- and dimethylation (Dehe et al., 2006; South et al., 2010; Roguev et al., 2001). In addition, knock-down of ASH2L using siRNA globally decreases H3K4 trimethylation (Steward et al., 2006; Dou et al., 2006). These data suggest that ASH2L may act in a similar manner to yeast Bre2.

From these studies it is clear that ASH2L is playing an important role in histone methyltransferase complexes in order to maintain proper H3K4 methylation and gene expression (Patel et al., 2009; Roguev et al., 2001).

Alternative to ASH2L’s function in H3K4 methylation ASH2L may also be playing a role in endosomal trafficking (Xu et al., 2009). ASH2L, DPY-30 and WDR5 were originally implicated in endosomal trafficking when siRNA knock-down of these genes increased the amount of internalized CD8-CMPR and overexpression increased the amount of cells displaying a altered CMPR distribution (Xu et al., 2009). This affect was limited to components of H3K4 methyltransferases and not to other methyl marks such as lysine 9 (Xu et al., 2009). The mechanism in which ASH2L and other components of H3K4 methyltransferase complexes modulate endosomal trafficking remains unclear. However, two possible mechanisms have been suggested, one is that the H3K4 methyltransferase components are part of an unknown complex that regulates trafficking, or that changes in H3K4 methylation lead to changes in expression of another regulating factor (Xu et al., 2009).

**ASH2L Structure**

One way to better understand the function of ASH2L is to determine the role of specific domains within ASH2L in facilitating H3K4 methylation. There are three known isoforms of ASH2L (Wang et al., 2001). Isoform 1 is considered the canonical sequence and consists of 628 amino acids (Wang et al., 2001). Isoform 2 is missing amino acids 1-94 and 541-573 from isoform 1 (Wang et al., 2001). Isoform 3 is missing the amino acids 1-94 from isoform 1 (Fig. 2) (Wang et al., 2001). There are four identified domains within ASH2L which include a N-terminus containing a PHD finger and a winged helix motif (WH) and the C-terminus containing a SPRY domain and a newly identified Sdc1 DPY-30 Interacting domain (SDI) (Fig. 2) (Wang et al., 2001; Roguev et al., 2001; South et al., 2010; Sarvan et al., 2011; Chen et al., 2011).

Interestingly, the domains with known biological function are the C-terminal SDI domain, which is responsible for the interaction with another histone methyltransferase component DPY-30 and the winged helix motif which binds to DNA (South et al., 2010; Sarvan et al., 2011; Chen et al., 2011). The function of the SDI domain was determined using *in vitro* binding experiments. ASH2L was shown to directly interact with DPY-30 without any additional MLL or Set1 complex components (South et al., 2010). The function of the SDI domain is conserved from yeast to humans because the yeast ASH2L homolog Bre2 was also shown to interact with the DPY-30 homolog Sdc1 (South et al., 2010). There are conserved hydrophobic residues in both the SDI domain of ASH2L and the Dpy-30 domain of DPY-30 that are important for binding, which suggests that the interaction between the SDI domain of ASH2L and the DPY-30 domain of DPY-30 is through hydrophobic interactions (South et al., 2010). In addition, binding affinities between ASH2L and DPY-30, as well as ASH2L and RB5 have been determined by sedimentation velocity analytical ultracentrifugation showing dissociation constants of 0.1 μM and 0.75 μM respectively (Patel et al., 2009). Interestingly, in yeast the ASH2L homolog Bre2 must interact with Sdc1 through the SDI domain to interact with the yeast Set1 histone methyltransferase complex (South et al., 2010). In contrast, *in vitro* experiments have shown ASH2L does not require DPY-30 to interact with MLL complex. To better understand how ASH2L interacts with MLL, *in vivo* studies must be done to determine if DPY-30 is required for ASH2L interaction. However, it is quite possible that the yeast and human complexes assemble differently.

**Figure 2. ASH2L has three known isoforms.** Schematic model of the three known isoforms of ASH2L and the amino acid sequence changes compared to the canonical isoform 1 (aa 1-628). The positions of known domains within ASH2L are displayed. PHD finger (aa 95-161), WH motif (aa 162-273), SPRY domain (aa 360-583), and SDI domain (aa 602-628). Isoform 2 and 3 are numbered according to isoform 1.
The N-terminal winged helix (WH) motif was recently discovered when the crystal structure of the N-terminus of ASH2L was solved (Sarvan et al., 2011; Chen et al., 2011). Using in vitro DNA binding analyses as well as chromatin immunoprecipitation, it was determined that ASH2L can bind DNA at the H52 promoter region and the β-globin locus as well as non-specific DNA sequence (Sarvan et al., 2011; Chen et al., 2011). The DNA binding activity of ASH2L promotes H3K4 methylation and gene expression at the β-globin locus by 50% when overexpressed in a cell line where ASH2L is knocked-down by siRNA (Sarvan et al., 2011). In addition, chromatin immunoprecipitation followed by a tiling array (ChIP-chip) analysis shows that disruption of the winged helix motif causes mis-localization of ASH2L (Chen et al., 2011). It was also shown that the DNA binding activity of the N-terminus of ASH2L increases when the C-terminal SPRY and SDI domains are present (Chen et al., 2011). Altogether, these data suggests that multiple domains in ASH2L may contribute to its ability to bind chromatin. However, more work will be needed to clearly establish the function of each domain.

The largest of the three identified domains within ASH2L is the SPRY domain, which is also conserved from yeast to humans. SPRY domains were originally named after the SPla kinase and the α1-adonine receptor proteins in which it was first identified (Rhodes et al., 2005). Multiple crystal structures have been solved for proteins that contain an SPRY domain. Crystal structures of SPRY domain containing proteins show primarily a β-sandwich structure with extending loops (Woo et al., 2006b; Kuang et al., 2009; Filippakopoulos et al., 2010; Simonet et al., 2007). The SPRY domain is thought to be a specific protein-protein interaction domain with specific partners, but instead of recognizing a particular motif or interaction domain the SPRY domain binds to interaction partners using non-conserved binding loops (Filippakopoulos et al., 2010; Woo et al., 2006b; Woo et al., 2006a). SPRY domain-containing proteins are involved in a wide array of functions including RNA metabolism, calcium release, and developmental processes (Woo et al., 2006b; Kuang et al., 2009; Filippakopoulos et al., 2010; Simonet et al., 2007; Woo et al., 2006a). Recent work has shown that the C-terminus of ASH2L that contains the SPRY domain and the SDI domain are able to interact with the other MLL complex member RBBP5 in vitro (Avdic et al., 2011). This interaction is most likely through the SPRY domain and not the SDI domain, though further work would need to be done to better map this interaction.

ASH2L also contains a putative Plant Homeo Domain (PHD) finger in its N-terminus (Wang et al., 2001). PHD fingers are a family of zinc finger domains that are known to bind to both modified and unmodified histone tails (Bienz, 2006; Mellor, 2006). The structure of PHD fingers shows that conserved cysteine and histidine residues bind to Zn²⁺ ions (Champagne et al., 2008; van Ingen et al., 2008; Champagne and Kutateladze, 2009). PHD fingers generally form a globular fold, consisting of a two-stranded beta-sheet and an alpha-helix. Loop regions of PHD fingers tend to vary giving rise to specificity of the domain. Some PHD fingers are considered to be readers of epigenetic marks by binding to specific modifications or sites on histones to stabilize or localize an interaction (Mellor, 2006). Primarily, PHD fingers have been shown to interact with trimethylated histone residues such as trimethylated histone H3 lysine 4 and lysine 9 (Mellor, 2006). There is no known function attributed to the PHD finger in ASH2L, though in conjunction with the winged helix motif it may be necessary for DNA binding. However, the PHD finger may also be needed in binding to MLL, other MLL/SET1 components, or recognizing a specific histone modification or for binding to a histone tail. Additional studies are needed to determine how the PHD finger of ASH2L and the SPRY domain may help the MLL and Set1 methyltransferase complexes interact and catalyze H3K4 methylation.

Conclusion

Currently, relatively little is known about the contribution of ASH2L to facilitate and or regulate the degree of methylation along the eukaryotic genome, but disruption of ASH2L and H3K4 methylation both appear to play a key role in oncogenesis (Lüsscher-Firzlaff et al., 2008; Hess, 2006). Interestingly, recent work has suggested that ASH2L in combination with WDR5 and RBBP5 exhibits H3K4 methyltransferase activity (Cao et al., 2010; Patel et al., 2009; Patel et al., 2011). In addition, this catalytic activity is not dependent on the SET domain containing proteins such as MLL1 (Patel et al., 2009; Cao et al., 2010; Patel et al., 2011). One report shows the catalytic activity of the ASH2L, WDR5, RBBP5, DPY-30 complex in an in vitro histone methyltransferase assay is observed but only after eight hours of incubation (Patel et al., 2009; Patel et al., 2011). In contrast, more methyltransferase activity and much shorter incubation times are required when these components are incubated with the MLL1 SET domain containing methyltransferase (Patel et al., 2009; Patel et al., 2011). This indicates the subcomplex has poor catalytic activity when the main catalytic SET domain-containing subunit is not present in the reaction. However, Cao et al. shows that only ASH2L/RBBP5 heterodimer is needed for weak H3K4 methyltransferase activity (Cao et al., 2010). Because ASH2L, WDR5, RBBP5, and
DPY-30 complex does not contain a known methyltransferase domain, more work needs to be done to determine if a new class of methyltransferase has been identified and whether or not this methyltransferase activity is biologically relevant.

ASH2L is found to be over abundant in many cancer cell lines and knock-down of ASH2L by siRNA can prevent tumorigenesis (Lüscher-Firzlaff et al., 2008). ASH2L is important for proper H3K4 methylation but how ASH2L contributes to the distribution and degree of methylation and its role in gene expression remains unclear. To better understand the role of ASH2L in methylation and gene expression several questions need to be addressed. What is the mechanism of interaction that contributes to ASH2L’s interaction with histone methyltransferase complexes? What is ASH2L’s role in regulating the degree of methylation along genes and what genes are affected by changes in ASH2L? Additional structural studies will help address the mechanism of how ASH2L interacts with other methyltransferase complex members and microarray experiments will be needed to determine the genes that are affected by changes in ASH2L expression levels. Addressing these questions could provide valuable information for the development specific inhibitors for the treatment of various cancers.

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Mellor J.. It takes a PHD to read the histone code. Cell. 2006 Jul 14;126(1):22-4. (REVIEW)


This article should be referenced as such:

A new case of t(4;12)(q12;p13) in a secondary acute myeloid leukemia with review of literature

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Clinics

Age and sex
57 years old male patient.

Previous history
No preleukemia. Previous malignancy Hodgkin's Lymphoma, stage IVA at age 25 year, treated with ABVD for 12 months. Tumor mass in the upper cervical spine diagnosed at age 27 year, treated with laminectomy and five doses of radiation. No inborn condition of note.

Organomegaly
No hepatomegaly, no splenomegaly, no enlarged lymph nodes, no central nervous system involvement.

Blood
WBC : 0.8X 10^9/l
HB : 9.7g/dl
Platelets : 21.0X 10^9/l
Blasts : 18%
Bone marrow : Variably cellular with 20% myeloblasts and dysplastic changes in the erythroid and myeloid cell lines.

Cyto-Pathology Classification

Cytology
His bone marrow showed 60% blasts, and dysplastic changes were noted in the erythroid and myeloid cell lines.

Immunophenotype
Flow cytometry (FCM) revealed that the blasts were of myeloid lineage expressing CD13, CD33, CD34, CD117, HLA-DR, and CD56.

Diagnosis
Acute myeloid leukemia (AML) with dysplastic changes.

Survival

Date of diagnosis: 08-2007

Treatment
He was treated with Idarubicin+Ara-c (3+7) regimen. Because of 15% residual blasts in bone marrow, patient received additional 2+5 therapy, and then he underwent consolidation with Ara-C. Result of karyotype: 46,XY[20]. On April 2008, the patient received a matched unrelated female donor stem cell transplant (SCT). 30 days post transplant; bone marrow revealed no morphological evidence of leukemia and the karyotype was 46,XX[20]. On June 2008; patient developed pancytopenia; WBC: 2.2 x 10^9/l; Hb: 11.6 g/dl; platelets: 18.0 x 10^9/l. His bone marrow showed an increased dysplastic changes and <5% blasts, suggestive of possible early relapse. The karyotype became abnormal (see below). On June 2010; bone marrow was hypocellular with 20% blasts and dysplastic changes in the erythroid and myeloid lineages. FCM revealed myeloblasts expressing CD4, CD7, CD33, CD34, CD56, CD117 and HLA-DR, myeloperoxidase was negative. Non-specific esterase was positive in occasional blasts. Cytology: AML possibly of monocytic origin (AML-M5).

Treatment related death: no
A new case of t(4;12)(q12;p13) in a secondary acute myeloid leukemia with review of literature

Heaton SM, et al.

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990

Figure 1. G-banded karyotype showing the balanced t(4;12)(q12;p13) translocation.

Figure 2. FISH on abnormal metaphases; (A) Metaphase hybridized with LSI 4q12 tricolor DNA probe showed a translocation of PDGFRA (SA) to derivative chromosome 12 (arrow), with the dual fusion of spectrumOrange (SO) and spectrumGreen (SG) remained on derivative 4. (B) Metaphase hybridized with LSI ETV6/RUNX1 ES dual color probe revealed a split of ETV6 (SG) with the smaller signal being translocated to derivative 4 (arrows). (C) Metaphase hybridized with both LSI 4q12 and ETV6/RUNX1 probes showed PDGFRA (SA) translocated to derivative 12 adjacent to ETV6 locus (arrows).

Phenotype at relapse: M5-AML
Status: Alive. Last follow up: 06-2010.
Survival: 24 months

Karyotype

Sample: Bone marrow
Culture time: 24 and 48h with 10% conditioned medium
Banding: GTG
Results
46.XY.t(4;12)(q12;p13)[6]/46,XX[14] in June 2008 (post transplant)

Karyotype at Relapse
46.XY.t(4;12)(q12;p13)[12]/46.idem,del(7)(q22q36)[4]/47.idem,+19[2]/46.XX[2], consistent with the recurrence and clonal evolution of the leukemic clone.

Other molecular cytogenetics techniques
Fluorescence in situ hybridization (FISH) using LSI 4q12 tricolor and LSI ETV6/RUNX1 ES dual color DNA probes were performed (Abbott Molecular. Downers Grove, IL) on the abnormal metaphase cells.

Other molecular cytogenetics results
Translocation of the PDGFRA gene in Toto, spectrumAqua (SA), to derivative 12 and colocalized with centromeric region of ETV6; Break within ETV6 gene locus, spectrumGreen (SG) and the telomeric region of ETV6 translocated to derivative 4 (Figure 2 A-C).

Comments
Acute leukemia with t(4;12)(q11-q12;p13) is a rare, nonrandom event with an estimated incidence of 0.6% among adults according to Harada et al. (Harada et al., 1997). This translocation is seen mostly in adult AML but less frequent in pediatric ALL (Hamaguchi et al., 1999). A review of the literature revealed at least twenty-two additional cases with a t(4;12)(q11-q12;p13); eighteen adults and four children. The male to female ratio is 1.5:1 (1.7:1 in adults and 1:1 in children). The majority of patients are adults, aged 18 to 82 with the mean being 58.9 years old (Harada et al., 1995; Harada et al., 1997; Ma et al., 1997; Cools et al., 1999; Hamaguchi et al., 1999; Chaufaille et al., 2003; Manabe et al., 2010). Four children have been reported, aged 3-14 years old, of which three had ALL and the oldest had AML (Harada et al., 1997). Among the 23 cases including our case with t(4;12) leukemia; 19 had AML; 3 ALL, and one unclassified leukemia. Common features to t(4;12) AML include dysplasia of three hematopoietic lineages (erythroid, myeloid and megakaryocytic), low or absent myeloperoxidase activity, basophilia and a pseudo-lymphoid morphology. The surface markers of the blasts show positivity for CD7, CD13, CD33, CD34 and HLA DR, suggesting that the leukemic cells have an immature myeloid stem
A new case of t(4;12)(q12;p13) in a secondary acute myeloid leukemia with review of literature

Heaton SM, et al.


Ma SK, Lie AK, Au WY, Wan TS, Chan LC. CD7+ acute myeloid leukaemia with 'mature lymphoid' blast morphology, marrow basophilia and t(4;12)(q12;p13) Br J Haematol. 1997 Dec;99(4):978-80


This article should be referenced as such:

Unbalanced rearrangement, der(9;18)(p10;q10) in a patient with myelodysplastic syndrome: Case 0002M

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Clinics

Age and sex
85 years old male patient.

Previous history

Organomegaly
No hepatomegaly, no splenomegaly, no enlarged lymph nodes, no central nervous system involvement.

Blood

WBC : 1.9X 10^9/l
HB : 10.9g/dl
Platelets : 57X 10^9/l

Cyto-Pathology Classification

Cytology
MDS (normocellular marrow with dysmegakaryopoiesis and dysgranulopoiesis; consistent with myelodysplastic syndrome)

Immunophenotype: NA
Rearranged Ig Tcr: NA
Diagnosis: MDS

Survival

Date of diagnosis: 03-2005
Treatment: not on any treatment
Complete remission : None
Treatment related death : NA
Relapse : no
Phenotype at relapse: NA
Status: Alive. Last follow up: 12-2010
Survival: 66 months.

Karyotype

Culture time : 24 and 72 hours with overnight Colcemid
Banding: GTW at 400 bands
Results
3/2005 BM 45,X,-Y[5]/46,XY,+9, der(9;18)(p10;q10)[11]/46,XY[4];
6/2007 BM 45,X,-Y[5][4]/46,XY[16];
12/2010 BM 46,XY,+9,
der(9;18)(p10;q10)[15]/46,XY[5]
Karyotype at Relapse: NA
Other molecular cytogenetics technics: None
Unbalanced rearrangement, der(9;18)(p10;q10) in a patient with myelodysplastic syndrome. Case 0002M.

Comments

Both the cases described in this study were followed for >5 years. Case 0001M, had thrombocytosis and could not tolerate Interferon or Hydrea treatment and hence was treated with Busulfan. The patient was positive for JAK2 mutation (on chromosome 9). A recent study was to rule out transformation of MPN as there was myelofibrosis, splenomegaly and apparent progression of the disease. The der(9;18) was first identified in the stem line and a sideline had partial deletion of chromosome 13q. Case 0002M was a MDS case with a der(9;18) detected in the initial study and again when the patient was suspected to be transforming >5 years later. This patient had very little symptoms and was not treated.

In this report for the first time a long standing MDS case was found to have the der(9;18). Der(9;18) is the sole abnormality in most reported cases, balanced translocations or complex aberrant karyotypes were reported as additional abnormalities. Our patient had del(13) in a sideline and this abnormality is observed in MPN. Among the 9 patients with der(9;18) two arose post treatment (present case 0001M and Andrieux et al 2003), and the other were at diagnosis. The der(9;18) supports progression of the disease in case 0001M but in case 0002M with MDS it reappears when there is suspicion of transformation and its role is less uncertain.

References


This article should be referenced as such:

Case Report Section

Paper co-edited with the European LeukemiaNet

Unbalanced rearrangement, der(9;18)(p10;q10) in a patient with myeloproliferative neoplasm: Case 0001M

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Clinics

Age and sex
71 years old male patient.

Previous history
Preleukemia. No previous malignancy. No inborn condition of note.

Organomegaly
No hepatomegaly, splenomegaly (Spleen appears enlarged measures 15.8 cm in length), no enlarged lymph nodes, no central nervous system involvement.

Blood

WBC: 112.7 X 10^9/l
HB: 13.3 g/dl
Platelets: 42 X 10^9/l

Cyto-Pathology Classification

Cytology
MPN (near 100% cellular marrow with granulocytic and megakaryocytic hyperplasia consistent with chronic myeloproliferative neoplasm).

Immunophenotype: NA
Rearranged Ig Ter: NA
Diagnosis: CMPN

Survival

Date of diagnosis: 10-2004
Treatment: Could tolerate Interferon or Hydrea and is on regulated dose of Busulfan.
Complete remission: None
Treatment related death: NA
Relapse: No
Status: Alive. Last follow up: 12-2010.
Survival: 74 months

Karyotype

Culture time: 24 and 72 hours with overnight Colcemid
Banding: GTW at 400 bands
Results
10/2004 BM 46,XY[20];
6/2007 PB 46,XY[10];
12/2010 BM 46,XY,+9,der(9;18)(p10;q10)[8]/46,sl,del(13)(q12q14)[cp6]/46.5,XY[6]
Karyotype at Relapse: NA
Other molecular cytogenetics technics: None

Other Molecular Studies

Technics: PCR
Results: JAK2V617F mutation
Unbalanced rearrangement, der(9;18)(p10;q10) in a patient with myeloproliferative neoplasm. Case 0001M.

In this report for the first time a long standing MDS case was found to have the der(9;18) at initial diagnosis and after over 5 years. Others reported with der(9;18)(n 7) had PV (n 3) or post PV myelofibrosis (n 4) and one had sAML after ET. The JAK2V617F is a gain in function mutation on chromosome 9. Hence, the extra copy of 9p may exacerbate the MPN as observed in 0001M case. The patient had splenomegaly and also myelofibrosis when the patient was found with the der(9;18). Der(9;18) is the sole abnormality in most reported cases, balanced translocations or complex aberrant karyotypes were reported as additional abnormalities. Our patient had del(13) in a sideline and this abnormality is observed in MPN. Among the 9 patients with der(9;18) two arose post treatment (present case 0001M and Andrieux et al 2003), and the other were at diagnosis.

The der(9;18) supports progression of the disease in case 0001M but in case 0002M with MDS it reappears when there is suspicion of transformation and its role is less uncertain.

References


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