MLL: Deep Insight

Jay L. Hess M.D. Ph.D.
Department of Pathology, University of Michigan Medical School
5240 Medical Sciences Building 1, 1301 Catherine Road
Ann Arbor, MI 48109-0602
E mail: jayhess@umich.edu

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Introduction

The mixed lineage leukemia gene, MLL (also known as MLL1), is disrupted in a variety of aggressive human B and T lymphoid as well as myeloid leukemias [Hess, J. L., et al., 1997;Brock, H. W.and van Lohuizen, M., 2001] (Fig. 1, Table 1). MLL is homologous to Drosophila Trithorax, a positive regulator of transcription during development. The best understood target genes of MLL are the clustered homeobox or Hox genes, which are transcription factors that are involved in the specification of cell fate during development. MLL is widely expressed during development and is expressed in most adult tissues including myeloid and lymphoid cells and is required for definitive hematopoiesis [Hess, J. L., et al., 1997;Ernst, P., et al., 2001] . Previous studies showed that Mll (Mll = murine MLL) plays an important role in maintenance of Hox gene expression during development because heterozygous Mll knockout mice showed posterior shifts in Hox gene expression, and Mll knockout mice, which are embryonic, show loss of Hox gene expression after embryonic day 9.5 following normal initiation of expression [Yu, B. D., et al., 1995].

MLL structure

MLL (3968 aa) is rapidly proteolytically cleaved into two fragments before entering the nucleus [Nakamura, T., et al., 2002;Yokoyama, A., et al., 2002;Hsieh, J. J., et al., 2003a;Hsieh, J. J., et al., 2003b] (Fig. 1). The amino terminus of (MLLN) is a 320 kD protein that targets MLL to specific chromosomal sites (i.e. Hox genes). These sequences span the three N-terminal AT hooks, which have been shown to bind the minor groove of DNA. A second region with |40347| homology to DNA methyltransferases (DNMT1) and methyl CpG |41308||41668| binding proteins (MBD1/PCM1) termed RD1 contains a CXXC zinc finger domain that binds CpG rich DNA [Birke, M., et al., 2002]. Both the RD1 domain and a C terminal RD2 domain act as independent repressors of transcription [Xia, Z. B., et al., 2003]. MLL contains two short domains SNL-1 and SNL-2 conserved with Drosophila trithorax (TRX) required for its punctate subnuclear localization [Yano, T., et al., 1997]. The C terminus of MLLN contains a region with high homology to trx. This region contains four cysteine-rich zinc finger domains (termed PHD for plant homeodomain) that flank a divergent bromodomain, a domain implicated in binding to acetylated histones [Aasland, R., et

al., 1995](Fig. 1). This region of MLL homodimerizes and is non-covalently associated with the C terminal MLL fragment [Fair, K., et al., 2001;Nakamura, T., et al., 2002;Yokoyama, A., et al., 2002;Hsieh, J. J., et al., 2003a]. The PHD finger region also interact with Cyp33, which may result in transcriptional repression through enhancing binding of histone deacetylases HDAC 1 and 2 to the RD1 and RD2 domains [Xia, Z. B., et al., 2003].

MLL is cleaved C terminal to the PHD fingers at an evolutionarily conserved site by a novel endoprotease termed taspase [Hsieh, J. J., et al., 2003a] into a 180 kD fragment, (MLLC) with potent transcriptional activating activity [Yokoyama, A., et al., 2002]. In addition inhibition of cleavage by taspase knockdown results in inhibition of 3' Hox expression [Hsieh, J. J., et al., 2003a]. Once cleaved the two halves of MLL remain non-covalently associated through an interaction between the FYRN domain of MLLN and the FYRC and SET domain of MLLC. Part of the transcriptional activation by MLLC appears to be the result of recruitment of the histone acetyltransferases CBP and MDF [Ernst, P., et al., 2001] resulting in acetylation of histones H3 and H4 at target genes. In addition the evolutionarily conserved SET domain has intrinsic histone methyltransferase activity specific for histone H3 lysine 4 [Milne, T. A., et al., 2002;Yokoyama, A., et al., 2002]. The SET methyltransferase preferentially methylates histone tails that are already acetylated. The MLL SET domain homodimerizes and also interacts with INI1, a core component of the SWI/SNF chromatin remodeling complex [Rozenblatt-Rosen, O., et al., 1998], which may also contribute to transcriptional activation.
In addition to its multiple domains involved in transcriptional regulation MLL has been reported to associate with more than 30 different proteins including core components of the SWI/SNF chromatin remodeling complex (BAF170, BAF155, INI1) that are likely involved in transcriptional activation, including |42481| basal transcription factors (TBP, TAFII250, TAFII80, TAFII31, TAFII20), which may be involved in targeting MLL to promoters or else MLL delivers to promoters and two different histone deacetylase (HDAC) containing corepressor |40802||40803| complexes NuRD (Mi2, MTA1-L1, HDAC1, HDAC2, |41310||42298||42202||42201| RbAp46, RbAp48, MBD3, KIAA0601) and Sin3A (Sin3A, SAP30, SAP18, HDAC1, HDAC2, RbAp48, RbAp46 [Nakamura, T., et al., 2002]. The MLL complex reported is somewhat controversial in that the complex differs dramatically from other, more recently reported MLL complexes which include MLL complex members WDR5 and Rbpp5 as well as other mammalian homologs of the proteins in the yeast Set1 complex [Cui, X., et al., 1998;Ernst, P., et al., 2001;Petruk, S., et al., 2001]. Surprisingly this core complex also contains menin, the protein mutated in multiple endocrine neoplasia syndrome type I (MEN1), which was required for Hox gene activation [Hughes, C. M., et al., 2004]. Finally the PHD fingers of MLL interact with the cyclophilin Cyp33, an RNA binding protein that may modulate the recruitment of corepressors to the RD2 domains of MLLN [Fair, K., et al., 2001;Xia, Z. B., et al., 2003].

MLL regulates Hox transcription through direct promoter binding and histone modifications

MLL directly binds to Hox promoters such as Hox c8 and Hox a9 promoters and regulates their transcription through both acetylation of histones H3 and H4 at Hox promoter and enhancer sequences as well as histone H3 lysine 4 di- and

trimethylation [Milne, T. A., et al., 2002;Nakamura, T., et al., 2002]. Because no known histone demethylases have been identified lysine methylation appears to be a long-term epigenetic mark for sustained transcription [Lachner, M.and Jenuwein, T., 2002]. The repressive PcG proteins are involved in Lys 9 and Lys 27 methylation strongly suggesting that histone methylation accounts for the antagonist effects of trx and PcG proteins on transcription [Cao, R., et al., 2002;Czermin, B., et al., 2002;Kuzmichev, A., et al., 2002;Muller, J., et al., 2002].

It is unclear whether H3 Lys 4 trimethylation is an absolute requirement for transcription and what the mediators are of this mechanism. Lys 4 methylation might block corepressor recruitment as it is for the histone deacetylase containing NuRD complex [Zegerman, P., et al., 2002]. A second possibility is that Lys4 di- or trimethylation creates a docking site for a transcriptional coactivator. The DNA dependent ATPase yeast protein ISW1p and its mammalian homolog hSNF2H, core components of the ISW1 chromatin remodeling complex preferentially bind to di- or trimethylated histone H3 lysine 4 [Santos-Rosa, H., et al., 2003]. ISW1p exists in two complexes, one of which ISW1b is required for promoting early stages of transcriptional elongation as well as termination by RNA polymerase II. In yeast both SET1, a lysine 4 methyltransferase homologous to MLL and Isw1p are required for full activation of target genes. Interestingly hSNF2 was also in the MLL complex [Nakamura, T., et al., 2002]. These findings suggest that MLL is intimately involved in a Lys 4 methylation and ATPase dependent mechanism to promote transcription [Krogan, N. J., et al., 2003]. Recent work indicates that MLL interacts with RNA polymerase II and acts to promote transcriptional elongation [Lachner, M.and Jenuwein, T., 2002].

MLL fusion proteins

Leukemogenic MLL rearrangements take a variety of forms including balanced translocations, partial tandem duplications of internal coding regions as well as amplification of apparently unrearranged forms of MLL (Fig. 1, Table 1). In rare cases of T-ALL exon 8 sequences are deleted resulting in disruption of the first PHD finger of MLL [Ayton, P. M.and Cleary, M. L., 2001]. However the most common MLL rearrangements are balanced translocations. The most frequent translocations in ALL are the t(4;11) and t(11;19) translocations, associated with expression of MLL-AF4 and MLL-ENL respectively, and pro-B cell or mixed lineage phenotype. Rarely MLL rearrangements such as MLL-ENL are seen in T-ALL. MLL translocations are also common in acute myelogenous leukemia, occurring in about 10% of cases. These leukemias are associated with a different set of translocations including the t(9;11) and t(6;11), which express MLL-AF9 and MLL-AF6 respectively. MLL rearrangements are also common in secondary acute leukemias arising following therapy with topoisomerase inhibitors such as etoposide [Felix, C. A., 1998].

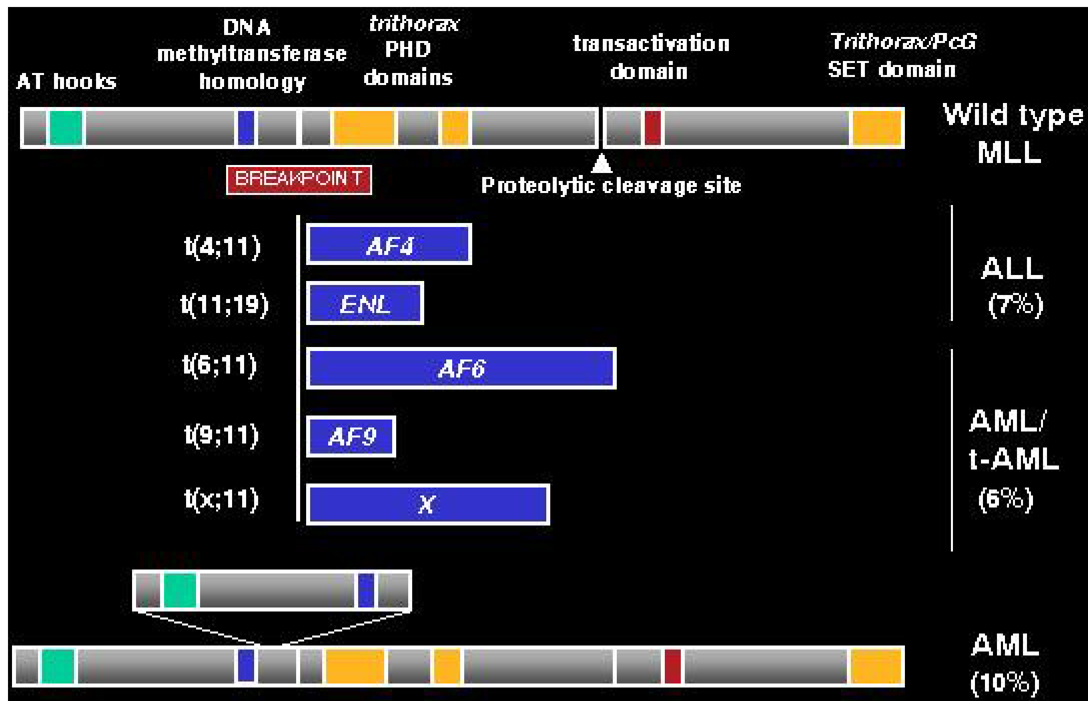

Fig. 1- MLL rearrangements associated with acute lymphoid and myeloid leukemias. MLL is homologous to Drosophila trithorax (trx) in a central PHD finger domain as well as in the C terminal SET domain (yellow). The AT hook and DNA methyltransferase homology regions are retained in all MLL rearrangements and are thought to mediate binding to specific chromosomal regions. Balanced translocations disrupt MLL in a breakpoint cluster region that spans exons 8 through 14 thereby deleting the sequences conserved with trx and replacing them with one of over 40 different translocation partners. Some such as MLL-AF4 and MLL-ENL are characteristically associated with ALL. Others such as AF6, AF9 and the majority of other translocations (X) are associated with AML, myelodysplasia or etoposide therapy related acute leukemia. In addition about 10% of AML cases without cytogenetic evidence of 11q23 rearrangements show internal tandem duplications of MLL, sometimes in association with trisomy 11.

AF4 related

AF4 (FEL) 4q21

Central transcriptional activation domain

pro-B ALL

AF5q31Ý 5q31.1

Central transcriptional activation domain

pro-B ALL

LAF4Ý 2q11.2~q12

Central transcriptional activation domain

Ýpro-B ALL

AF9 related

AF9Ý 9p22

Central transcriptional activation domain

AML

ENLÝ 19p13.3

Anc1 homology

C-terminal transcriptional activationÝ domain

Anc1 homology

AML,

pro-B ALL

ELL related

ELL (MEN) 19p13.1

C-terminal transcriptional activation domain

RNA polymerase II elongation factor

AML

AF10 related

AF10Ý 10p12

N-terminal PHD finder domain, leucine zipper

SWI/SNF interaction, transcriptional activation

AML

AF17Ý 17q21

N-terminal PHD finder domain, leucine zipper

AML

CBP related

ÝCBP 16p13.3

Transcriptional activation, bromodomain

Histone acetyltransferase

AML

P300Ý 22q13

Transcriptional activation, bromodomain

Histone acetyltransferase

AML

Forkhead related

AFXÝ Xq13

C-terminal transcriptional activation domain, forkhead DNA binding|1374|

T-ALL

FKHR-L1Ý 6q21

C-terminal transcriptional activation domain, forkhead DNA binding domain

AML

Table 1-Common MLL translocation partners occurring in leukemia

Balanced translocations involving MLL cluster between exons 8 and 14 resulting in deletion of the PHD and distal domains and in frame fusion to one of many different translocation partners (Fig. 2). The fusion proteins apparently do not interact with MLLC [Yokoyama, A., et al., 2002]. Several lines of evidence suggest that MLL fusion proteins transform by a gain of function rather than loss of function mechanism. First growth of MLL null hematopoietic progenitors is impaired rather than enhanced [Hess, J. L., et al., 1997;Yagi, H., et al., 1998;Ernst, P., et al., 2001]. Heterozygous MLL knockout mice do not have an increased incidence of leukemia nor do knock-in mice in which murine Mll is truncated by a Myc epitope tag [Corral, J., et al., 1996]. However, if the murine Mll is fused in frame to AF9 so that an Mll-AF9 fusion protein is expressed all of the mice develop first an expansion of myeloid progenitors and ultimately acute myeloid leukemias after a several month latency period [Dobson, C. L., et al., 1999]. These studies suggest that transformation by MLL-AF9 (and presumably other MLL fusions) is mediated by gain of function and in addition that additional genetic "hits" are likely to be required for full transformation. Retroviral transduction of MLL fusion proteins such as MLL-ENL has shown similar findings [Lavau, C., et al., 1997]. Studies of conditional forms of MLL fusion proteins suggest this is mediated by imposition of a reversible block on myeloid differentiation [Martin, M. E., et al., 2003;Zeisig, B. B., et al., 2004]

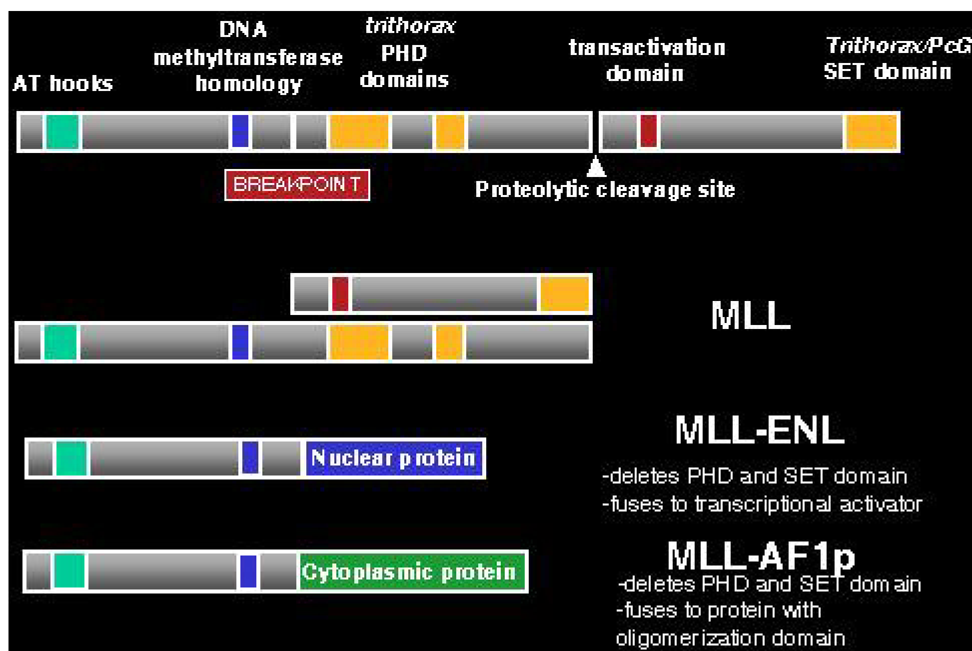

Fig 2. Possible mechanisms of transcriptional activation by MLL fusion proteins. Wild type MLL is composed of a heterodimers of MLLN and MLLC. MLLN directs the MLL complex to specific chromosomal sites including a subset of Hox genes where the complex serves as a regulatable activator of Hox genes. All MLL translocations result in loss of the conserved PHD fingers and SET domain and in frame fusion of MLL to one of more than 40 different translocation partners. The most common MLL fusion proteins involve nuclear translocation partners that act as potent transcriptional coactivators. Recent work suggests that some of the most common translocation partners, such as AF4 and AF9, interact and possibly recruit CDK9 and cyclin T1 to target promoters MLL [Zeisig, D. T., et al., 2005]. This potentially could promote transcriptional elongation through phosphorylation of RNA pol II 6 terminal domain by CDK9. Less commonly, MLL is fused to cytoplasmic translocation partners such as GAS7 and AF1p. These dimerize the truncated MLL molecule. This may involve recruitment of yet to be identified coactivators through MLLN sequences. This does not exclude the possibility that the translocation partner is also involved in coactivator recruitment.

The domains in MLL fusion proteins required for transformation includes a serine threonine-rich sequence of unknown function at the extreme amino terminal of MLL as well as the DNMT homology region of MLL that is likely to be important for DNA binding [Slany, R. K., et al., 1998;Birke, M., et al., 2002;So, C. W., et al., 2003b]. The end result of these fusions is to convert the truncated MLL into a potent transcriptional activator [Schreiner, S. A., et al., 1999;Zeisig, B. B., et al., 2003]. In most cases this is the result of fusion of MLL to translocation partners that are strong transcriptional activators. For example, both ENL and AF9 are nuclear proteins that activate transcription when tethered to heterologous promoters. An 84 amino acid C terminal domain of ENL conserved with AF9 is all that is required for transformation. Recently ENL has been found to be present in an SWI/SNF like complex termed EBAF, which has nucleosomal remodeling activity [Nie, Z., et al., 2003]. The complex includes at least 8 proteins found in other SWI/SNF complexes including INI1 and the Brg1 DNA-dependent ATPase.

The AF4 translocation partner is homologous to two other MLL translocation partners AF5q31 and LAF4, both of which are associated with pro-B cell leukemia. AF4 is also a potent activator of transcription when tethered to target promoters but less is known about its mechanism of activation in part because MLL-AF4 is unable to transform murine bone marrow in standard assays [Ayton, P. M.and Cleary, M. L., 2001]. AF4 and AF9 physically interact and colocalize at subnuclear foci suggesting that AF4

activation of transcription involves AF9 and SWI/SNF recruitment. The colocalization of AF4 and AF9 has prompted the "MLL Web hypothesis" that many MLL translocation partners are components of a larger supercomplex containing AF5q31, which itself interacts with CDK9 and cyclin T1 [Debernardi, S., et al., 2002;Erfurth, F., et al., 2004]. This is of potential significance because this complex phosphorylates the c terminal domain of RNA polymerase II and therefore may promote transcriptional elongation[Zeisig, D. T., et al., 2005].
MLL is fused to the known histone acetyltransferases CBP or p300 in some leukemias suggesting that abnormal histone acetyltransferase (HAT) activity may also play a role in MLL-mediated leukemogenesis. Structure function analysis of the MLL-CBP fusion protein shows that both the CBP HAT domain as well as an adjacent bromodomain are required for transformation [Lavau, C., et al., 2000]. Given that CBP also interacts with wild type MLL the question arises why when fused to MLL the protein becomes leukemogenic. One possibility is that deletion of potential negative regulatory sequences in CBP results in its abnormal activation. Alternatively covalent fusion may be important because this precludes regulated interactions with CBP that might be required for proper transcriptional regulation. CBP has also been implicated in transformation by other MLL fusion proteins. The MLL translocation partners AFX and FKHRL1 share two domains CR2 and CR3 that have been shown to cooperate in transcriptional activation and transformation [So, C. W.and Cleary, M. L., 2003]. The CR3 domain of interacts with CBP [So, C. W.and Cleary, M. L., 2002]. Like other forkhead transcription factors AFX induces cell cycle arrest and apoptosis by upregulating expression of p27Kip-1 [Medema, R. H., et al., 2000]. Interestingly MLL-AFX acts as a dominant negative inhibitor that suppresses FKHRL1 mediated apoptosis in myeloid cells suggesting that disruption of the normal activity of the translocation partner may play a role in the pathogenesis of the leukemia [So, C. W.and Cleary, M. L., 2002].
ELL is another translocation partner of MLL that was originally biochemically isolated as an elongation factor for RNA polymerase II [Shilatifard, A., et al., 1996]. The central R2 domain of ELL promotes elongation by suppressing polymerase pausing. However structure-function studies show that a carboxyl terminal R4 domain with transcriptional activating activity and not the R2 domain is necessary and sufficient for myeloid transformation [DiMartino, J., et al., 2000;Luo, R. T., et al., 2001]. This domain has transcriptional activating activity, possibly as a result of recruitment of an ELL associated protein EAF1, which contains a serine/aspartic acid/glutamic acid rich transactivation domain conserved with AF4, LAF4, and AF5q31 [Luo, R. T., et al., 2001]. EAF1 fused to MLL also is transforming in retroviral transformation assays suggesting EAF1 is the critical transcriptional activator required for transformation [Luo, R. T., et al., 2001]. Recent work suggests that menin is required for transformation by multiple MLL fusion proteins. The protein interacts with amino acid sequences in an evolutionarily conserved domain at the extreme amino terminus of MLL, which is shared by both MLL and MLL fusion proteins [Dobson, C. L., et al., 2000] . Deletion of this domain blocks transformation. In addition, genetic ablation of menin blocks transformation and reduces Hox gene expression thought to be pivotal for leukemogenesis.
Despite similarities between some of the more common MLL translocations, many MLL translocation partners are not transcription factors. Some MLL translocation partners have self-association motifs, suggesting that dimerization of MLL is transforming. Further evidence for this is that fusion of MLL to Beta galactosidase, which is a tetramer in solution [Dobson, C. L., et al., 2000]. Subsequent experiments

have conclusively shown that dimerization of MLL contributes to transformation by some MLL fusion proteins [Martin, M. E., et al., 2003;So, C. W., et al., 2003b]
The mechanisms by which dimerization of MLL converts it into an oncogene are unknown. Dimerization converts truncated MLL into an extremely potent transcriptional transactivator that has increased binding affinity for Hox promoters and that increases the amount of wild type MLL at target loci [Milne, T. A., et al., 2005b] . Whether the wild type MLL is required for transformation is not known. The end result of dimerization of fusion proteins, however, is |40850||41331| upregulation of Hox a7, hox a9, and Meis1 expression to levels similar to those seen in leukemias with MLL fused to nuclear translocation partners [Martin, M. E., et al., 2003] (Fig. 3, Fig. 4).

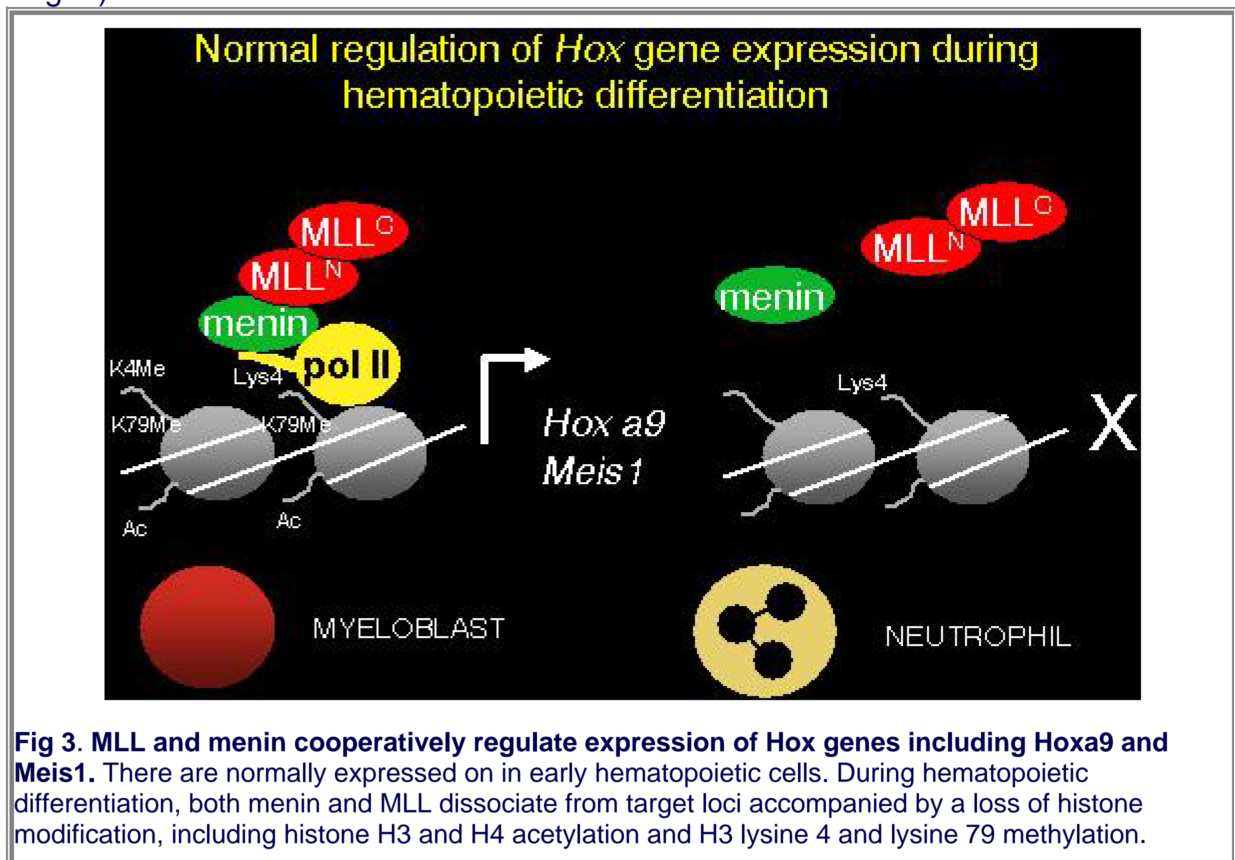

Fig 3. MLL and menin cooperatively regulate expression of Hox genes including Hoxa9 and Meis1. There are normally expressed on in early hematopoietic cells. During hematopoietic differentiation, both menin and MLL dissociate from target loci accompanied by a loss of histone modification, including histone H3 and H4 acetylation and H3 lysine 4 and lysine 79 methylation.

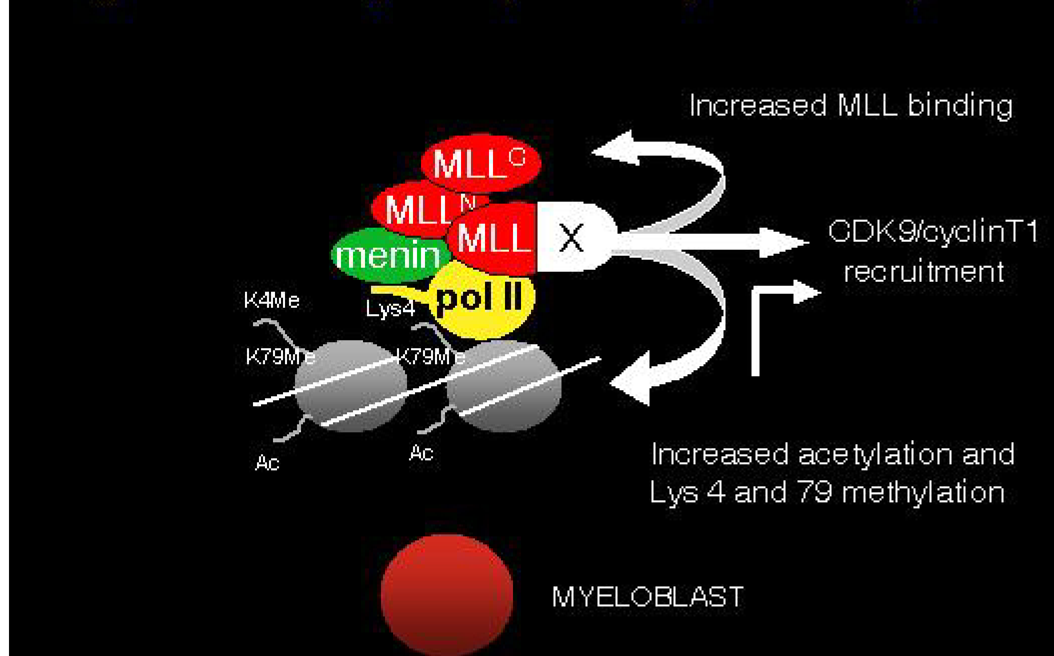

Fig 4. MLL fusion proteins potentially deregulate Hox gene expression through multiple mechanisms. The MLL fusion proteins increase the amount of wild type MLL at target loci [Milne, T. A., et al., 2005a]. Some MLL translocation partners such as AF5q31 interact with CDK9/cyclin T1 and therefore may influence transcriptional elongation via phosphorylation of the C-terminal domain of RNA polymerase II [Zeisig, D. T., et al., 2005 Lin, M. 2005]. Either directly or indirectly, MLL fusion proteins induce increased histone acetylation, lysine 4 methylation and, for some fusion proteins such as MLL-ENL, histone H3 lysine 79 methylation [Zeisig, D. T., et al., 2005].

Partial tandem duplication of MLL

About 10% of AML with normal cytogenetics harbor internal tandem duplications of MLL (Fig. 1), an important finding because these cases are associated with a worse prognosis than those without MLL rearrangements [Schichman, S. A., et al., 1994]. Microarray studies on human leukemias with MLL PTD do not show the characteristic “signature” of Hox gene deregulation as leukemias with MLL translocations, leaving the mechanism of transformation unclear[Ross, M. E., et al., 2004].

MLL amplification

In some cases of MDS and AML MLL is present in increased copy number either as the result of additional copies of chromosome 11 or MLL amplification, either cytogenetically undetectable or in high copy number cases where MLL is present in homogeneous staining regions or double minute chromosomes [Thorsteinsdottir, U., et al., 2002;Poppe, B., et al., 2004]. The coding region of MLL is apparently unaltered but overexpressed in these cases. Amplification of MLL is also associated with upregulation of at least some of the genes consistently expressed in leukemias with MLL rearrangements including HOX A9, MEIS1, PROML1, ADAM10, NKG2D and ITPA expression, suggesting similar mechanisms of pathogenesis [Poppe, B., et al., 2004].

Hox genes are critical targets of leukemogenic forms of MLL

Hox genes appear to be the critical targets of MLL fusion proteins required for transformation. Hox genes such as Hox a9 are important regulators of hematopoiesis that act in part by promoting stem cell renewal [Sauvageau, G., et al., 2001;Thorsteinsdottir, U., et al., 2002]. The A cluster Hox genes including Hox a7 and a9 and the Hox cofactor Meis 1 are normally only expressed in early Sca1+Lin- hematopoietic stem cells and then their expression is rapidly downregulated [Pineault, N., et al., 2002] (Fig. 3). Studies of revealed that Hox a7 and Hox a9 are commonly overexpressed as a result of retroviral integration in leukemias spontaneously arising in BXH2 mice [Moskow, J. J., et al., 1995;Nakamura, T., et al., 1996]. Mice transplanted with murine bone marrow cells transduced with Hox a9 alone resulted in AML with a long latency of up to 6 months [Kroon, E., et al., 1998]. The Hox proteins bind to DNA as heterodimers and trimers with members of the TALE (three amino acid loop extension proteins) family members including PBX1, |41647||41648| PBX2, and PBX3 as well as Meis 1 [Schnabel, C. A., et al., 2000]. Notably overexpression of Meis 1 is commonly associated with Hox a7 and a9 expression in BXH2 leukemias, and cotransduction of Hox a9 and Meis 1 rapidly accelerates leukemia development in transplanted mice [Kroon, E., et al., 1998]. Human ALL with MLL rearrangements consistently express HOX A7, HOX A9 and MEIS1 in sharp contrast to morphologically and immunophenotypically similar leukemias that lack MLL rearrangements [Rozovskaia, T., et al., 2001;Armstrong, S. A., et al., 2002;Yeoh, E. J., et al., 2002;Ferrando, A. A., et al., 2003]. Recent experiments with a conditionally transforming version of MLL-ENL show that expression of Hox a9 and Meis1 can replace the gain of function activity of the fusion proteins indicating these are critical MLL fusion protein targets [Zeisig, B. B., et al., 2004] and in addition retroviral transformation assays showing transformation by MLL-ENL requires functional Hox a7 and Hox a9 [Ayton, P. M.and Cleary, M. L., 2003].

Recently some questions have arisen regarding the role of Hox genes in MLL leukemogenesis. MLL-GAS7 was recently shown to transform Hox a9 knock-out bone marrow [So, C. W., et al., 2003a]. In addition Mll-AF9 knock-in mice develop leukemia with the same incidence and latency on either a Hox a9 null or wild type background [Kumar, A. R., et al., 2003]. One possible explanation is that MLL fusion proteins upregulate |40846| multiple other Hox genes including Hox a7, Hox a10 and Meis1 as well as non Hox targets such as Lmo2, N-Myc, and Flt3 [Kumar, A. R., et al., 2003] and that under certain conditions this is sufficient for transformation.

Bibliography

ALL-1 partial duplication in acute leukemia.
Schichman, S. A., Caligiuri, M. A., Gu, Y., Strout, M. P., Canaani, E., Bloomfield, C. D. and Croce, C. M.
Proc Natl Acad Sci U S A 1994; (91) 13:6236-9.
Medline 8016145
The PHD finger: implications for chromatin-mediated transcriptional regulation.
Aasland, R., Gibson, T. J. and Stewart, A. F.
Trends Biochem Sci 1995; (20) 2:56-9.
Medline 7701562
Meis1, a PBX1-related homeobox gene involved in myeloid leukemia in BXH-2 mice.
Moskow, J. J., Bullrich, F., Huebner, K., Daar, I. O. and Buchberg, A. M.

Mol Cell Biol 1995; (15) 10:5434-43.
Medline 7565694
Altered Hox expression and segmental identity in Mll-mutant mice.
Yu, B. D., Hess, J. L., Horning, S. E., Brown, G. A. and Korsmeyer, S. J.
Nature 1995; (378) 6556:505-8.
Medline 7477409
An Mll-AF9 fusion gene made by homologous recombination causes acute leukemia in chimeric mice: a method to create fusion oncogenes.
Corral, J., Lavenir, I., Impey, H., Warren, A. J., Forster, A., Larson, T. A., Bell, S., McKenzie, A. N., King, G. and Rabbitts, T. H.
Cell 1996; (85) 6:853-61.
Medline 8681380
Cooperative activation of Hoxa and Pbx1-related genes in murine myeloid leukaemias.
Nakamura, T., Largaespada, D. A., Shaughnessy, J. D., Jr., Jenkins, N. A. and Copeland, N. G.
Nat Genet 1996; (12) 2:149-53.
Medline 8563752
An RNA polymerase II elongation factor encoded by the human ELL gene.
Shilatifard, A., Lane, W. S., Jackson, K. W., Conaway, R. C. and Conaway, J. W.
Science 1996; (271) 5257:1873-6.
Medline 8596958
Defects in yolk sac hematopoiesis in Mll-null embryos.
Hess, J. L., Yu, B. D., Li, B., Hanson, R. and Korsmeyer, S. J.
Blood 1997; (90) 5:1799-806.
Medline 9292512
Immortalization and leukemic transformation of a myelomonocytic precursor by retrovirally transduced HRX-ENL.
Lavau, C., Szilvassy, S. J., Slany, R. and Cleary, M. L.
EMBO Journal 1997; (16) 14:4226-37.
Medline 9250666
Nuclear punctate distribution of ALL-1 is conferred by distinct elements at the N terminus of the protein.
Yano, T., Nakamura, T., Blechman, J., Sorio, C., Dang, C. V., Geiger, B. and Canaani, E.
Proceedings of the National Academy of Sciences of the United States of America 1997; (94) 14:7286-91.
Medline 9207083
Association of SET domain and myotubularin-related proteins modulates growth control.
Cui, X., De Vivo, I., Slany, R., Miyamoto, A., Firestein, R. and Cleary, M. L.
Nature Genetics 1998; (18) 4:331-7.
Medline 9537414
Secondary leukemias induced by topoisomerase-targeted drugs.
Felix, C. A.
Biochim Biophys Acta 1998; (1400) 1-3:233-55.
Medline 9748598
Hoxa9 transforms primary bone marrow cells through specific collaboration with Meis1a but not Pbx1b.
Kroon, E., Krosl, J., Thorsteinsdottir, U., Baban, S., Buchberg, A. M. and Sauvageau,

G.
Embo J 1998; (17) 13:3714-25.
Medline 9649441
The C-terminal SET domains of ALL-1 and TRITHORAX interact with the INI1 and SNR1 proteins, components of the SWI/SNF complex.
Rozenblatt-Rosen, O., Rozovskaia, T., Burakov, D., Sedkov, Y., Tillib, S., Blechman, J., Nakamura, T., Croce, C. M., Mazo, A. and Canaani, E.
Proc Natl Acad Sci U S A 1998; (95) 8:4152-7.
Medline 9539705
The oncogenic capacity of HRX-ENL requires the transcriptional transactivation activity of ENL and the DNA binding motifs of HRX.
Slany, R. K., Lavau, C. and Cleary, M. L.
Molecular & Cellular Biology 1998; (18) 1:122-9.
Medline 9418860
Growth disturbance in fetal liver hematopoiesis of Mll-mutant mice.
Yagi, H., Deguchi, K., Aono, A., Tani, Y., Kishimoto, T. and Komori, T.
Blood 1998; (92) 1:108-17.
Medline 9639506
The mll-AF9 gene fusion in mice controls myeloproliferation and specifies acute myeloid leukaemogenesis.
Dobson, C. L., Warren, A. J., Pannell, R., Forster, A., Lavenir, I., Corral, J., Smith, A. J. and Rabbitts, T. H.
EMBO Journal 1999; (18) 13:3564-74.
Medline 10393173
The leukemogenic fusion of MLL with ENL creates a novel transcriptional transactivator.
Schreiner, S. A., Garcia-Cuellar, M. P., Fey, G. H. and Slany, R. K.
Leukemia 1999; (13) 10:1525-33.
Medline 10516753
A carboxy-terminal domain of ELL is required and sufficient for immortalization of myeloid progenitors by MLL-ELL.
DiMartino, J., Miller, T., Ayton, P. M., Landewe, T., Hess, J. L., Cleary, M. L. and Shilatifard, A.
Blood 2000; (96) 3887-993.
Medline 11090074
Tumorigenesis in mice with a fusion of the leukaemia oncogene Mll and the bacterial lacZ gene.
Dobson, C. L., Warren, A. J., Pannell, R., Forster, A. and Rabbitts, T. H.
EMBO Journal 2000; (19) 5:843-51.
Medline 10698926
Chromatin-related properties of CBP fused to MLL generated a myelodysplastic-like syndrome that evolves into myeloid leukemia.
Lavau, C., Du, C., Thirman, M. and Zeleznik-Le, N.
EMBO Journal 2000; (19) 4655-64.
Medline 10970858
AFX-like Forkhead transcription factors mediate cell-cycle regulation by Ras and PKB through p27kip1.
Medema, R. H., Kops, G. J., Bos, J. L. and Burgering, B. M.
Nature 2000; (404) 6779:782-7.
Medline 10783894

HoxA9-mediated immortalization of myeloid progenitors requires functional interactions with TALE cofactors Pbx and Meis.
Schnabel, C. A., Jacobs, Y. and Cleary, M. L.
Oncogene 2000; (19) 5:608-16.
Medline 10698505
Molecular mechanisms of leukemogenesis mediated by MLL fusion proteins.
Ayton, P. M. and Cleary, M. L.
Oncogene 2001; (20) 40:5695-707.
Medline 11607819
The Polycomb group--no longer an exclusive club?
Brock, H. W. and van Lohuizen, M.
Curr Opin Genet Dev 2001; (11) 2:175-81.
Medline
MLL and CREB bind cooperatively to the nuclear coactivator CREB-binding protein.
Ernst, P., Wang, J., Huang, M., Goodman, R. H. and Korsmeyer, S. J.
Mol Cell Biol 2001; (21) 7:2249-58.
Medline 11259575
Protein interactions of the MLL PHD fingers modulate MLL target gene regulation in human cells.
Fair, K., Anderson, M., Bulanova, E., Mi, H., Tropschug, M. and Diaz, M. O.
Mol Cell Biol 2001; (21) 10:3589-97.
Medline 11313484
The elongation domain of ELL is dispensable but its ELL-associated factor 1 interaction domain is essential for MLL-ELL-induced leukemogenesis.
Luo, R. T., Lavau, C., Du, C., Simone, F., Polak, P. E., Kawamata, S. and Thirman, M. J.
Mol Cell Biol 2001; (21) 16:5678-87.
Medline 11463848
Trithorax and dCBP acting in a complex to maintain expression of a homeotic gene.
Petruk, S., Sedkov, Y., Smith, S., Tillib, S., Kraevski, V., Nakamura, T., Canaani, E., Croce, C. M. and Mazo, A.
Science 2001; (294) 5545:1331-4.
Medline 11701926
Upregulation of Meis1 and HoxA9 in acute lymphocytic leukemias with the t(4: 11) abnormality.
Rozovskaia, T., Feinstein, E., Mor, O., Foa, R., Blechman, J., Nakamura, T., Croce, C. M., Cimino, G. and Canaani, E.
Oncogene 2001; (20) 7:874-8.
Medline 11314021
MLL translocations specify a distinct gene expression profile that distinguishes a unique leukemia.
Armstrong, S. A., Staunton, J. E., Silverman, L. B., Pieters, R., den Boer, M. L., Minden, M. D., Sallan, S. E., Lander, E. S., Golub, T. R. and Korsmeyer, S. J.
Nat Genet 2002; (30) 1:41-7.
Medline 11731795
The MT domain of the proto-oncoprotein MLL binds to CpG-containing DNA and discriminates against methylation.
Birke, M., Schreiner, S., Garcia-Cuellar, M. P., Mahr, K., Titgemeyer, F. and Slany, R. K.

Nucleic Acids Res 2002; (30) 4:958-65.
Medline 11842107
Role of histone H3 lysine 27 methylation in Polycomb-group silencing.
Cao, R., Wang, L., Wang, H., Xia, L., Erdjument-Bromage, H., Tempst, P., Jones, R. S. and Zhang, Y.
Science 2002; (298) 5595:1039-43.
Medline 12351676
Drosophila Enhancer of Zeste/ESC Complexes Have a Histone H3 Methyltransferase Activity that Marks Chromosomal Polycomb Sites.
Czermin, B., Melfi, R., McCabe, D., Seitz, V., Imhof, A. and Pirrotta, V.
Cell 2002; (111) 2:185-96.
Medline 12408863
The MLL fusion partner AF10 binds GAS41, a protein that interacts with the human SWI/SNF complex.
Debernardi, S., Bassini, A., Jones, L. K., Chaplin, T., Linder, B., de Bruijn, D. R., Meese, E. and Young, B. D.
Blood 2002; (99) 1:275-81.
Medline 11756182
Histone methyltransferase activity associated with a human multi-protein complex containing the enhancer of Zeste Protein.
Kuzmichev, A., Nishioka, K., Erdjument-Bromage, H., Tempst, P. and Reinberg, D.
Genes Dev 2002; (16) 2893-905.
Medline 12435631
The many faces of histone lysine methylation.
Lachner, M. and Jenuwein, T.
Curr Opin Cell Biol 2002; (14) 3:286-98.
Medline 12067650
MLL targets SET domain methyltransferase activity to Hox gene promoters.
Milne, T. A., Briggs, S. D., Brock, H. W., Martin, M. E., Gibbs, D., Allis, C. D. and Hess, J. L.
Mol Cell 2002; (10) 5:1107-17.
Medline 12453418
Histone methyltransferase activity of a Drosophila polycomb group repressor complex.
Muller, J., Hart, C. M., Francis, N. J., Vargas, M. L., Sengupta, A., Wild, B., Miller, E. L., O'Connor, M. B., Kingston, R. E. and Simon, J. A.
Cell 2002; (111) 2:197-208.
Medline 12408864
ALL-1 is a histone methyltransferase that assembles a supercomplex of proteins involved in transcriptional regulation.
Nakamura, T., Mori, T., Tada, S., Krajewski, W., Wassell, R., Dubois, G., Mazo, A., Croce, C. M. and Canaani, E.
Mol Cell 2002; (10) 1119-28.
Medline 12453419
Differential expression of Hox, Meis1, and Pbx1 genes in primitive cells throughout murine hematopoietic ontogeny.
Pineault, N., Helgason, C. D., Lawrence, H. J. and Humphries, R. K.
Exp Hematol 2002; (30) 1:49-57.
Medline 11823037

MLL-AFX requires the transcriptional effector domains of AFX to transform myeloid progenitors and transdominantly interfere with forkhead protein function.
So, C. W. and Cleary, M. L.
Mol Cell Biol 2002; (22) 18:6542-52.
Medline 12192052
Overexpression of the myeloid leukemia-associated Hoxa9 gene in bone marrow cells induces stem cell expansion.
Thorsteinsdottir, U., Mamo, A., Kroon, E., Jerome, L., Bijl, J., Lawrence, H. J., Humphries, K. and Sauvageau, G.
Blood 2002; (99) 1:121-9.
Medline 11756161
Classification, subtype discovery, and prediction of outcome in pediatric acute lymphoblastic leukemia by gene expression profiling.
Yeoh, E. J., Ross, M. E., Shurtleff, S. A., Williams, W. K., Patel, D., Mahfouz, R., Behm, F. G., Raimondi, S. C., Relling, M. V., Patel, A., Cheng, C., Campana, D., Wilkins, D., Zhou, X., Li, J., Liu, H., Pui, C. H., Evans, W. E., Naeve, C., Wong, L. and Downing, J. R.
Cancer Cell 2002; (1) 2:133-43.
Medline 12086872
Leukemia proto-oncoprotein MLL is proteolytically processed into 2 fragments with opposite transcriptional properties.
Yokoyama, A., Kitabayashi, I., Ayton, P. M., Cleary, M. L. and Ohki, M.
Blood 2002; (100) 10:3710-8.
Medline 12393701
Histone H3 lysine 4 methylation disrupts binding of nucleosome remodeling and deacetylase (NuRD) repressor complex.
Zegerman, P., Canas, B., Pappin, D. and Kouzarides, T.
J Biol Chem 2002; (277) 14:11621-4.
Medline 11850414
Transformation of myeloid progenitors by MLL oncoproteins is dependent on Hoxa7 and Hoxa9.
Ayton, P. M. and Cleary, M. L.
Genes Dev 2003; (17) 18:2298-307.
Medline 12952893
Gene expression signatures in MLL-rearranged T-lineage and B-precursor acute leukemias: dominance of HOX dysregulation.
Ferrando, A. A., Armstrong, S. A., Neuberg, D. S., Sallan, S. E., Silverman, L. B., Korsmeyer, S. J. and Look, A. T.
Blood 2003; (102) 1:262-8.
Medline 12637319
Taspase1: a threonine aspartase required for cleavage of MLL and proper HOX gene expression.
Hsieh, J. J., Cheng, E. H. and Korsmeyer, S. J.
Cell 2003a; (115) 3:293-303.
Medline 14636557
Proteolytic cleavage of MLL generates a complex of N- and C-terminal fragments that confers protein stability and subnuclear localization.
Hsieh, J. J., Ernst, P., Erdjument-Bromage, H., Tempst, P. and Korsmeyer, S. J.
Mol Cell Biol 2003b; (23) 1:186-94.
Medline 12482972

The Paf1 complex is required for histone H3 methylation by COMPASS and Dot1p: linking transcriptional elongation to histone methylation.
Krogan, N. J., Dover, J., Wood, A., Schneider, J., Heidt, J., Boateng, M. A., Dean, K., Ryan, O. W., Golshani, A., Johnston, M., Greenblatt, J. F. and Shilatifard, A.
Mol Cell 2003; (11) 3:721-9.
Medline 12667454
Hoxa9 influences the phenotype but not the incidence of Mll-AF9 fusion gene leukemia.
Kumar, A. R., Hudson, W. A., Chen, W., Nishiuchi, R., Yao, Q. and Kersey, J. H.
Blood 2003; (Published online November 13) Medline 14615372
Dimerization of MLL fusion proteins immortalizes hematopoietic cells.
Martin, M. E., Milne, T. A., Bloyer, S., Galoian, K., Shen, W., Gibbs, D., Brock, H. W., Slany, R. and Hess, J. L.
Cancer Cell 2003; (4) 3:197-207.
Medline 14522254
Novel SWI/SNF chromatin-remodeling complexes contain a mixed-lineage leukemia chromosomal translocation partner.
Nie, Z., Yan, Z., Chen, E. H., Sechi, S., Ling, C., Zhou, S., Xue, Y., Yang, D., Murray, D., Kanakubo, E., Cleary, M. L. and Wang, W.
Mol Cell Biol 2003; (23) 8:2942-52.
Medline 12665591
Methylation of histone H3 K4 mediates association of the Isw1p ATPase with chromatin.
Santos-Rosa, H., Schneider, R., Bernstein, B. E., Karabetsou, N., Morillon, A., Weise, C., Schreiber, S. L., Mellor, J. and Kouzarides, T.
Mol Cell 2003; (12) 5:1325-32.
Medline 14636589
Common mechanism for oncogenic activation of MLL by forkhead family proteins.
So, C. W. and Cleary, M. L.
Blood 2003; (101) 2:633-9.
Medline 12393557
Leukemic transformation of hematopietic progenitors by MLL-GAS7 in the absence of Hoxa7 or Hoxa9.
So, C. W., Karsunky, H., Wong, P., Weissman, I. L. and Cleary, M. L.
Blood 2003a; (Published online December 30) Medline 14701684
Dimerization contributes to oncogenic activation of MLL chimeras in acute leukemias.
So, C. W., Lin, M., Ayton, P. M., Chen, E. H. and Cleary, M. L.
Cancer Cell 2003b; (4) 2:99-110.
Medline 12957285
MLL repression domain interacts with histone deacetylases, the polycomb group proteins HPC2 and BMI-1, and the corepressor C-terminal-binding protein.
Xia, Z. B., Anderson, M., Diaz, M. O. and Zeleznik-Le, N. J.
Proc Natl Acad Sci U S A 2003; (100) 14:8342-7.
Medline 12829790
Transcriptional activation is a key function encoded by MLL fusion partners.
Zeisig, B. B., Schreiner, S., Garcia-Cuellar, M. P. and Slany, R. K.
Leukemia 2003; (17) 2:359-65.
Medline 12592336
MLL fusion partners AF4 and AF9 interact at subnuclear foci.
Erfurth, F., Hemenway, C. S., De Erkenez, A. C. and Domer, P. H.

Leukemia 2004; (18) 1:92-102.
Medline 14603337
Menin associates with a trithorax family histone methyltransferase complex and with the hoxc8 locus.
Hughes, C. M., Rozenblatt-Rosen, O., Milne, T. A., Copeland, T. D., Levine, S. S., Lee, J. C., Hayes, D. N., Shanmugam, K. S., Bhattacharjee, A., Biondi, C. A., Kay, G. F., Hayward, N. K., Hess, J. L. and Meyerson, M.
Molecular Cell 2004; (13) 4:587-97.
Medline 14992727
Expression analyses identify MLL as a prominent target of 11q23 amplification and support an etiologic role for MLL gain of function in myeloid malignancies.
Poppe, B., Vandesompele, J., Schoch, C., Lindvall, C., Mrozek, K., Bloomfield, C. D., Beverloo, H. B., Michaux, L., Dastugue, N., Herens, C., Yigit, N., De Paepe, A., Hagemeijer, A. and Speleman, F.
Blood 2004; (103) 1:229-35.
Medline 12946992
Gene expression profiling of pediatric acute myelogenous leukemia.
Ross, M. E., Mahfouz, R., Onciu, M., Liu, H. C., Zhou, X., Song, G., Shurtleff, S. A., Pounds, S., Cheng, C., Ma, J., Ribeiro, R. C., Rubnitz, J. E., Girtman, K., Williams, W. K., Raimondi, S. C., Liang, D. C., Shih, L. Y., Pui, C. H. and Downing, J. R.
Blood 2004; (104) 12:3679-87.
Medline 15226186
Hoxa9 and Meis1 Are Key Targets for MLL-ENL-Mediated Cellular Immortalization.
Zeisig, B. B., Milne, T., Garcia-Cuellar, M. P., Schreiner, S., Martin, M. E., Fuchs, U., Borkhardt, A., Chanda, S. K., Walker, J., Soden, R., Hess, J. L. and Slany, R. K.
Mol Cell Biol 2004; (24) 2:617-28.
Medline 14701735
MLL associates specifically with a subset of transcriptionally active target genes.
Milne, T. A., Dou, Y., Martin, M. E., Brock, H. W., Roeder, R. G. and Hess, J. L.
Proceedings of the National Academy of Sciences of the United States of America 102(41):14765-70, 2005 Oct 11 2005a; Medline 16199523
Leukemogenic MLL fusion proteins bind across a broad region of the Hox a9 locus, promoting transcription and multiple histone modifications.
Milne, T. A., Martin, M. E., Brock, H. W., Slany, R. K. and Hess, J. L.
Cancer Research 65(24):11367-74, 2005 Dec 15 2005b; Medline 16357144
The eleven-nineteen-leukemia protein ENL connects nuclear MLL fusion partners with chromatin.
Zeisig, D. T., Bittner, C. B., Zeisig, B. B., Garcia-Cuellar, M. P., Hess, J. L. and Slany, R. K.
Oncogene 2005; (24) 35:5525-32.
Medline 15856011

Contributor(s)

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