Caspase-8 and Cancer

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Abstract

Caspase-8 belongs to the family of cysteine proteases that plays a critical role in the regulation of programmed cell death (apoptosis). For example, caspase-8 function is required for proper signaling via the death receptor (extrinsic) pathway. Accordingly, the disturbance of caspase-8 expression or function may contribute to cancer formation and progression. In addition, inactivation of caspase-8 may promote resistance to current treatment approaches, which critically require signaling via the death receptor pathway. Thus, restoration of caspase-8 function presents a promising approach to overcome resistance to apoptosis in human cancers.

Introduction

Apoptosis (programmed cell death) is one of the most common forms of cell death in multicellular organisms and is a crucial component of normal development as well as a variety of physiological processes (Lockshin and Zakeri, 2007). This implies that too little or too much apoptosis can shift the tightly regulated balance between cell growth and cell death towards one or the other side and disturbs cellular homeostasis (Evan and Vousden, 2001). For example, a decreased rate of apoptosis favors tumor formation as well as its progression (Lowe and Lin, 2000). Accordingly, evasion of apoptosis can be found as a characteristic feature in most human malignancies (Hanahan and Weinberg, 2000). Over the last years key signaling pathways and molecules have been identified. For example, one of these critical regulators of apoptosis is caspase-8, a member of the caspase family of proteases (Degterev et al., 2003). Caspase-8 plays a central role in the transmission of the death signal in the death receptor (extrinsic) pathway of apoptosis by coupling the stimulation of death receptors to the activation of intracellular signaling cascades that eventually lead to cell death (Barnhart et al., 2003). Consequently, reduced expression or dysfunction of caspase-8 fosters carcinogenesis as well as the progression and treatment resistance in various different cancers (Fulda, 2008). This review focuses on the role of caspase-8 in cancer.

Apoptosis signaling pathways
There are two principle apoptosis signaling pathways: the death receptor (extrinsic) pathway and the mitochondrial (intrinsic) pathway (Fulda and Debatin, 2006). In the death receptor pathway, ligation of cell surface receptors of the tumor necrosis factor (TNF) receptor superfamily, including CD95 (APO-1/Fas) or TRAIL receptors, leads to the activation of caspase-8 in the death-inducing signaling complex (DISC) that contains besides caspase-8 and activated death receptors also the adaptor molecule FADD (Ashkenazi, 2008). Within the caspase family, caspase-8 is an initiator that following its activation can either directly cleave downstream effector caspases such as caspase-3 or, alternatively, can indirectly promote effector caspase activation via the cleavage of Bid (Ashkenazi, 2008). Bid is a pro-apoptotic protein of the Bcl-2 family with a BH3 domain only, which moves to mitochondria upon its cleavage to stimulate the mitochondrial signaling pathway (Adams and Cory, 2007). This involves the release of intermembrane space proteins such as cytochrome c and second mitochondria-derived activator of caspase (Smac)/direct IAP Binding protein with Low pi (DIABLO) from the mitochondria into the cytosol, which in turn triggers activation of caspase-3 (Kroemer et al., 2007). Once in the cytosol, cytochrome c causes caspase-3 activation via the formation of the apoptosome complex, a multimeric protein complex that contains Apaf-1 and caspase-9 besides cytochrome c (Kroemer et al., 2007). By comparison, activation of caspases is triggered by Smac/DIABLO via its opposing effect against IAPs (Kroemer et al., 2007).

Caspase-8: structure and function

Caspase-8 is one of the initiator caspases and belongs to the family of cysteine proteases (Degterev et al., 2003). As enzymes, caspases function as effector molecules of many forms of cell death and as such, play a central role in the execution phase of apoptosis (Degterev et al., 2003). In humans, the caspase-8 gene maps to chromosome 2q33 (Kischkel et al., 1998). From the structural point of view, caspase-8 is evolutionary highly conserved. For example, there is about 20% identity between mammalian caspase-8 and its homologue in the nematode c. elegans, which is the ced-3 protein (Degterev et al., 2003). Caspase-8 contains 480 amino acids and is a 55 kDa protein with two N-terminal death-effector domains (DED), which function as platforms for protein-protein interaction (Barnhart et al., 2003). The proteolytic domain is located at the C-terminus with a preferred substrate specificity of I/L/V/E X D, as caspase-8 belongs to the class of cysteine proteases (Degterev et al., 2003). Activation of caspase-8 results in the formation of an active heterotetramer of caspase-8 with two large and two small subunits (Degterev et al., 2003).

A number of different isoforms of caspase-8 with distinct functions can be distinguished. Isoforms caspase-8a and -8b are the pro-apoptotic variants that are most commonly expressed in mammalian cells (Scaffidi et al., 1997). Caspase-8 long (caspase-8L) is a splice variant, where a 136 bp insertion between exon 8 and exon 9 of full-length caspase-8 mRNA generates a premature stop codon via alternative splicing (Horiuchi et al., 2000; Himeji et al., 2002). This leads to the production of a truncated protein, which contains only the two N-terminal DED domains, but lacks the C-terminal protease domain (Horiuchi et al., 2000; Himeji et al., 2002). Accordingly, caspase-8L can be recruited into the DISC via its DED domains, but remains proteolytically inert due to absence of its protease domain (Miller et al., 2006; Mohr et al., 2005). Consequently, caspase-8L interferes in a dominant-negative manner with the transduction of the death signal from activated death receptors.

Besides its key role in the regulation of apoptosis, caspase-8 also has non-apoptotic properties, e.g. in the regulation of T cell homeostasis via control of IL-2 generation (Algeciras-Schimnich et al., 2002; Launay et al., 2005), in the control of differentiation and proliferation in the hematopoietic system (Algeciras-Schimnich et al., 2002; Launay et al., 2005) or in the regulation of adhesion, migration and metastasis in a complex manner (Stupack et al., 2006; Stupack and Cheresh, 2002; Senft et al., 2007; Helfer et al., 2006; Finlay and Vuori, 2007; Stegh et al., 2000). These data highlight the relevance of caspase-8 in various physiological contexts.

Caspase-8 is frequently inactivated in human cancers

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Evasion of apoptosis, a hallmark of human cancers, can be caused by the inactivation of caspase-8 via multiple mechanisms. These comprise genetic alterations, epigenetic modifications, alternative splicing or posttranslational changes. Mutations of caspase-8 have been detected at relatively low frequency, for example in head and neck carcinoma or colorectal and gastric cancer (Kim et al., 2003; Mandruzzato et al., 1997; Soung et al., 2005). In its mutated form, caspase-8 interferes with the recruitment of wild-type caspase-8 to activated death receptors in a dominant-negative fashion (Kim et al., 2003; Mandruzzato et al., 1997). Additionally, homo- or heterozygous genomic deletions of caspase-8 as well as allelic imbalance on chromosome 2q associated with alterations of the caspase-8 gene have also been described, e.g. in neuroblastoma (Teitz et al., 2000; Takita et al., 2001).

As far as epigenetic mechanisms are concerned, silencing of caspase-8 expression by hypermethylation of regulatory sequences of the caspase-8 gene has been detected in multiple cancers, including several pediatric cancers such as neuroblastoma, medulloblastoma, Ewing tumor, retinoblastoma and rhabdomyosarcoma as well as glioblastoma or lung carcinoma (Teitz et al., 2000; Fulda et al., 2001; Hopkins-Donaldson et al., 2003; Pingoud-Meier et al., 2003; Harada et al., 2002; Hopkins-Donaldson et al., 2000; Iolascon et al., 2003; Takita et al., 2000; Grotzer et al., 2000; Shivapurkar et al., 2002a; Shivapurkar et al., 2002b). As discussed in more detail in the previous section, alternative splicing of caspase-8 can result in the production of caspase-8L as a dominant-negative splice variant, for example in leukemia and neuroblastoma (Miller et al., 2006; Mohr et al., 2005). Another mechanism of inactivation is caused by inhibitory phosphorylation on tyrosine 308 of caspase-8, e.g. via Src kinase (Cursi et al., 2006). This phosphorylation event may also promote cell migration via caspase-8 (Barbero et al., 2008). Recent evidence suggests that loss of caspase-8 favors cellular transformation, at least in in vitro models (Krelin et al., 2008).

Conclusions

Since caspase-8 presents a key regulator of apoptosis, inactivation of caspase-8 can confer resistance to cell death. Genetic, epigenetic as well as posttranslational changes can contribute to inactivation of caspase-8 in human malignancies. Thus, restoration of caspase-8 function presents a promising strategy to either directly trigger apoptosis in cancer cells or to restore sensitivity for apoptotic stimuli.

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