Targeting apoptosis signaling pathways for anticancer therapy

Health & Medicine

Introduction

Tissue homeostasis is the result of a delicate balance of proliferation on one side and cell death on the other side (Evan and Vousden, 2001). Tipping this balance can contribute to either tumor formation or inappropriate tissue loss via too little or too much apoptosis (Fulda, 2009b). Apoptosis (also called programmed cell death) is a cellular death program that is inherent to all mammalian cells and plays an important role in the regulation of various physiological and pathological conditions (Taylor et al., 2008). For example, deregulation of apoptosis programs can lead to resistance of cancers to current treatment strategies, since the ability to activate cell death programs in cancer cells critically determines the efficacy of current cancer therapies (Makin and Dive, 2001 ; Johnstone et al., 2002 ; Fulda and Debatin, 2006). Furthermore, apoptosis of circulating tumor cells can have an impact on the metastatic process (Larson et al., 2004 ; Fehm et al., 2006). This calls for a better understanding of the regulatory mechanisms that control cell death and survival pathways in human cancers, since this knowledge is expected to translate into the development of new approaches to rationally and selectively target deregulated signaling pathways in cancer cells. This strategy will likely pave the avenue to an innovative approach to bypass treatment resistance in various human cancers.

Apoptosis Pathways

The central apoptotic machinery can be divided into two major signaling pathways, comprising the death receptor (extrinsic) and the mitochondrial (intrinsic) pathway (Fulda and Debatin, 2006). Both pathways eventually

fuel into a common effector phase that is characterized by the activation of caspases (Fulda and Debatin, 2006). Caspases are a family of proteases that act as common death effector molecules in various forms of cell death (Logue and Martin, 2008).

In the extrinsic pathway, the ligation of death receptors by their ligands including tumor necrosis factor (TNF) receptor, CD95 (APO-1/Fas), or TNF-related apoptosis-inducing ligand (TRAIL) receptors, initiates the formation of a multimeric protein complex called the death-inducing signaling complex (DISC) that drives activation of caspase-8 (Ashkenazi, 2008b). Caspase-8 can transmit the apoptosis signal directly by cleaving other caspases such as caspase-3 (Ashkenazi, 2008b). Alternatively, caspase-8 indirectly transfers the signal to apoptosis via mediators, for example Bid, a proapoptotic, BH3-only domain containing protein of the Bcl-2 family (Adams and Cory, 2007). Once Bid is cleaved by caspase-8, the resulting cleaved form tBid translocates to mitochondrial membranes to engage mitochondrial outer membrane permeabilization (Adams and Cory, 2007).

In the mitochondrial pathway, the release of apoptogenic factors such as cytochrome *c* or second mitochondrial activator of caspases (Smac) from the mitochondrial intermembrane space constitutes a key event that controls the activation of downstream apoptosis pathways (Fulda et al., 2010). To this end, mitochondrial proteins that are released from the mitochondrial intermembrane space in the course of mitochondrial outer membrane permeabilization are critical mediators (Kroemer et al., 2007). For example, cytochrome *c* initiates caspase-3 activation via the cytochrome *c*

/Apaf-1/caspase-9-containing apoptosome complex following its release into the cytosol (Kroemer et al., 2007). Smac, another mitochondrial intermembrane space protein, antagonizes “ inhibitor of apoptosis” (IAP) proteins via binding to these proteins, thereby releasing their inhibitory effect on caspases (Fulda et al., 2010).

Apoptosis pathways are tightly regulated by antiapoptotic factors to prevent their accidental activation. The same mechanisms that dampen the inappropriate initiation of cell death can also confer resistance in cancer cells, for example in the context of drug resistance. Therefore, these mechanisms of apoptosis resistance can be exploited as therapeutic targets to elicit cell death in cancer cells as discussed in more detail in the following chapters.

Exploiting Apoptosis Pathways for Cancer Therapy

Since the escape of apoptosis presents a characteristic feature of a variety of human cancers that plays an important role in promoting tumor formation and progression, there has been much interest to design strategies to target the apoptotic machinery in cancer cells. In principle, cell death pathways can be activated by agents that directly trigger apoptosis pathways. Alternatively, apoptosis-targeted therapies can be used to increase the responsiveness of human cancers toward classical treatment approaches that are currently used in clinical therapies, e. g., chemo-, radio-, or immunotherapy, as these therapies primarily exert their antitumor activity by inducing apoptosis in cancer cells.

Exploiting the Death Receptor (Extrinsic) Pathway

Alterations in the death receptor (extrinsic) pathway in human cancers

As far as the extrinsic pathway is concerned, alterations that interfere with signal transduction to apoptosis have been identified at various levels within the pathway. For example, surface expression of death receptors may simply be reduced or even completely absent in apoptosis-resistant cancers. Accordingly, downregulation of CD95 expression was detected in drug-resistant leukemia or neuroblastoma cells, linking CD95 signaling to drug sensitivity (Friesen et al., 1997 ; Fulda et al., 1998). Furthermore, the transport of death receptors, i. e., TRAIL receptors TRAIL-R1 and -R2, from intracellular stores such as the endoplasmatic reticulum to the cell surface may be defective resulting in resistance toward TRAIL as described in colon carcinoma (Jin et al., 2004). Moreover, genetic alterations may disturb death receptor expression or function. For example, mutations of the CD95 gene were reported in solid cancers and in hematological malignancies (Fulda, 2009a). Also, the chromosomal location of the two agonistic TRAIL receptors on chromosome 8p is frequently altered in human cancers, e. g., by loss of heterozygosity (LOH; Ashkenazi, 2008a). Deletions or mutations resulting in loss of both copies of TRAIL-R1 or -R2 have been detected in several cancers, e. g., non-Hodgkin’s lymphoma, colorectal, breast, head and neck cancer, osteosarcoma, or lung carcinoma (Pai et al., 1998 ; Dechant et al., 2004). Another mechanism of resistance is due to the expression of decoy receptors that interfere with death receptor signaling. To give one example, genetic amplification or overexpression of decoy receptor 3 (DcR3) has been reported as a resistance mechanism in CD95-triggered apoptosis in

lung or colon carcinoma as well as glioblastoma, as DcR3 competes with CD95 for CD95 ligand binding (Pitti et al., 1998 ; Roth et al., 2001). As far as decoy receptors in the TRAIL system are concerned, TRAIL-R3 has been shown to be overexpressed in gastric carcinoma (Sheikh et al., 1999).

In addition to genetic modifications, also epigenetic alterations can perturb death receptor signaling. Accordingly, hypermethylation of gene promoters of death receptors may impair their expression levels and may also contribute to immune escape (Van Noesel et al., 2002 ; Petak et al., 2003). Expression of epigenetically silenced CD95 could be restored upon treatment with histone deacetylase inhibitors, thereby enhancing NK cell-dependent cytotoxicity (Maecker et al., 2002).

Next, death receptor signaling may be disturbed because of insufficient formation of the DISC that is critical to drive caspase-8 activation. Overexpression of antiapoptotic molecules such as cFLIP or phosphoprotein enriched in diabetes/phosphoprotein enriched in astrocytes-15 kDa (PED/PEA-15) that block the recruitment of caspase-8 to the DISC (Hao et al., 2001 ; Krueger et al., 2001) frequently occurs in tumors and has been correlated with resistance to death receptor- and also to chemotherapy-induced apoptosis (Fulda et al., 2000 ; Longley et al., 2006). Caspase-8 expression can also be impaired by epigenetic silencing as reported in a variety of cancers including Ewing tumor, neuroblastoma, medulloblastoma, retinoblastoma, rhabdomyosarcoma, or small lung cell carcinoma both in cell lines as well as in primary tumor specimens (Teitz et al., 2000 ; Fulda et al.,

2001 ; Harada et al., 2002 ; Hopkins-Donaldson et al., 2003 ; Pingoud-Meier et al., 2003).

Strategies to target the death receptor pathway

Since the TRAIL ligand/receptor system presents the most promising target for therapeutic intervention and clinical translation among the death receptors, the following paragraph will focus on the use of TRAIL receptor agonists for the treatment of cancer. Intravenous infusion of even high doses of TRAIL showed no toxicity in chimpanzees and cynomolgus monkeys that were used as non-human primates (Ashkenazi et al., 1999). Similarly, TRAIL exerted no detectable cytotoxic activity against various non-malignant human cells of different lineages including fibroblasts, endothelial cells, smooth muscle cells, epithelial cells, or astrocytes (Lawrence et al., 2001). It is still not exactly known what determines the differential sensitivity of malignant versus normal cells toward TRAIL.

Recombinant soluble TRAIL proved to be a potent apoptosis-inducer in a large panel of preclinical studies both *in vitro* as well as *in vivo* (Ashkenazi, 2008a). Similarly, monoclonal TRAIL receptor antibodies targeting the proapoptotic TRAIL receptors TRAIL-R1 or -R2 resulted in suppression of tumor growth (Chuntharapai et al., 2001 ; Ichikawa et al., 2001). Of note, TRAIL-R2 antibody-based therapy also stimulated tumor-specific T cell memory, leading to protection from tumor relapse (Takeda et al., 2004). Further, several gene therapy approaches have been developed to deliver TRAIL specifically to tumor cells. Adenovirally expressed TRAIL yielded high expression levels of TRAIL resulting in tumor-specific induction of apoptotic

cell death with little transgene expression in non-malignant human primary mammary epithelial cells (Lin et al., 2002). Proof-of-concept studies were also performed using intralesional injection of adenoviral TRAIL, which led to growth inhibition of human breast cancer xenografts and tumor-free survival of mice (Lin et al., 2002).

Since TRAIL may not exert sufficient antitumor activity as monotherapy in most cancers for long-term suppression of tumor growth, various TRAIL-based combination therapies together with chemo-, radio-, or immunotherapy or targeted therapeutics have been developed. Cooperativity between TRAIL receptor agonists and DNA-damaging chemo- or radiotherapy occurred in a multitude of solid cancers as well as leukemia in cell lines and in mouse cancer models (Gliniak and Le, 1999 ; Chinnaiyan et al., 2000 ; Keane et al., 2000 ; Nagane et al., 2000 ; Belka et al., 2001 ; Rohn et al., 2001 ; Ray and Almasan, 2003 ; Singh et al., 2003). This synergism combining TRAIL and DNA-damaging insults may involve various mechanisms of action, e. g., transcriptional upregulation of the agonistic TRAIL receptors TRAIL-R1 and -R2 upon DNA damage in a p53-dependent or -independent manner (Takimoto and El-Deiry, 2000 ; Meng and El-Deiry, 2001) or increased formation of the CD95 or TRAIL DISC (Lacour et al., 2003). Recombinant TRAIL and TRAIL receptor antibodies are evaluated in early clinical trials as mono- or combination therapy, for example with chemotherapeutics (Younes and Aggarwall, 2003 ; Mom et al., 2005 ; Chow et al., 2006 ; Herbst et al., 2006 ; Patnaik et al., 2006 ; Tolcher et al., 2007).

In addition to triggering apoptosis, TRAIL has also been reported to stimulate proliferation and survival, at least under certain conditions. For example in TRAIL-resistant cancers, the addition of TRAIL was shown to result in proliferation in a NF-κB-dependent manner (Ehrhardt et al., 2003). Thus, TRAIL might not only be ineffective in resistant forms of cancers, but may paradoxically even enhance tumor growth.

Exploiting the Mitochondrial (Intrinsic) Pathway

Defects in the mitochondrial (intrinsic) pathway in human cancers

Apoptosis pathways can also be altered at the level of mitochondria in human cancers, leading to tumor formation and treatment resistance. For example, overexpression of antiapoptotic proteins of the Bcl-2 family such as Bcl-2 frequently occurs in various tumors. In follicular lymphoma, Bcl-2 is expressed at high levels because of chromosomal translocation of the Bcl-2 oncogene into the immunoglobulin heavy chain gene locus (Tsujimoto et al., 1984). Besides genetic alterations, aberrant Bcl-2 expression may also be caused by oncogenic activation of survival pathways, e. g., PI3K/Akt signaling. Another possible cause for the disturbed balance between pro- and antiapoptotic Bcl-2 family proteins are somatic mutations of the *bax* gene, a proapoptotic protein of the Bcl-2 family that plays a key role in the regulation of mitochondrial cytochrome *c* release. Colon cancer or hematopoietic malignancies that are mismatch repair-deficient were reported to harbor frameshift mutations or single nucleotide substitution of the *bax* gene (Rampino et al., 1997 ; Kitada et al., 2002). Furthermore, genetic alterations in BH3-only proteins, which also belong to the Bcl-2 family and harbor a BH3 domain only, have been detected in malignant tumors, e. g., homozygous

deletions of the *bim* gene in mantle cell lymphoma (Tagawa et al., 2005). The observation that *bid*- deficient mice spontaneously develop a myeloproliferative disease and subsequently a chronic myelomonocytic form of leukemia (Zinkel et al., 2003) further supports the notion that proapoptotic Bcl-2 proteins may exert tumor suppressive functions.

Moreover, the mitochondrial pathway of apoptosis can also be impaired in human cancers at the postmitochondrial level, for example by decreased or absent activity of Apaf-1 in melanoma and leukemia that contributes to caspase-3 activation via formation of the apoptosome complex (Soengas et al., 2001 ; Fu et al., 2003). Abnormal expression of IAP proteins can impair effector caspase activation, thereby interfering with the common effector phase of both the death receptor and the mitochondrial pathway. Factors that can contribute to aberrant expression of IAP proteins include increased mRNA or protein expression (Tamm et al., 2000), enhanced protein stability, e. g., due to phosphorylation by Akt (Dan et al., 2004) or chromosomal translocation, for the *t* (11; 18; q21; q21) translocation that leads to aberrant *cIAP2* gene expression that frequently occurs in mucosa-associated lymphoid tissue (MALT) lymphoma (Dierlamm et al., 1999). Alternatively, loss of endogenous antagonists such as XAF1 can result in unrestrained signaling of IAP proteins (Tamm et al., 2000 ; Chakravarti et al., 2002 ; Byun et al., 2003). Overexpression of survivin can antagonize apoptosis by binding to Smac, thereby releasing XIAP to block caspase activation (Song et al., 2003 ; Dohi et al., 2004).

Cancer therapeutics targeting Bcl-2 family proteins

A variety of approaches have been developed over the years to neutralize antiapoptotic Bcl-2 proteins. A prototype example is the design of small molecule inhibitors that interfere with the protein–protein interaction site of antiapoptotic Bcl-2 proteins (i. e., Bcl-2, Bcl-X_L, Bcl-w) and the multidomain proteins Bax or Bak (Oltersdorf et al., 2005). The first generation compound originating from this development program is ABT-737 (Oltersdorf et al., 2005), which has been reported to either directly trigger apoptosis or enhance the sensitivity to apoptosis in combination treatments (Oltersdorf et al., 2005). To this end, ABT-737 acted together with various classical anticancer drugs to trigger apoptosis (Oltersdorf et al., 2005 ; Konopleva et al., 2006 ; Van Delft et al., 2006). High levels of Mcl-1 expression have been associated with resistance to ABT-737, as ABT-737 does not antagonize Mcl-1, another antiapoptotic member of the Bcl-2 family (Konopleva et al., 2006 ; Van Delft et al., 2006). This Mcl-1-mediated resistance can be overcome by combination strategies, e. g., using proteasome inhibitors that trigger upregulation of Noxa, a BH3-only domain protein that specifically antagonizes Mcl-1, or alternatively CDK inhibitors (e. g., roscovitine, flavopiridol, seliciclib) or Raf/Mek inhibitors such as sorafenib, which all proved to augment the cytotoxicity following treatment with ABT-737 (Chen et al., 2001 ; Konopleva et al., 2006 ; Van Delft et al., 2006 ; Lin et al., 2007 ; Tahir et al., 2007).

Besides small molecule inhibitors, antisense strategies against antiapoptotic Bcl-2 proteins were developed (Tolcher et al., 2005). The most prominent example are Bcl-2 antisense oligonucleotides, which have been evaluated

both as single agents as well as in combination with chemotherapy (Tolcher et al., 2005). Furthermore, BH3 peptides mimicking BH3-only domain proteins have been designed to directly engage the multidomain proapoptotic Bax and Bak proteins (Letai et al., 2002). Together, these tools to neutralize antiapoptotic Bcl-2 proteins are considered as promising strategies to engage the mitochondrial pathway of apoptosis in cancer cells.

Exploiting “ Inhibitor of Apoptosis” Proteins

“ Inhibitor of apoptosis” proteins comprise a family of endogenous caspase inhibitors highly conserved in evolution (Lacasse et al., 2008). The human analogs include eight members, i. e., neuronal apoptosis inhibitory protein (NAIP/BIRC1/NLRB) cellular IAP1 (cIAP1)/human IAP2 (HIAP2)/BIRC2, cellular IAP2 (cIAP2)/human IAP1 (HIAP1)/BIRC3, X-linked IAP (XIAP)/BIRC4, survivin/BIRC5, BIR-containing ubiquitin conjugating enzyme (BRUCE)/apollon/BIRC6, livin/melanoma-IAP (ML-IAP)/BIRC7/KIAP, and testis-specific IAP (Ts-IAP)/hILP-2/BIRC8; Lacasse et al., 2008). To be classified as IAP proteins, they contain at least one baculoviral IAP repeat (BIR) domain of 70–80 amino acids. Additional domains include the really interesting new gene (RING) domain harboring E3 ubiquitin ligase activity and the caspase activating and recruitment domain (CARD) domain, a motif for protein–protein interaction (Lacasse et al., 2008).

Cancer Therapeutics Targeting “ Inhibitor of Apoptosis” Proteins

In order to design inhibitors that mimic the apoptosis-inducing properties of the endogenous IAP antagonist Smac, the groove of the BIR3 domain of XIAP has served as a scaffold that binds the native Smac protein upon its release into the cytosol (Shiozaki and Shi, 2004). For example, Smac peptides

comprising the N-terminal amino acid stretch of Smac that is critical for its interaction with XIAP proved to trigger caspase activation and to prime cancer cells for apoptosis together with other cytotoxic stimuli (Fulda et al., 2002). For enhanced intracellular uptake such Smac peptides were coupled to various forms of carrier proteins (Arnt et al., 2002 ; Fulda et al., 2002 ; Yang et al., 2003). Furthermore, the design of Smac peptidomimetics binding to XIAP-BIR3, cIAP1-BIR3, cIAP2-BIR3, or livin-BIR domains resulted in potent apoptosis sensitizers in combination therapies, e. g., together with TRAIL, TNFα, or chemotherapeutics (Li et al., 2004 ; Sun et al., 2004a , b , 2005 , 2006 ; Bockbrader et al., 2005 ; Zobel et al., 2006). IAP antagonists also engage cell death pathways by initiating autoubiquitination of cIAPs leading to activation of non-canonical NF-κB and TNFα-mediated apoptosis (Petersen et al., 2007 ; Varfolomeev et al., 2007 ; Vince et al., 2007). Furthermore, antisense oligonucleotides targeting XIAP demonstrated antitumor activity in preclinical models both as monotherapy as well as in combination with anticancer drugs (Lacasse et al., 2005 , 2006). Taken together, strategies to antagonize IAP proteins present promising novel approaches to induce apoptotic cell death in cancer cells or to lower the threshold for the induction of apoptosis.

Conclusion

Intact apoptosis programs are critically required for the antitumor activity of most current cancer therapies that are used in clinical oncology. However, apoptosis signaling pathways are frequently disturbed at various levels in human cancers. Further insights into the regulation of apoptosis signaling pathways in response to anticancer drug treatment will likely have important

implications for the development of molecular targeted therapies. In addition, targeting apoptosis pathways in circulating tumor cells may present a means to interfere with metastasis. Several strategies to target elements of the apoptotic machinery in cancer cells have already progressed up to clinical evaluation. Such strategies may pave the avenue to more effective cancer treatments.

Conflict of Interest Statement

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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