Seminars in Cancer Biology 31 (2015) 84–88

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

Targeting apoptosis for anticancer therapy

Simone Fulda*

Institute for Experimental Cancer Research in Pediatrics, Goethe-University, Komturstr. 3a, 60528 Frankfurt, Germany

ARTICLE INFO

Keywords:
Apoptosis
Cell death
Cancer
Death receptor
Mitochondria

ABSTRACT

Programmed cell death via apoptosis is characteristically disturbed in human cancers. This facilitates not only tumor formation and progression, but also treatment resistance. Since many currently applied anticancer treatment strategies rely on intact cell death signaling pathways for their therapeutic efficacy, a better understanding of the regulatory mechanisms that control cell death signaling pathways is critical to bypass resistance. Thus, reactivation of cell death programs in cancer cells may open new perspectives for more effective and more tumor-selective, yet less toxic anticancer therapies.

1. Introduction

Programmed cell death is a fundamental cellular program that is inherent in every cell of the human body [1]. Apoptosis represents one of the most extensively studied forms of programmed cell death that plays a critical role during various physiological processes as well as in a variety of pathological conditions [1]. Against the background that tissue homeostasis is maintained by a subtle balance between cell death on one side and cell proliferation on the other side, any changes in one of these parameters can form the basis for human diseases. The fact that under normal conditions apoptosis represents a safeguard mechanism to prevent tumorigenesis implies that evasion of apoptosis constitutes a characteristic feature of human cancers [2]. Too little cell death not only contributes to cancer formation, but also to cancer progression and treatment resistance [3]. A better understanding of the mechanisms that are involved in the regulation of apoptosis and their dysregulation in human cancers is expected to provide novel opportunities for exploiting this cellular program for cancer therapy.

2. Apoptosis programs

Two principal apoptosis signal transduction pathways have been delineated that constitute the basic machinery for triggering apoptosis in mammalian cells [4]. First, the death receptor (extrinsic) pathway links signals from the exterior of the cell into the intracellular signal transduction machinery to engage apoptosis [5]. Cell surface receptors of the death receptor family are integrated into the plasma membrane and become activated upon ligation by their cognate ligands. Death receptors comprise CD95 (Fas/Apo1), Tumor-Necrosis-Factor-related apoptosis-inducing ligand (TRAIL) receptors as well as tumor necrosis factor (TNF) receptor [5]. Corresponding death receptor ligands are CD95 ligand, TRAIL and TNFα [5]. Ligation of death receptors by their ligands leads to oligomerization of death receptors followed by the recruitment of adaptor molecules to the intracellular part of death receptors. This results in the formation of a multimeric protein complex at the plasma membrane, the so-called death-inducing signaling complex (DISC), that drives activation of caspase-8. Once activated, caspase-8 can either directly cleave downstream effector caspases such as caspase-3 or can indirectly initiate activation of the mitochondrial (intrinsic) pathway of apoptosis via proteolytic cleavage of Bid into tBid. tBid in turn translocates to mitochondrial membranes to initiate mitochondrial outer membrane permeabilization, e.g. via interaction with other Bcl-2 family proteins on mitochondrial membranes.

Within the mitochondrial (intrinsic) pathway of apoptosis, apoptotic stimuli trigger the release of mitochondrial intermembrane space proteins including cytochrome c and second mitochondria-derived activator of caspases (Smac) into the cytosol [6]. Cytochrome c promotes activation of caspases by forming a protein complex composed of cytochrome c, Apaf-1 and caspase-9, leading to caspase-9 and subsequently caspase-3 activation. Smac facilitates apoptosis by neutralizing Inhibitor of Apoptosis (IAP) proteins [6]. This Smac mimetic-mediated inhibition of IAP proteins releases the brake on caspases resulting in caspase activation and eventually cell death.

Signaling to apoptosis is tightly regulated at various levels to ensure that this program is not accidentally activated, as inappropriate engagement of apoptosis programs imposes a serious threat to the cell's survival. These physiological restraints on apoptosis signaling pathways have been abused by cancer

* Tel.: +49 69 67866557; fax: +49 69 6786659157.
E-mail address: simone.fulda@kgu.de

http://dx.doi.org/10.1016/j.semcancer.2014.05.002
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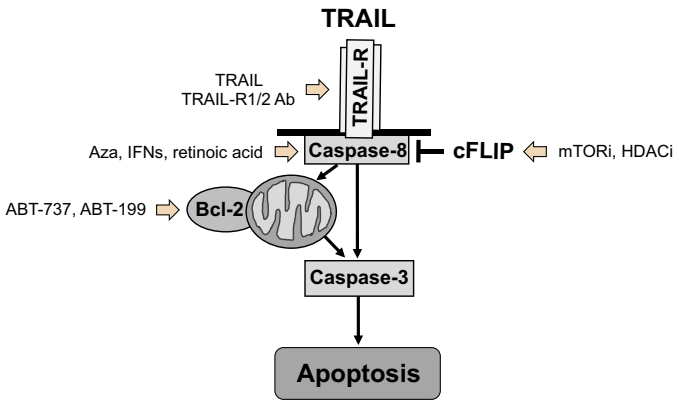

Fig. 1. Examples of targeting apoptosis pathways for cancer therapy. The death receptor pathway can be targeted by engaging TRAIL receptors using TRAIL or TRAIL receptor 1 or 2 antibodies (TRAIL-R1/2 Ab), by restoring caspase-8 expression using 5-aza-2′-deoxycytidine (Aza), interferons (IFNs) or retinoic acid and by downregulating cFLIP using mTOR inhibitors (mTORi) or histone deacetylase (HDAC) inhibitors. The mitochondrial receptor pathway can be targeted by antagonizing antiapoptotic Bcl-2 family proteins using ABT-737 or ABT-199.

cells in order to evade apoptosis. For example, various antiapoptotic factors are expressed at high levels in cancer cells and confer apoptosis resistance. Moreover, cancer cells have evolved mechanisms to inactivate proapoptotic molecules in order to escape the induction of apoptosis. In addition to caspase-dependent apoptosis, also caspase-independent forms of apoptotic cell death exist. For example, apoptosis-inducing factor (AIF) and endonuclease G (ENDOG) were described as mitochondrial intermembrane proteins that cause large-scale DNA fragmentation independently of caspases upon their translocation to the nucleus [7,8].

3. Therapeutic opportunities to exploit apoptosis for cancer therapy

The elucidation of the molecular mechanisms that underlie the intrinsic apoptosis resistance of human cancers over the last decades has led to the identification of target structures that can be exploited for therapeutic purposes. The following paragraphs will focus on key target structures for the development of apoptosis-targeted drugs (Fig. 1).

4. Target 1: death receptor pathway

Signaling to apoptosis via the death receptor pathway can be disabled at various levels of the signal transduction cascade in human cancers. At the level of the plasma membrane, cell surface expression of death receptors can be impaired. Decreased surface expression of CD95 has been reported in drug-resistant variants of leukemia or neuroblastoma cells and has been connected to drug resistance [9]. In addition to CD95, alterations in TRAIL receptors have been implicated as a mechanism of resistance. This involves deficient transport of TRAIL receptors from intracellular stores toward the cell surface as well as deletions or mutations in genes encoding for the apoptosis-promoting TRAIL receptors TRAIL-R1 or -R2 [10–12]. Similarly, CD95 mutations were encountered, for example, in hematological malignancies [13,14]. In addition, aberrant expression of the decoy receptor TRAIL-R3 has been linked to apoptosis resistance, as the TRAIL system not only comprises proapoptotic TRAIL receptors that engage apoptosis, but also decoy receptors that are expressed at the cell surface, but do not transmit a death signal [15].

Apart from genetic causes, epigenetic mechanisms have frequently been shown to be involved in conferring apoptosis resistance. Epigenetic inactivation of key apoptosis regulatory proteins involves not only silencing of death receptors such as CD95 or TRAIL receptors but also epigenetic inactivation of key components of the intracellular signal transduction machinery that mediate death receptor signaling. One prominent example is epigenetic silencing of caspase-8, one of the initiator caspases that usually becomes activated upon formation of the DISC upon receptor ligation [16]. Silencing of caspase-8 has been reported in a variety of pediatric malignancies, including neuroblastoma, medulloblastoma, Ewing sarcoma and rhabdomyosarcoma in addition to small-cell lung carcinoma, and has been linked to evasion of apoptosis [17–21].

Another key regulator of death receptor signaling is cellular FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein (cFLIP) that blocks apoptosis by interfering with the recruitment of caspase-8 to the DISC [22]. Overexpression of cFLIP has been implicated in conferring resistance to apoptosis induced by death receptor stimulation or by anticancer drugs in a variety of cancers [23,24].

Death receptors provide a suitable structure for targeted interference with apoptosis signaling pathways, since they contain as transmembrane receptors both an extracellular domain for binding of recombinant ligands or agonistic antibodies as well as an intracellular domain for interaction with signaling proteins. Recombinant death receptor ligands as well as therapeutic antibodies directed against death receptors have been developed in order to engage death receptors on the surface of cancer cells. Since ligation of TNFR1 by TNFα not only leads to the induction of cell death, but also provides an inflammatory signal, systemic administration of TNFα proved to be associated with severe toxicity [25]. Therefore, the exploitation of the TNFα/TNFR1 system for cancer therapy has mainly been restricted to local administration of TNFα, for example using isolated limb perfusion to deliver high doses of TNFα locoregionally [25].

By comparison, the TRAIL/TRAIL receptor system is considered as a promising representative of the death receptor family for cancer therapy, especially since TRAIL has been shown to preferentially trigger cell death in cancer cells compared to non-malignant human cells. Pharmacokinetic and pharmacodynamic studies in non-human primates confirmed the safety of TRAIL administration even at relatively high concentrations [5]. TRAIL receptor agonists including recombinant TRAIL as well as humanized antibodies against the agonistic TRAIL receptors have been evaluated in early clinical trials both as single agents as well as in various combination regimens [26–29]. However, the clinical trials did not recapitulate the promising results obtained in preclinical in vivo models, which might be due to insufficient cross-linking of TRAIL receptors by the available TRAIL agonists. Preclinical studies have also demonstrated the requirement of rationally designed TRAIL-based combination therapies in order to maximize the antitumor activity of TRAIL. To this end, various combinations have been developed, including conventional chemotherapeutics, radiotherapy and targeted signal transduction modulators. The synergistic interaction of TRAIL receptor agonists together with DNA-damaging therapeutics, including DNA-damaging drugs or radiotherapy, has been linked to the upregulation of TRAIL receptors in response to DNA damage [30,31]. In addition, enhanced assembly of the TRAIL DISC upon DNA damage has been proposed to confer increased sensitivity in TRAIL-based combination regimens [32]. Also, modulation of pro- and antiapoptotic signaling molecules in response to DNA-damaging agents may account for the increased apoptosis sensitivity by changing the ratio of pro- versus antiapoptotic factors in favor of apoptosis [4].