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Review

Therapeutic opportunities based on caspase modulation

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ABSTRACT

Caspases are a family of proteolytic enzymes that play a critical role in the regulation of programmed cell death via apoptosis. Activation of caspases is frequently impaired in human cancers, contributing to cancer formation, progression and therapy resistance. A better understanding of the molecular mechanisms regulating caspase activation in cancer cells is therefore highly important. Thus, targeted modulation of caspase activation and apoptosis represents a promising approach for the development of new therapeutic options to elucidate cancer cell death.

Contents

1. Introduction

Programmed cell death is an intrinsic program that is evolutionary highly conserved [1]. Programmed cell death is not only important during embryonal development and a series of physiological processes, but also highly relevant for many human diseases [1]. This is due to the fact that tissue homeostasis critically depends on the balance between cell growth and cell death. This implies that deregulation of the ratio of cell growth and cell death can lead to various human diseases. One prominent example of too little cell death under pathophysiological conditions is cancer [2]. Of note, a decreased rate of cell death promotes tumorigenesis, progression as well as resistance to current cancer therapies [3]. Among the various forms of cell death apoptosis is one of the best char-

Abbreviations: 5-Aza, 5-Aza-2-deoxycytidine; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BIR, baculoviral inhibitor of apoptosis repeat; CAD, caspase-activated deoxyribonuclease; CDK, cyclin-dependent kinase; cIAP, cellular inhibitor of apoptosis; CLL, chronic lymphocytic leukemia; FADD, fas-associated protein with death domain; HDAC, histone deacetylase; HDACIs, HDAC inhibitors; IAP, inhibitor of apoptosis; IFN, interferon; ILP2, inhibitor of apoptosis-like protein 2; IRF, interferon-regulatory factor; ML-IAP, melanoma inhibitor of apoptosis; MOMP, mitochondrial outer membrane permeabilization; NAIP, neuronal apoptosis inhibitory protein; NF-κB, nuclear factor-kappa B; NIK, NF-κB-inducing kinase; RING, Really Interesting New Gene; RIP, receptor-interacting protein; Smac, second mitochondria-derived activator of caspases; TMZ, temozolomide; TNF, tumor necrosis factor; TNFR, TNF receptor; TRAIL, TNF-related apoptosis-inducing ligand; XIAP, X-chromosome-linked Inhibitor of Apoptosis.

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acterized [1]. Elucidation of the molecular mechanisms regulating apoptosis advances our understanding of this key cellular program and also provides the basis for exploiting apoptosis for therapeutic purposes.

2. Apoptosis programs

The engagement of apoptosis via a large variety of stimuli leads to the activation of signal transduction pathways that typically fuel into the activation of caspases [4]. Caspases are a family of cysteine proteases that share high homology across different species [4]. There are a large number of target proteins that are cleaved upon caspase activation, for example the inhibitor of caspase-activated deoxyribonuclease (CAD) [5] which inactivates its CAD-inhibitory effect, thereby enabling activation of CAD that is responsible for internucleosomal DNA degradation during apoptosis [6]. In principle, two main signal transduction pathways can result in the activation of caspases [7]. There is the death receptor (extrinsic) pathway where transmembrane cell surface receptors named death receptors are engaged by binding of their corresponding death receptor ligands to transmit extracellular signals into the cell [8]. CD95 (Fas/Apo1), tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptors and TNF receptors are well-known examples of death receptors with CD95 ligand, TRAIL and TNFα as their cognate ligands [8]. Upon binding, the death receptors become oligomerized which initiates the recruitment of adaptor and signaling proteins to form signaling complexes that can lead to the activation of caspase-8. Activated caspase-8 transmits the apoptotic signal by cleaving caspase-3 as one of the key effector caspases. Alternatively, activated caspase-8 can cleave Bid into tBid, which translocates to mitochondrial membranes where it binds to other BCL-2 family proteins to engage the mitochondrial (intrinsic) pathway of apoptosis. Upon the engagement of the mitochondrial (intrinsic) pathway of apoptosis, the mitochondrial outer membrane becomes permeabilized leading to the release of apoptogenic proteins from the intermembrane space of mitochondria into the cytosol, including cytochrome c and second mitochondria-derived activator of caspases (Smac) [9]. Cytochrome c drives the activation of caspases by stimulating the formation of a complex called the apoptosome that comprises cytochrome c, APAF-1 and caspase-9, thereby promoting the activation of caspase-9 and subsequently caspase-3. Smac supports caspase activation by binding to Inhibitor of Apoptosis (IAP) proteins [9], which disrupts the interaction of IAP proteins with caspase-3, -7 and -9, thereby facilitating their activation.

3. Therapeutic opportunities to trigger apoptosis based on the activation of caspases

The elucidation of the molecular mechanisms of apoptosis over the last decades has led to the identification of suitable target structures that can be exploited for the activation of programmed cell death, for example in cancer. The following paragraphs will focus on key target structures for the development of apoptosis-targeted drugs that eventually cause activation of caspases as downstream effector proteins.

3.1. Targeting death receptors

Death receptors provide a suitable structure for targeted activation of apoptosis signaling pathways, since as transmembrane receptors they contain, on the one side, an extracellular domain that connects to the extracellular microenvironment by binding recombinant ligands or agonistic antibodies and, on the other side, an intracellular domain for the interaction with signaling proteins. To activate transmembrane death receptors a variety of therapeutic antibodies as well as recombinant death receptor ligands have been developed. As far as the TNFα/TNFR1 system is concerned, its exploitation for cancer therapy is largely limited to local administration of TNFα, since systemic administration of TNFα causes severe toxicity [10]. One example of therapeutic exploitation of TNFα is the loco-regional administration of high TNFα doses that is used for isolated limb perfusion [10].

The TRAIL receptor ligand pair is considered as the most promising death receptor ligand system for the design of cancer therapeutics. Potentially, there might be a therapeutic window for using TRAIL receptor agonists in the clinic, since a preferential sensitivity of cancer *versus* non-malignant cells towards TRAIL has been reported [8]. The existence of both agonistic TRAIL receptors (i.e. TRAIL-R1 and -2) and antagonistic TRAIL receptors (i.e. TRAIL-R3 and -4) might contribute to this tumor selectivity. However, via its receptors TRAIL can also trigger additional non-apoptotic signaling events which might not only antagonize the induction of cell death upon exposure to TRAIL receptor agonists, but also support their malignant phenotype of cancer cells by stimulating their proliferation, invasion, migration, and metastasis [11]. Thus, the engagement of TRAIL receptors can paradoxically increase instead of decrease apoptosis, depending on the context.

In the last two decades agonistic antibodies directed against the agonistic TRAIL receptors as well as soluble recombinant TRAIL have been developed to target the TRAIL receptor ligand system. For the use in clinical protocols, fully human antibodies selectively targeting the agonistic receptors TRAIL-R1 or TRAIL-R2 have been developed that were evaluated as single agents as well as together with a range of different other anticancer agents [12–14]. Besides monoclonal antibodies, a recombinant version of human TRAIL has been designed [15]. However, all in all these clinical studies testing TRAIL receptor agonists did not meet the expectations, as anticipated based on a large set of very promising preclinical data. As one possible explanation for the limited clinical efficacy, it has been discussed that the ability of clinical-grade TRAIL receptor agonists was insufficient to ensure potent crosslinking of human TRAIL receptors. In recent years, this has led to the design of a new series of TRAIL receptor agonists that comprise multivalent TRAIL receptor-binding sites and exhibit superior clustering ability [16]. Also, a large variety of TRAIL-based combination therapies has been developed to maximize the ability of TRAIL receptor agonists to trigger caspase activation and apoptosis. This includes conventional chemotherapeutics that cause DNA damage and have been shown to enhance the potency of TRAIL by upregulating DNA damage-responsive genes including proapoptotic factors [17–23]. Another class of agents that has been found to synergize with TRAIL receptor agonists are histone deacetylase (HDAC) inhibitors (HDACIs) that can re-modulate the chromatin, thereby changing the overall ratio of factors that promote or inhibit apoptosis in favor of cell death [24–29]. Also, the inhibition of the proteasome has been identified as a mean to sensitize cells to TRAIL-induced apoptotic proteins [30–37]. Several mechanisms have been implicated in this proteasome inhibitor-conferred sensitization to TRAIL, including upregulation of agonistic TRAIL receptors or other proapoptotic factors, suppression of antiapoptotic factors or increased assembly of the TRAIL receptor-associated signaling complex that transmits the cell death signal from the membrane to the intracellular components [30–37].

3.2. Targeting caspases

Caspase-8 represents a critical initiator caspase that plays an important role, for example, in mediating the activation of effector caspases in the death receptor pathway of apoptosis [38].

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