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Review

Targeting extrinsic apoptosis in cancer: Challenges and opportunities

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ABSTRACT

Apoptosis is a form of programmed cell death that plays a critical role in the regulation of various physiological and pathophysiological processes. Since apoptosis is typically disturbed in human cancers, therapeutic targeting of apoptosis represents a promising avenue for the development of novel therapeutic approaches. This strategy is particularly relevant, since many currently used anticancer therapies utilize apoptosis signaling pathways to exert their antitumor activities. A better understanding of these signaling networks and their deregulation in human cancers is anticipated to open new perspectives for the development of apoptosis-targeted therapies for the treatment of cancer.

Contents

1. Introduction

Programmed cell death represents an intrinsic cellular program that plays a crucial role in the regulation of various physiological conditions as well as pathological states [1]. Among the different forms of programmed cell death, apoptosis is one of the best characterized and most intensively investigated modes of programmed cell death [2]. Tissue homeostasis is the result of a delicate balance between cell growth, survival and/or proliferation on one side and programmed cell death, e.g. via apoptosis, on the other side. This implies that already subtle alterations in the relative contribution of cell growth versus cell death can result in too high or too low cell numbers which could be the cause of pathological conditions leading to human diseases. Conceptually, apoptosis can be viewed as a safeguard mechanism that is in place to control tissue homeostasis. For example, in the context of cancer, apoptosis poses a barrier against cancer formation by eliminating pre-cancerous cells from survival and multiplication. Consequently, decreased cell death by apoptosis can contribute to carcinogenesis as well as to progression of cancer once it has been established [3]. In addition, defects in apoptosis programs can lead to treatment resistance, since most anticancer therapies, including chemotherapy, radiation or immunotherapy, primarily act by engaging this intrinsic cell death program in cancer cells. Thus, a hallmark of cancer resides in

Abbreviations: 5-Aza, 5-Aza-2′-deoxycytidine; cFLIP, cellular FLICE inhibitory protein; CREB, cAMP response element-binding protein; DEDs, death effector domains; DISC, death-inducing signaling complex; FADD, Fas-Associated protein with Death Domain; HDAc, histone deacetylase; IAP, Inhibitor of Apoptosis; LOH, loss of heterozygosity; PPAR-γ, proliferator-activated receptor-γ; RIP1, receptor-interacting protein 1; TNF, tumor necrosis factor; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand.

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the ability to evade apoptosis in order to be able to grow and survive [4]. Taking these aspects into consideration, a better understanding of the molecular events that are in place to control apoptosis induction and execution as well as the mechanisms that lead to dysregulation of programmed cell death will likely be instrumental to develop rational approaches for targeting apoptosis pathways in the treatment of human cancers. The current review focusses on targeting the death receptor pathways of apoptosis.

2. Signaling via the death receptor pathway

In principle, signal transduction to apoptosis can proceed via two main signaling pathways, i.e. the death receptor (extrinsic) and the mitochondrial (intrinsic) pathway of apoptosis [5]. The death receptor pathway of apoptosis provides a connection to the extracellular surroundings and links signals coming e.g. from the microenvironment to the intracellular signaling networks that eventually control the execution of programmed cell death [6]. At this interface, receptors of the death receptor family of proteins at the cell membrane can translate cues from the extracellular space and neighboring cells to signaling components at the cell membrane and in the cytoplasm.

The death receptor family of proteins comprises a variety of cell surface receptors including CD95 (Fas/Apo1), tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptors and TNF receptors [6]. For each of these death receptors, cognate ligands exist that activate these receptors upon binding, such as CD95 ligand, TNFα as well as TRAIL [6]. The signal transduction sequence of events starts with binding of death receptor ligands to their corresponding death receptors on the cell surface which in turn results in death receptor aggregation, recruitment of signaling proteins to the intracellular domain of death receptors, formation of a multiprotein signaling platform called the death-inducing signaling complex (DISC) at the plasma membrane, followed by activation of signaling events that initiate the apoptotic process. In the context of CD95 and TRAIL receptors, this signaling cascade involves activation of the initiator caspase-8 as a critical event which engages signaling of the caspase cascade to mediate apoptosis. Upon activation, caspase-8 can directly cleave other caspases including caspase-3 or, alternatively, can promote the engagement of the mitochondrial pathway by proteolytic processing of Bid, a proapoptotic protein of the Bcl-2 family. Upon cleavage, tBid travels to mitochondrial membranes where it contributes to mitochondrial perturbations.

Apart from the death receptor pathway of apoptosis, the mitochondrial pathway exerts key regulatory functions [7]. A large variety of upstream signals and second messengers impinge on the control of mitochondrial outer membrane permeabilization as a critical step that marks engagement of the mitochondrial pathway of apoptosis in the course of cell death [7]. This involves the release of mitochondrial intermembrane space proteins from mitochondria into the cytosol. For example, cytochrome c is one of the mitochondrial intermembrane space proteins that is released in the course of apoptosis and triggers activation of caspases by building a multiprotein complex comprising cytochrome c, Apaf1 and caspase-9 in the cytosol, the so-called apoptosome [8]. Within this complex, the initiator caspase-9 is activated by induced proximity and in turn cleaves and activates caspase-3 to engage the caspase cascade. Besides cytochrome c, also Smac is released from the mitochondrial intermembrane space proteins in the course of apoptosis [9]. Smac promotes the induction of apoptosis by binding to and antagonizing antiapoptotic proteins of the Inhibitor of Apoptosis (IAP) family of proteins. Neutralization of IAP proteins by Smac disrupts the binding of IAP proteins to caspases, thereby releasing IAP protein-imposed inhibition of caspases which in turn results in apoptosis [9].

Engagement of the death receptor pathway of apoptosis eventually leads to activation of caspases which constitute key effector molecules of apoptosis [10]. By proteolytic processing of a large variety of different substrates, caspase activation contributes to many of the characteristic features of apoptotic cell death, including DNA fragmentation, cellular shrinkage and exposure of phosphatidylserine on the outer surface of the plasma membrane [10].

Since the apoptotic machinery represents a powerful instrument to execute cell death, it is pivotal for cellular homeostasis to tightly control this program in order to prevent its accidental activation. Accordingly, there are different layers of built-in control mechanisms including pro- and antiapoptotic proteins that regulate the signal transduction events at different levels of the cascade. It is interesting to note that cancer cells have developed the ability to misuse these physiological regulatory mechanisms in order to evade apoptosis and to survive [3]. Many antiapoptotic proteins are aberrantly expressed at high levels in cancer cells, whereas proapoptotic proteins are typically inactivated or even lost during the malignant process [3]. For example, cellular FLICE inhibitory protein (c-FLIP) is an antiapoptotic protein that blocks signaling via the death receptor pathway of apoptosis by preventing activation of caspase-8 within the DISC [11]. Genetic alterations including loss of heterozygosity (LOH), mutations or deletions as well as epigenetic events and post-translational modifications can lead to dysregulation of apoptosis signaling components in human cancers. This implies that such aberrations in apoptosis signaling pathways can be used as targets for the development of therapeutic approaches to reactivate apoptosis signaling networks in cancer cells for the treatment of human cancers.

3. Targeting the death receptor pathway for cancer therapy

A better understanding of the molecular events that regulate the apoptotic signaling network provides the basis for exploiting this program for cancer therapy. Since evasion of apoptosis belongs to the hallmarks of human cancers, reactivation of apoptosis represents a promising avenue for the development of novel and more effective cancer therapeutics. Targeting the death receptor pathway is of particular interest for cancer therapy, since death receptors on the cell surface can be accessed from the exterior via therapeutic antibodies or the use of recombinant death receptor ligands [6]. In addition, death receptors provide a direct link to the intracellular signaling machinery of cell death.

4. Targeting the TRAIL system

Among the different death receptor ligand systems, the TRAIL/TRAIL receptor system has gained most attention in the last decade as target for the development of cancer therapeutics. This is at least in part due to the fact that TRAIL has been reported to preferentially trigger cell death in malignant versus non-malignant cells, thereby providing a potential therapeutic window that can be exploited for the treatment of cancer [6]. The TRAIL receptor system comprises two agonistic TRAIL receptors (i.e. TRAIL-R1 and -2) as well as two antagonistic TRAIL receptors (i.e. TRAIL-R3 and -4). This built-in ability in the TRAIL receptor system to promote or antagonize apoptosis may provide the basis for the tumor selectivity of TRAIL, but may also cause primary or secondary resistance. Since TRAIL can bind to all four of these TRAIL receptors, the relative expression of agonistic versus antagonistic TRAIL receptors