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Review

The role of XIAP in resistance to TNF-related apoptosis-inducing ligand (TRAIL) in Leukemia

Raedeh Saraei[a,b,c], Masoud Soleimani[d], Ali Akbar Movassaghpour Akbari[e], Majid Farshdousti Hagh[e,f], Ali Hassanzadeh[c], Saeed Solali[a,e,*]

[a] Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Department of Immunology, Division of Hematology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[d] Department of Hematology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
[e] Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[f] Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

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ABSTRACT

The treatment for leukemic malignancies remains a challenge despite the wide use of conventional chemotherapies. Therefore, new therapeutic approaches are highly demanded. TNF-related apoptosis-inducing ligand (TRAIL) represents a targeted therapy against cancer because it induces apoptosis only in tumor cells. TRAIL is currently under investigation for the treatment of leukemia. Preclinical studies evaluated the potential therapeutic efficacy of TRAIL on cell lines and clinical samples and showed promising results. However, like most anti-cancer drugs, resistance to TRAIL-induced apoptosis may limit its clinical efficacy. It is critical to understand the molecular mechanisms of TRAIL. Therefore, rational therapeutic drug combinations for clinical trials of TRAIL-based therapies might be achieved. In a variety of leukemic cells, overexpression of X-linked inhibitor of apoptosis protein (XIAP), a negative regulator of apoptosis pathway, has been discovered. Implication of XIAP in the ineffective induction of cell death by TRAIL in leukemia has been explored in several resistant cell lines. XIAP inhibitors restored TRAIL sensitivity in resistant cells and primary leukemic blasts. Moreover, TRAIL resistance in leukemic cells could be overcome by the effects of several anti-leukemic agents via the mechanisms of XIAP downregulation.

Here, we discuss targeting XIAP, a strategy to restore TRAIL sensitivity in leukemia to acquire more insights into the mechanisms of TRAIL resistance. The concluding remarks may lead to identify putative ways to re-sensitize tumors.

Key points: The X-linked inhibitor of apoptosis protein (XIAP) plays role in resistance to TRAIL-induced apoptosis in leukemic malignancies

1. Introduction

Many cancer therapies have limited clinical benefit because of resistance problems. Over the past decade, mechanisms of cancer drug resistance had been one of the most important subjects driving much research in tumor biology. The two most important features characterizing cancer cells are the marked increase in proliferation and their reduced apoptosis due to a variety of alterations such as apoptotic signal pathways [1,2]. Apoptosis is a major process in normal development and maturation and regulates the homeostatic balance between the cell growth and death. Most of the current anti-cancer strategies share the same properties in biological mechanisms. These strategies aim to eliminate cancer cells by activating apoptosis. In fact, apoptosis is the most frequent outcome of these therapeutics, while the effects of these drugs might be different [3]. Therefore, cell death by apoptosis

Abbreviations: TRAIL, TNF-related apoptosis-inducing ligand; XIAP, X-linked inhibitor of apoptosis protein; cFLIP, cellular FLICE-inhibitory protein; bcl-2, B-cell lymphoma 2; IAP, inhibitor of apoptosis proteins; Mcl-1, myeloid cell leukemia-1; Apo-2L, Apo2 ligand; DR, Death Receptor; DcR, decoy receptor; DISC, death-inducing signaling complex; FADD, Fas-associated protein with death domain; Bid, BH3 interacting-domain death agonist; BAX, Bcl-2-associated X protein; NK cell, natural killer cell; NFκB, nuclear factor kappa B; IκBα, inhibitor of kappa B

* Corresponding author at: Department of Immunology, Division of Hematology and Blood Banking, Faculty of Medicine, Tabriz University of Medical Sciences, Daneshgah Ave, Tabriz, Iran.
E-mail address: ssolali@gmail.com (S. Solali).

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may play an important role in cancer eradication, and modulation of apoptosis in malignant cells should be an essential part of cancer drug development [4]. However, many tumor cells resist the drug-induced apoptosis and thereby impose a barrier for effective cancer therapy [5]. Thus, apoptosis is a mechanism through which tumor cells develop resistance to such therapies.

TNF-related apoptosis-inducing ligand (TRAIL) is a member of the TNF family. It has raised promises of improved cancer therapy due in part to the absence of pro-inflammatory effects that is seen by the use of TNF. TRAIL also has the capability to induce pro-apoptotic pathways exclusively in transformed cells without affecting normal cells. As with other death-inducing receptors, stimulation of TRAIL receptors is responsible for transmitting death signals leading to the activation of a canonical pathway of apoptosis. TRAIL is a transmembrane protein and is capable of interacting with membrane receptors that induce cell death. Membrane-bound TRAIL is present on natural killer (NK) cells and cytotoxic T cells. It has a physiological role in tumor immunosurveillance. This is supported by in vivo experiments in which TRAIL-deficient mice showed more susceptibility to tumor initiation [6]. TRAIL can also be produced in a soluble form, cleaved by extracellular metalloproteases. Like the membrane-bound TRAIL, the soluble variant also possesses biological functions. On the basis of these findings, soluble recombinant TRAIL has gained increasing attention for the treatment of several solid and hematopoietic malignancies [7]. As with soluble TRAIL, monoclonal antibodies agonists DR4 and DR5 human receptors of TRAIL demonstrated potent cytotoxic effects against human cancers. However, drug resistance is a major problem in cancer treatment and should be overcome to take the maximum advantage of cancer treatment with TRAIL.

A number of mechanisms of TRAIL resistance have been described. In one set of resistance mechanisms, TRAIL-specific surface receptors and downstream signaling pathways are implicated. For example, impairment of death receptor expression or aberrant expression of decoy receptors which counteracts TRAIL-mediated apoptosis via competing with death receptors for ligand binding can confer tumor cell survival against TRAIL-mediated cytotoxic responses [8]. Cellular FLICE-inhibitory protein (cFLIP), which is an anti-apoptotic molecule, blocks the activation of caspase-8 at death receptor, and its overexpression contributes to resistance at the inner parts of apoptotic cascade [9]. In addition, defective function or expression of caspase-8 by genetic or epigenetic alterations may also cause resistance towards TRAIL [10–12]. A subsequent step of TRAIL resistance is mediated by factors that can generally influence apoptosis. These factors include reduced caspase expression, upregulation of pro-survival factors that suppress apoptosis including Bcl-2 [13], and the inhibitor of mitochondrial pathway of apoptosis, Mcl-1 [14], as well as a pivotal class of intrinsic inhibitors of apoptosis called the inhibitor of apoptosis proteins (IAP) family [15,16]. The IAPs are a group of similar regulatory proteins that participate in blocking apoptosis, cell cycle arrest, and signal transduction [17]. Mechanisms of IAP-mediated inhibition of apoptosis involve both caspases-dependant and caspase-independent. IAPs were initially discovered in baculovirus in 1933, and the mammalian counterparts were then described. The first identified human IAP member is the X-linked IAP (XIAP) protein. Among various IAP members XIAP is the best characterized and most potent inhibitor of apoptosis and influences both the mitochondrial and death receptor pathways in cells. Many studies have demonstrated that XIAP can render malignant cells resistant to apoptosis in vitro and in vivo [18]. High levels of XIAP have been detected in solid tumors such as bladder carcinoma, transitional cell cancer (TCC) [19], non-small cell lung cancer (NSCLC) [20] and prostate cancers [21]. XIAP also plays a part in hematological malignancies. The majority of human leukemia cell lines have been shown to be resistant to treatment with TRAIL. In view of the increased level of XIAP in leukemia which will be discussed in more detail below, whether the death-inducing potential of TRAIL could be enhanced by downregulation of XIAP in leukemia remains unclear.

We first review the current knowledge of IAP family function, particularly XIAP and TRAIL signaling pathways. Then, XIAP expression and its biological significance in different types of leukemia will be discussed. Finally, we summarize findings of XIAP targeting strategies for re-sensitizing TRAIL-resistant leukemic cells.

2. TRAIL induces apoptosis in cancer cells

Tumor necrosis factor (TNF) family of cytokines has been linked to various biological functions from differentiation and proliferation to induction of cell death by apoptosis [22]. TRAIL (also known as Apo-2 L) is a member of the TNF family. It was first identified in 1995 as a tumor-selective death ligand. At molecular level, four cell surface receptors have been identified to interact with TRAIL including death receptor 4 (DR4/TRAIL-R1), death receptor 5 (DR5/TRAIL-R2), decoy receptor 1 (DcR1/TRAIL-R3), and decoy receptor 2 (DcR2/TRAIL-R4) [23]. TRAIL can bind to each of these receptors although only some of these receptor-ligand interactions can elicit apoptosis signals. TRAIL-R1 and -R2 are two well-characterized inducers of apoptosis in sensitive target cells because they have death domains in cytoplasmic area. Both the membrane-bound TRAIL-R4 and TRAIL-R3 have similar extracellular binding domains as with TRAIL-R1 and -R2. However, membrane-bound TRAIL-R4 and TRAIL-R3 are not able to mediate signaling due to the presence of a truncated form or lack of the intracellular death domains, respectively [23]. Decoy receptors are expressed on the surface of normal cells but not transformed cells. Therefore, normal cells are not sensitive to TRAIL, and transformed cells are sensitive [24]. Nevertheless, many tumor cells are weakly responsive to TRAIL-induced apoptosis or are fully resistant to toxic effects of TRAIL [25].

Engagement of death receptors by TRAIL results in the formation of an apical signaling complex, called death-inducing signaling complex (DISC). DISC consists of Fas-associated protein with death domain adaptor protein (FADD), which is recruited to the death domains of the receptors, caspase-8, and caspase-10 [26]. Fig. 1 depicts the signaling pathways downstream of pro-apoptotic TRAIL death receptors. Dimerization of pro-caspase 8 in the DISC complex activates caspases-8 [27]. Subsequently, fully activated homodimers are released, and then the activated caspases-8 cleaves downstream effector caspases to kill the cell. Apoptosis is initiated at the mitochondrial level as a result of catalytic cleavage of BH3-only protein (Bid) by caspase-8. This leads to the amplification of death signals stimulated by TRAIL receptors [28]. This additional pathway is employed by type II cells. In this regard, pro-apoptotic Bid directly activates BAX or BAK, the two Bcl-2 family members, whose functions may permeabilize mitochondrial outer membrane allowing cytochrome c release. Consequently, the multimeric apoptosome complex is formed. Apoptosome is a machinery that converts pro-caspase 9 to its active form and triggers processing of effector caspases that ultimately leads to cell death [29]. Type I cells are a distinct category of apoptotic cells in which caspase-8 is sufficient to effectively induce caspase-3 activity to drive apoptosis. In this type of apoptotic signals, DISC activity is strong enough to trigger the activation of caspases following death receptor oligomerization. Therefore, these cells are independent of additional mitochondria-induced cleavage of caspase-3. In principle, the strategies to interfere with apoptosis differ between these cell systems, where they show different responses to cytotoxic drugs and different resistance mechanisms. The capacity of forming active DISC complex is crucial in making a distinction between type I and type II cells [30]. However, subsequent studies demonstrated that XIAP anti-apoptotic factor is the discriminating element between the distinct cell types [31]. Indeed, both the efficiency of DISC to cleave caspase-3 and the activity of XIAP to counteract apoptosis are decisive factors in type I and type II apoptosis signaling.

3. Leukemia cells show resistance to TRAIL-induced apoptosis

TRAIL exhibits selective cytotoxicity towards a variety of