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Chapter 6

TRAIL Induces Apoptosis and Autophagy

Zhenyu Yao and Dexian Zheng

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Abstract

It is known that tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) could induce both apoptosis and autophagy. Here, we summarized the recent findings of the key regulators and the crosstalk pathway that highlights the intricate interplay between TRAIL-induced apoptosis and autophagy.

Keywords: apoptosis, autophagy, caspase-8, RIP1, TRAIL

1. Introduction

Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), also known as Apo-2 ligand (Apo2L), is a multifunctional cytokine of the TNF superfamily (TNFSF) [1, 2]. TRAIL gained much attention due to its specific antitumor potential without toxic side effects [3], making TRAIL itself as well as agonists of its two receptors, which can submit an apoptotic signal, TRAIL-R1 (DR4) [4] and TRAIL-R2 (DR5) [5–8], promising novel biotherapeutics for cancer therapy [9–11]. Importantly, TRAIL can also induce autophagy, which has been linked to apoptosis, serving either a prosurvival or prodeath function [12, 13]. Recent findings reveal that the cellular contexts require a balanced interplay between apoptosis and autophagy. Here, we summarized the recent findings of the key regulator and the crosstalk pathway that highlights the intricate interplay between TRAIL-induced apoptosis and autophagy.

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2. TRAIL-induced apoptosis and autophagy

2.1. TRAIL signaling

There are four TRAIL transmembrane receptors: TRAIL-R1 (DR4), TRAIL-R2 (DR5), TRAIL-R3, also known as decoy receptor 1 (DcR1), and TRAIL-R4 (DcR2), and a soluble receptor osteoprotegerin (OPG) [4, 7, 14]. Only TRAIL-R1 and TRAIL-R2 are able to induce apoptosis, whereas TRAIL-R3, TRAIL-R4, and OPG lack the intracellular functional domain, which is required for apoptosis induction [15, 16]. This domain is characteristic for all apoptosis-inducing members of the TNFR superfamily (SF) and is called the death domain (DD). TRAIL-R3 and TRAIL-R4 have been suggested to act as decoy receptors that inhibit apoptosis induction [17]. It has been delineated that TRAIL triggers two major apoptosis signaling pathways, the death receptor (extrinsic) and the mitochondrial (intrinsic) pathways. TRAIL triggers the extrinsic apoptosis pathway upon binding of the TRAIL trimer to TRAIL-R1 and/or TRAIL-R2, resulting in receptor trimerization, which in turn leads to recruitment of the adaptor protein Fas-associated DD (FADD). FADD in turn recruits procaspase-8 and procaspase-10 through homotypic interactions of death-effector domains (DED) presenting in FADD and caspase-8 and caspase-10, respectively. This multiprotein complex is called death-inducing signaling complex (DISC) [18–21]. The DISC is an aggregation of the intracellular death domain of the death receptor. In "type I" cells, the procaspase-8 and procaspase-10 form homodimers. This induces a conformational change that exposes their proteolytical active sites, resulting in autoactivation and subsequent cleavage of additional procaspase-8 and procaspase-10 molecules leading to activation of sufficient caspase-8 to stimulate effector caspase-3 to induce apoptosis [22–24]. However, "type II" cells generate less-active caspase-8 at the DISC. These cells induce apoptosis requiring further signal amplification by the intrinsic/mitochondrial pathway. In this situation, an intracellular complex is activated [25–27]. The next is triggered by caspase-8-mediated cleavage of Bid to truncated Bid (tBid) as the active fragment of this protein [28–31]. Subsequently, tBid activates the mitochondrial pathway eventually leading to mitochondrial outer membrane permeabilization (MOMP) and releasing of cytochrome C and Smac/DIABLO [30, 32]. In the cytosol, cytochrome c Apaf-1 and caspase-9v forms a multimeric complex called apoptosome. Activated caspase-9 as the initiator caspase cleaves and activates the effector caspases. Release of Smac augments apoptosis by antagonizing the inhibitor of apoptosis (IAP) proteins, a family of antiapoptotic proteins that block apoptosis by binding to and inhibiting effector caspases such as caspase-3 and caspase-7 [33, 34].

In the DISC, the main regulator protein is cellular FLICE-like inhibitory protein (cFLIP) and caspase-8, cFLIP contains a death domain, which allows them to interact with proteins of the TRAIL DISC, thereby blocking the transmission of the proapoptotic signal and preventing caspase-8 activation [35–37]. cFLIP closely resembles caspase-8 but lacks the protease activity required for apoptosis induction [38, 39]. Two main variants of cFLIP are expressed on the protein level: a short isoform (cFLIP-S) and a long isoform (cFLIP-L) [40]. The cFLIP-S isoform can inhibit caspase-8 activation in a dominant-negative manner by competing with it for binding to FADD. cFLIP-L can also completely prevent DR-induced apoptosis when it is expressed at high levels. Several studies have demonstrated that cancer cells exploit overex-

pression of cFLIP to evade TRAIL-induced apoptosis [41–43]. Overexpression of cFLIP is a frequent event in human cancers and has been correlated with resistance to the induction of apoptosis, including TRAIL-mediated cell death [36, 37]. Consequently, downregulation of cFLIP may sensitize certain cancers to TRAIL-induced apoptosis [44–46]. Another key regulator in the DISC is caspase-8 that, besides caspase-10, represents the initiator caspase that is engaged during TRAIL-induced apoptosis [47]. Hypermethylation of a regulatory motif that controls caspase-8 expression has been shown to be responsible for low or even absent caspase-8 expression in several cancer entities, resulting in resistance or decreased sensitivity to TRAIL-induced apoptosis [48–51]. Caspase-8 function can be suppressed in a dominant-negative manner by aberrant expression of a splice variant of caspase-8, that is, caspase-8 long (caspase-8L) [52, 53]. This variant of caspase-8 was detected in cancer cells. Caspase-8L interferes with caspase-8 activation by competing with wild-type caspase-8 for the recruitment into the TRAIL DISC. Additional regulatory mechanisms that control caspase-8 activity include post-translational alterations of caspase-8 such as phosphorylation. The tyrosine kinase Src has been reported to phosphorylate caspase-8 on one specific residue (tyrosine-308), which impairs the enzymatic function of caspase-8 [54]. These regulation factors can influence the activity of caspase-8 that causes the change of TRAIL-induced apoptosis.

Except from inducing apoptosis, TRAIL can also induce cell survival signaling such as proinflammatory pathways (through NF-kB, Akt, MAPK, and JNK activation). TRAIL can promote a variety of cell survival cascades leading, for example, to proliferation, migration, invasion, and even metastasis, especially in cancers in which the cell death signaling part of the signaling network is impaired [55–57]. The induction of pathways has been suggested to be mediated by the formation of a secondary complex containing FADD, caspase-8, cFLIP, RIP1, TRAF2, and NEMO [25, 58]. RIP1 is an important regulatory protein in the DISC that can activate NF-κB and caspase-8 and generate reactive oxygen species (ROS) [59–61]. RIP1 function is modulated by ubiquitination and phosphorylation [62, 63]; a previous report showed that in TNF-α-induced DISC, RIP1, and NEMO form a stable chain of linear ubiquitin. This complex is involved in determining cell survival, necrosis, and apoptosis [64].

2.2. The regulators and pathways in TRAIL-induced apoptosis and autophagy

Apoptosis and autophagy are evolutionarily conserved processes that regulate cell fate together. Although apoptosis and autophagy has obvious difference, but their regulation is closely related; they share the same regulator molecules and same pathway; however, these same regulators may determine a different cell fate.

Nowadays, most studies focused on the relationship between TRAIL sensitivity and autophagy [12, 65–68], TRAIL has been shown to induce apoptosis and autophagy in a number of cancer cell lines, including colon, glioma, bladder and prostate, and breast carcinoma. Han et al. first explained TRAIL-mediated cytoprotective autophagy in apoptosis-deficient tumor cells. They found that TRAIL can induce autophagic response in apoptosis-defective tumor cells (Hct116-FLIP or $Bax^{-/-}$ Hct116). Engineered apoptotic deficiencies included stable FLIP transfection, which is expected to block the TRAIL-apoptotic cascade at the DISC level, and Bax knockout demonstrated to block the TRAIL apoptotic response of colon carcinoma Hct116

cells despite the processing of caspase-8 upstream of the mitochondria. Inhibition of autophagy by the knockdown of Beclin 1, UVRAG, Vps34, or Atg7 allows for the induction of significant apoptosis in response to TRAIL [69]. The following work from this laboratory demonstrates that TRAIL-mediated autophagic response counterbalances the TRAIL-mediated apoptotic response by the continuous sequestration of the large caspase-8 subunit in autophagosomes and its subsequent elimination in lysosome [66]. Inhibition of autophagy induces caspase-8 activity; these findings provide evidence for regulation of caspase activity by autophagy. These results suggest that the regulators, such as Beclin 1 and caspase-8, play an important role in the regulation of TRAIL-induced apoptosis and autophagy.

He et al. demonstrate that TRAIL induced cytoprotective autophagy in different cancer cell lines. MAPK8/JNK activation mediated by TRAF2 and RIP1 is required for TRAIL-induced autophagy. Blocking MAPK8 but not NF-κB effectively blocked autophagy, suggesting that MAPK8 is the main pathway for TRAIL-induced autophagy. TRAF2 and RIP1 modulated TRAIL-induced and MAPK8-mediated autophagy. These results reveal that inhibiting MAPK8 pathway-mediated autophagy will increase TRAIL's anticancer activity in cancer cells [65]. Inhibition of antiapoptosis factors in the DISC (cIAP1, cIAP2, XIAP, and c-FLIP, and so on) increases TRAIL-induced apoptosis. Also, some autophagy-related pathways, such as AMPK and MAPK/JNK pathway, are involved in TRAIL-induced apoptosis [65, 70, 71]. These results suggest that there are some regulators and pathways that are necessary for autophagy involved in the regulation of TRAIL-induced apoptosis and autophagy.

Following these researches, some new regulators were found. Caspase-9 is a novel coregulator of apoptosis and autophagy. Han et al. demonstrate that caspase-9 facilitates the early events leading to autophagosome formation; that it forms a complex with Atg7, and Atg7 represses the apoptotic capability of caspase-9, whereas the latter enhances the Atg7-mediated formation of light chain 3-II. The repression of caspase-9 apoptotic activity is mediated by its direct interaction with Atg7, and it is not related to the autophagic function of Atg7. The Atg7 caspase-9 complex performs a dual function of linking caspase-9 to the autophagic process while keeping in check its apoptotic activity [72]. So far it has been found that many regulators such as Beclin 1 and caspase 8 IAPs XIAP in TRAIL induced apoptosis and autophagy in cancer cells. Caspase-8L, cFLIP-L, and cFLIP-S act not only as antiapoptotic factors but also as suppressors of autophagy. Inhibition of autophagy by gene silencing of these regulators or small compounds targets these regulators sensitizing TRAIL-resistant tumor cells to TRAIL-induced apoptosis. Taken together, these researches suggest some potential targets in the prediction of tumor resistance to DR-targeted therapies. Interestingly, a basal level of autophagy is needed for TRAIL-induced apoptosis [73].

In addition to cancer cells, TRAIL has been shown to induce apoptosis and autophagy in other cell lines such as U937 cell, Jurkat T cell, breast epithelial cells, and so on. We found that TRAIL induces both apoptosis and autophagy in human U937 cells [74]. Inhibition of autophagy facilitates TRAIL-induced apoptosis, suggesting that autophagy of macrophages protects against TRAIL-induced apoptosis. RIP1 ubiquitination rapidly increased in U937 cells treated with TRAIL, and RIP1 ubiquitination was significantly reduced in the presence of 3-MA in the cells treated with TRAIL. RIP1 expression was also distinctly decreased in the presence of 3-

MA in the cells treated with TRAIL. Furthermore, c-FLIP-L cleaved into the p43 variant caspase-8 was degraded into p43/41 while autophagy was suppressed by 3-MA in the cells treated with TRAIL. Knockdown of RIP1 suppresses autophagy in macrophage. These data demonstrate that RIP1 is essential for the regulation of death receptor-mediated apoptosis and autophagy in macrophage and suggest that the expression and ubiquitination of RIP1 regulate TRAIL-induced apoptosis and autophagy. The results in this study contribute to understanding the regulation of apoptosis and autophagy in macrophages, and sheds light on inflammation and autoimmune diseases [74].

Wang et al. in our group demonstrate that HTLV-1 (human T cell leukemia virus type 1) Tax protein increases autophagosome accumulation in human U251 astroglioma cells. In addition, HTLV-1 Tax deregulated the autophagy pathway, which plays a protective role during the death receptor-mediated apoptosis. Tax-induced c-FLIP expression also contributes to the resistance against death receptor-mediated apoptosis. Tax-induced c-FLIP expression correlated with the phosphorylation of IKK and the transcriptional activation of NF-κB. But Tax-triggered autophagy only depends on the activation of IKK but not on the activation of NF-kB. TRAIL-induced apoptosis is correlated with the degradation of Tax, which can be facilitated by the inhibitors of autophagy [75]. These results outline a complex regulatory network between apoptosis and autophagy, and Tax-induced autophagy represents a new potential target for therapeutic intervention for the HTVL-1-related diseases.

Herrero-Martin et al. demonstrate that TRAIL triggers cytoprotective autophagy in untransformed human epithelial cells by the AMP-activated protein kinase pathway. Transforming growth factor-b-activating kinase 1 (TAK1) and TAK1-binding subunit 2 mediate TRAIL-induced activation of AMPK and autophagy. These data have broad implications for understanding the cellular control of energy homoeostasis as well as the resistance of untransformed cells against TRAIL-induced apoptosis [71]. These studies of macrophage, Jurkat T cell, and breast epithelial cells have shown that some new regulators are involved in TRAIL-induced apoptosis and autophagy, and the expression and ubiquitination of RIP1, HTLV-1 Tax protein, and TAK1-AMPK pathway regulate the balance of TRAIL-induced apoptosis and autophagy in different extent.

3. Conclusion

Taken together, both the regulators in apoptosis pathway such as caspase-8 and caspase-9 and the key factors in autophagy such as Beclin 1 and ATG7 can regulate the TRAIL-induced apoptosis and autophagy [66, 72]. Moreover, some molecular switchers, like RIP1, regulate the balance between TRAIL-induced apoptosis and autophagy by dynamic expression and modification [65, 74]. They share the same regulators even pathways to control the complicated process (**Table 1**).

Both apoptosis and autophagy are important biological processes that play essential roles in the development of tissue homeostasis and disease. Interactions among components of the two pathways indicate a complex crosstalk. Insight into the complex network of TRAIL-induced

apoptosis and autophagy contributes to the development of novel therapeutic strategies for the treatment of TRAIL-related diseases and deeply understand the molecular mechanism of apoptosis and autophagy.

Cell lines	Key regulators pathway	References
Hct116-FLIP or (Bax$^{-/-}$)Hct116	Beclin 1 and caspase-8	[66, 69]
UM-UC-3, PC-3, and A549	TRAF2 (RIP1)-MAPK8/JNK pathway	[65]
Hct116, HeLa, MB-MDA-231, and RKO	Atg7·caspase-9 complex	[72]
U937	RIP1 caspase-8 and cFLIP	[74]
U251	HTLV-1 Tax and cFLIP	[75]
MCF10A–eGFP–LC3	TAK1-AMPK pathway	[71]

Table 1. The regulators and pathways in TRAIL-induced apoptosis and autophagy in differences cell lines.

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