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Basic and applied research progress of TRAIL in hematologic malignancies

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Abstract

Hematological malignancies encompass a diverse range of blood-related cancers characterized by abnormal blood cell production. These cancers, classified by the World Health Organization based on lineage, cell origin, and progression, provide a more comprehensive framework for understanding cancer biology. This classification has significantly advanced cancer research, particularly in genetic analyses for diagnosis and treatment. Despite recent clinical improvements, challenges, such as relapse, resistance, and high mortality, remain unresolved. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a protein that induces apoptosis in cancer cells without affecting normal cells, has emerged as a promising therapeutic target. However, its clinical efficacy is limited by factors, such as tumor heterogeneity and resistance to TRAIL signaling. This review examines the mechanisms of TRAIL in hematological malignancies, factors contributing to resistance, and the current state of preclinical and clinical research, highlighting potential strategies to enhance TRAIL-based therapies in blood cancers.

Key Words: Clinical application; Drug tolerance; Hematologic malignancies; TRAIL

1. INTRODUCTION

Hematological malignancies include a diverse array of blood-related neoplasms, typically characterized by aberrant blood cell production. The World Health Organization (WHO) classifies these malignancies based on the neoplastic cell's lineage (myeloid or lymphoid), its origin (precursor, stem, differentiated, or committed cells) and its progression (acute or chronic), along with detailed clinical, morphological, and genetic characteristics.[1,2] Hematological malignancies have been at the forefront of cancer research, particularly in using genetic analyses for diagnosis, categorization, prognosis, and treatment guidance.[3,4]

Although the clinical management of hematological malignancies has seen substantial advancements, challenges remain concerning their socioeconomic impact, including relapse, refractory disease, and malignancy-related morbidity and mortality.[5–7] Recent discoveries of underlying genetic and epigenetic alterations offer opportunities for personalized medicine, though complicated by the extensive molecular diversity and complexity observed, particularly in leukemia. Among these findings, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has emerged as a key player.[8–12]

Encoded by the *TNFSF10* gene, TRAIL is a protein belonging to the tumor necrosis factor (TNF) superfamily. TRAIL offers a distinct advantage over traditional treatments like chemotherapy and radiotherapy by selectively inducing apoptosis in cancer cells while sparing normal tissues. Unlike chemotherapy and radiotherapy, which rely on the p53-dependent intrinsic pathway and often lack tumor selectivity, TRAIL activates the extrinsic apoptotic pathway and remains effective even in cancers with p53 mutations. This selectivity reduces collateral damage and side effects, making TRAIL a promising target for cancer therapy.[13–16] Although laboratory studies have shown its potential for clinical application, TRAIL's efficacy in clinical trials has been underwhelming.[17–21] This disparity may be due to tumor cell heterogeneity, resistance to TRAIL signaling, or issues with TRAIL's bioactivity and stability in the body.[22–28] This article reviews the progress in basic and clinical research on TRAIL in hematological malignancies, emphasizing its mechanisms of action, resistance mechanisms, and the current landscape of preclinical and clinical investigations. It also explores future avenues for TRAIL development.

2. THE MOLECULAR STRUCTURE AND SIGNALING PATHWAY OF TRAIL

TRAIL is a type II transmembrane protein with 4 domains: a C-terminal domain, an extracellular domain, a transmembrane domain, and an intracellular N-terminal signal sequence. TRAIL functions primarily by binding to its receptors, including death receptor 4 (DR4, also known as TRAIL-R1), death receptor 5 (DR5, also known as TRAIL-R2), TRAIL-R3 (also known as DcR1, which does not participate in apoptotic signaling), and TRAIL-R4 (also known as DcR2, which also does not participate in apoptotic signaling).[29,30] Upon binding to TRAIL, TRAIL

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receptor 1 (TRAIL-R1) and/or TRAIL-R2 cluster to form a death-inducing signaling complex (DISC), characterized by a receptor: FAS-associated death domain (FADD):pro-caspase 8 ratio of approximately 3:1. At this stage, FLICE-like inhibitory protein (FLIP) competitively interacts with FADD, restricting the incorporation of caspase 8. Caspase 8 undergoes ubiquitination by cullin 3, a process that enhances its aggregation and activation. In type I cells, the mere formation of DISC is sufficient to ignite the caspase cascade, culminating in apoptosis.[31–33]

Conversely, in type II cells, complete activation of caspase 3 is hindered by elevated X-linked inhibitor of apoptosis protein (XIAP) levels. This necessitates a maturation phase following the initial caspase 8-catalyzed cleavage. To overcome this, caspase 8 catalyzes the cleavage of BH3-interacting domain death agonist (BID), which, in its truncated state (tBID), migrates to the mitochondria and stimulates BAX and BAK to execute mitochondrial outer membrane permeabilization (MOMP). Concurrently with second mitochondria-derived activator of caspases (SMAC), cytochrome c is released, enabling the adapter molecule apoptotic protease activating factor 1 (APAF1) to assemble apoptozole, a platform that activates the intracellular initiator caspase 9. Apoptosis and the subsequent caspase 9 activation further amplify caspase 3 processing and activity[34–38] (**Fig. 1**).

3. THE ROLE AND MECHANISM OF TRAIL IN HEMATOLOGICAL TUMORS

TRAIL primarily exerts its effects through the following mechanisms:

3.1. Maintenance and regulation of hematopoietic stem cells

Hematopoietic stem cells (HSCs) are the foundation of the hematopoietic system, and their functional maintenance is crucial for hematopoiesis. Studies have shown that TRAIL and its receptors are expressed in HSCs and the hematopoietic microenvironment, suggesting a role for TRAIL in HSCs maintenance and regulation.[39–41] Xia et al[42] demonstrated that TRAIL R1/R2 upregulation in patients with acute myeloid leukemia (AML) regulates HSCs proliferation and differentiation, maintaining HSC homeostasis and inhibiting relapse after allogeneic hematopoietic cell transplantation (HCT). Bae et al[43] recently introduced an induced pluripotent stem cell (iPSC) strategy for reprogramming and revitalizing precursor-exhausted B-cell maturation antigen (BCMA)-specific T cells to effectively target multiple myeloma (MM), finding that TRAIL regulation played a significant role.[44] Ho et al[45] found that TRAIL indirectly influences HSC function by modulating their microenvironment (such as bone marrow stromal cells). In addition, TRAIL signaling pathway activation can promote HSC migration and homing, contributing to treatments like bone marrow transplantation.[45]

3.2. Dural regulation on human immune system

TRAIL is widely expressed in T cells, macrophages, natural killer (NK) cells, and dendritic cells, playing a key role in human antitumor immune responses. TRAIL, particularly when secreted by NK and T cells, is crucial for inducing apoptosis in cancer cells.

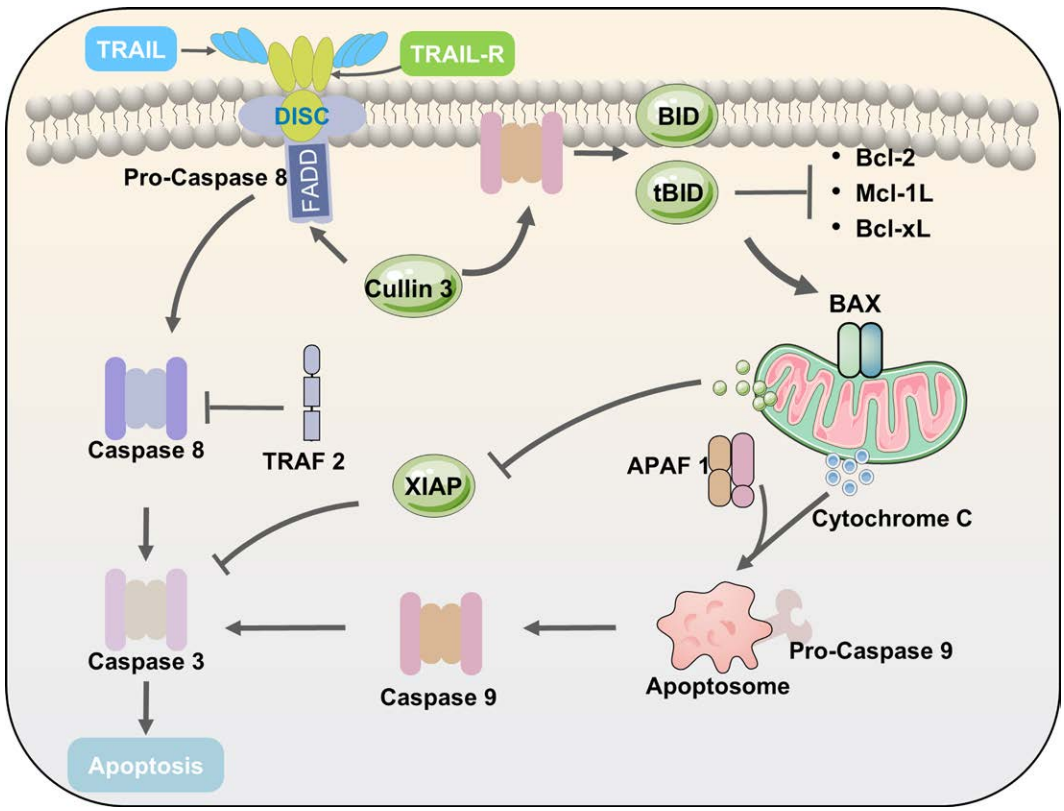

Figure 1. Pro-apoptotic TRAIL signaling pathway. The TRAIL signaling pathway triggers apoptosis by binding to its receptors, forming the DISC. In type I cells, DISC formation activates caspase 8, initiating a complete caspase cascade, and inducing apoptosis. In type II cells, caspase 8 activation alone is insufficient due to inhibition by XIAP. To overcome this, caspase 8 cleaves BID, which activates BAX and BAK in the mitochondria, causing MOMP. MOMP releases SMAC, which relieves the inhibition of caspases by XIAP, allowing full caspase activation. Additionally, released cytochrome c forms an apoptosome with APAF1, activating caspase 9. This cascade enhances caspase 3 activation, leading to apoptosis. APAF1 = apoptotic protease activating factor 1, BID = BH3-interacting domain death agonist, DISC = death-inducing signaling complex, MOMP = mitochondrial outer membrane permeabilization, SMAC = second mitochondria-derived activator of caspases, tBID = truncated state of BID, TRAF = TNF receptor-associated factor, TRAIL = tumor necrosis factor-related apoptosis-inducing ligand, XIAP = X-linked inhibitor of apoptosis protein.

It promotes macrophage polarization toward the M1 phenotype, enhancing cytotoxicity against malignant cells. TRAIL can also induce apoptosis in myeloid-derived suppressor cells (MDSCs) and trigger the production of pro-inflammatory cytokines like interleukin (IL)-6 and IL-1.[46–48] However, TRAIL may contribute inversely to an immunosuppressive microenvironment. For example, IL-35, promoted by TRAIL, can induce N2 neutrophil polarization and enhance neutrophil infiltration, augmenting the immunosuppressive function of neutrophils. In 2017, Hartwig et al[49] revealed that endogenous TRAIL/TRAIL-R-mediated CCL2 secretion promotes the accumulation of tumor-supportive immune cells in the cancer microenvironment, thereby revealing the tumor-supportive immunomodulatory role of the TRAIL/TRAIL-R system in cancer biology. In a murine model, Loeuillard et al[50,51] showed that TRAIL from cancer cells could facilitate MDSC proliferation through non-canonical TRAIL signaling, with consequent nuclear factor kappa B (NF-κB) activation. Moreover, TRAIL-induced immune tolerance may be a critical factor for immune escape.

3.3. Induction of tumor cell apoptosis

As type II transmembrane protein, TRAIL's extracellular carboxy-terminal portion can be cleaved into a soluble form, responsible for triggering apoptosis. Functional studies have shown that TRAIL induces cell death in a wide range of tumor cell lines but generally sparing normal cells. TRAIL selectively binds to tumor cells through death receptors (DR4/DR5), initiating the extrinsic apoptotic pathway. Most normal cells either do not express these receptors at high levels or express decoy receptors that prevent apoptosis, protecting them from TRAIL-induced damage.[52] Studies have indicated that leukemia and lymphoma cells are more sensitive to TRAIL than normal hematopoietic cells, underscoring TRAIL's potential in treating hematologic malignancies.

4. APPLICATIONS OF TRAIL IN HEMATOLOGIC MALIGNANCIES

Various TRAIL-based therapies and their derivatives are currently undergoing clinical investigation (Table 1). For example, Dulanermin, a recombinant human TRAIL, has shown significant antitumor effects in clinical trials of leukemia, lymphoma, and MM. Second-generation TRAIL derivatives, such as APO2L/TRAIL and DR5-specific monoclonal antibodies, have also demonstrated promising results.

4.1. Acute myeloid leukemia

AML is a highly heterogeneous hematologic malignancy with a limited response to conventional therapies. TRAIL induces apoptosis in AML cells, even in the presence of resistance. Strategies to overcome TRAIL resistance include combining TRAIL with chemotherapy or targeted small-molecule inhibitors. For example, the histone deacetylase (HDAC) inhibitor SAHA upregulates DR5 expression and enhances TRAIL sensitivity.[63] Chemotherapeutic agents like cytarabine and mitoxantrone also augment TRAIL-mediated apoptosis.[64,65]

4.2. Chronic lymphocytic leukemia (CLL)

CLL, a common type of adult leukemia, is characterized by its resistance to apoptosis. CLL cells exhibit low sensitivity to TRAIL; however, their sensitivity can be increased by modulating apoptotic signaling pathways. For example, inhibitors of the phosphatidylinositol 3-kinase/AKT (PI3K/Akt) pathway downregulate the expression of the anti-apoptotic protein Bcl-2, thereby enhancing TRAIL-induced apoptosis. In addition, immunomodulators such as interferon-alpha (IFN-α) increase CLL cell sensitivity to TRAIL, suggesting new therapeutic avenues.[66]

4.3. Multiple myeloma

MM, a malignancy characterized by the proliferation of plasma cells, often develops resistance to conventional treatments. TRAIL induces apoptosis in MM cells, but its sensitivity varies. Combinatorial approaches using proteasome inhibitors, such as bortezomib, significantly enhance TRAIL efficacy. Furthermore, studies have shown that IL-6 secreted by bone marrow stromal cells activates the JAK/STAT3 pathway and inhibits TRAIL-induced apoptosis; therefore, targeting IL-6 enhances TRAIL efficacy.[67]

Table 1

Clinical trials targeting TRAIL and TRAIL signaling pathways.

Type	Drugs	Cancers	Phases	Clinical trail ID
Rh TRAIL[53]	Dulanermin (AMG 951)	NHL	I/II(2016–2010)	NCT00671372
TRAIL-R1 mAb[54]	Mapatumumab (TRM-1/HGS-ETR1)	NHL	II (2004–2007)	NCT00094848
TRAIL-R1 mAb[55]	Mapatumumab (TRM-1/HGS-ETR1)	MM	II (2006–2010)	NCT00315757
TRAIL-R2 mAb[56]	Conatumumab (AMG 655)	Lymphoma	I (2008–2011)	NCT00791011
TRA[57]	ABBV-621	Solid or hematologic malignancy	I (2017–2022)	NCT03082209
Bcl-2 inhibitor[58]	Venetoclax (ABT-199/GDC-0199)	CLL	I/II (2015–2024)	NCT02427451
Bcl-2 inhibitor[59]	ABT-263 (Navitoclax)	CLL	II (2010–2012)	NCT01087151
Bcl-2 inhibitor	AVALON	AML	I (2019–2020)	NCT04070807
Bcl-2 inhibitor[60]	BGB-21447	Mature B-cell malignancy	I (2023–2026)	NCT05828589
Bcl-2 inhibitor	BGB-11417	Mature B-cell malignancy	I (2020–2027)	NCT04277637
Bcl-2 inhibitor	LOXO-338	Blood cancer	I (2021–2023)	NCT05024045
Bcl-2 inhibitor	FCN-338	CLL	I (2021–2024)	NCT04682808
Bcl-2 DNAi	PNT2258	Diffuse large B-cell lymphoma	II (2014–2016)	NCT02226965
L-Bcl-2	BP1002	AML	I (2022–2024)	NCT05190471
Bcl-2 and MCL-1 inhibitor[61]	VOB560-MIK665	NHL, MM, and AML	I (2021–2024)	NCT04702425
MCL-1 inhibitor	ABBV-467	MM	I (2020–2021)	NCT04178902
MCL-1 inhibitor[62]	Murizatoclax (AMG 397)	Hematological malignancy	I (2018–2019)	NCT03465540
MCL-1 inhibitor	PRT1419	Relapsed or refractory myeloid	I (2022–2024)	NCT05107856
MCL-1 inhibitor	MIK665(S64315)	MM	I (2017–2019)	NCT02992483
MCL-1 inhibitor	MIK665(S64315)	AML and MDS	I (2017–2020)	NCT02979366
MCL-1 inhibitor	MIK665(S64315)	AML	II (2021–2024)	NCT03672695

AML = acute myeloid leukemia, Bcl-2 family = Bcl-XL, Bcl-2, and Bcl-w, L-Bcl-2 = Bcl-2 antisense oligonucleotide, Bcl-2 DNAi = Bcl-2 targeted deoxyribonucleic acid inhibitor, CLL = chronic lymphocytic leukemia, MCL = mantle cell lymphoma, MDS = myelodysplastic syndrome, MM = multiple myeloma, NHL = non-Hodgkin lymphoma.

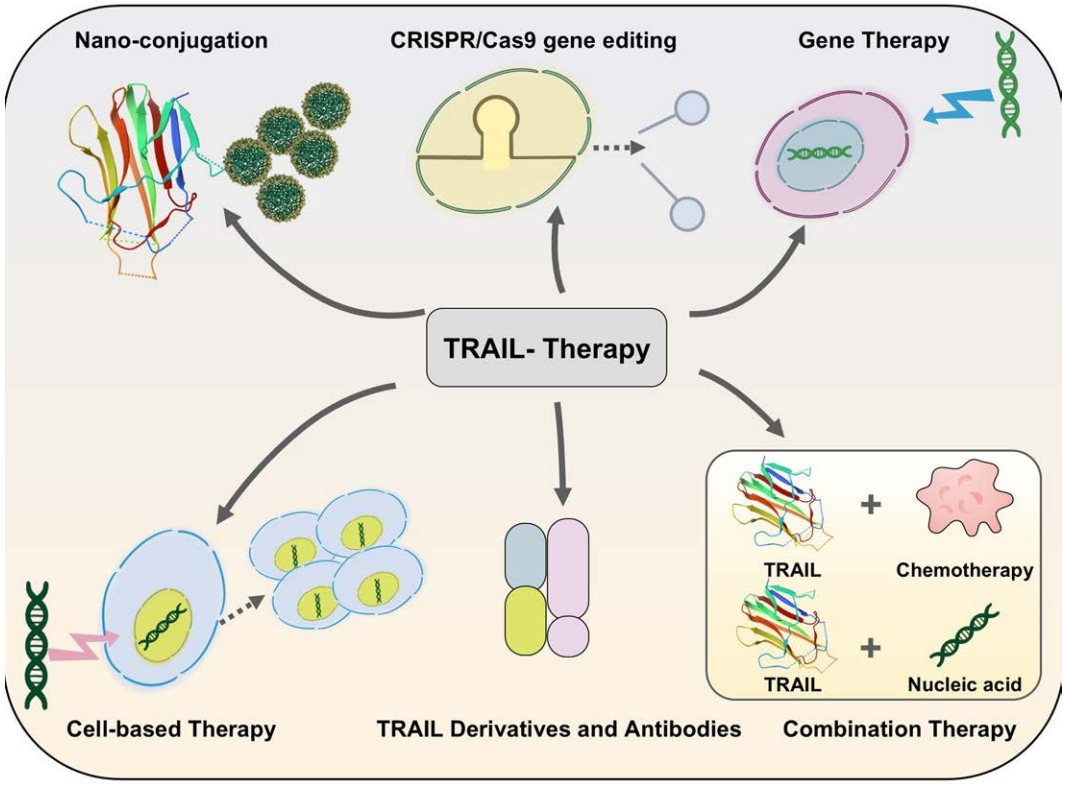

Figure 2. Schematic of various approaches to TRAIL-based cancer therapy. TRAIL proteins are conjugated with different moieties, including nanoparticles, to improve encapsulation efficiency, targeting specificity, and stability in the physiological environment. CRISPR/Cas9 gene editing is used to enhance TRAIL expression in tumor cells or modify mesenchymal stem cells for cell-based therapy. Gene therapy involves delivering TRAIL-encoding genes directly to cancer cells. This can be achieved by modifying cells to express TRAIL for therapeutic effects. TRAIL derivatives and antibodies are designed to improve receptor binding and induce apoptosis in a wider range of tumor cells. Combination therapy strategies incorporate TRAIL with chemotherapeutic agents or DNA/RNA-based therapeutics, enhancing synergistic anti-cancer activity. TRAIL = tumor necrosis factor-related apoptosis-inducing ligand.

5. MECHANISMS OF TRAIL RESISTANCE IN HEMATOLOGIC MALIGNANCIES

Resistance to TRAIL is a major obstacle to its clinical application. Resistance mechanisms include downregulation of death receptors, upregulation of anti-apoptotic proteins, and dysregulation of signaling pathways. These mechanisms are described in the following paragraph.

5.1. Alterations of TRAIL receptors

TRAIL induces apoptosis primarily by binding to DR4 (TRAIL-R1) and DR5 (TRAIL-R2). Many tumor cells evade TRAIL-induced apoptosis by downregulating or completely losing these receptors.[68,69]

5.2. Blockade of intracellular apoptotic signaling: impediments in DISC formation

DISC formation is critical in TRAIL-induced apoptosis. Deficiencies or functional impairments in DISC components, such as FADD and caspase 8, hinder apoptotic signal transduction.[70]

5.3. Overexpression of anti-apoptotic proteins

Overexpression of anti-apoptotic proteins like c-FLIP, Bcl-2, and Bcl-xL inhibits caspase activation, disrupting the apoptotic signaling pathway.[71]

5.4. Regulation of the mitochondrial pathway

(1) Inhibition of Bid Protein: Bid is a crucial regulator of the mitochondrial pathway mediated by caspase 8. Inactivation or inhibition of Bid affects mitochondrial pathway activation, suppressing apoptosis. (2) Maintenance of mitochondrial membrane potential: Some tumor cells maintain their mitochondrial membrane potential to prevent cytochrome c release, thereby evading TRAIL-induced apoptosis. (3) Cross-regulation of signaling pathways: NF-κB is a critical survival signaling pathway. TRAIL activates NF-κB, inducing expression of anti-apoptotic genes that promote cell survival. The PI3K/Akt signaling pathway plays a crucial role in cell survival and apoptosis. Akt activation inhibits TRAIL-induced apoptosis via multiple mechanisms.[72]

6. FUTURE RESEARCH DIRECTIONS OF TRAIL WITH OTHER DRUGS OR THERAPIES

6.1. Combination therapy

Recent interest in TRAIL-based therapies has spurred the development of various strategies such as TRAIL conjugates, combination therapies, TRAIL gene therapy, and cell-based treatments. Extensive research using both in vitro and in vivo models has yielded promising results (**Fig. 2**). Studies have shown that combining TRAIL with chemotherapeutic drugs, such as doxorubicin or paclitaxel, significantly enhances tumor cell cytotoxicity. In addition, combining TRAIL with epidermal growth factor receptor (EGFR) inhibitors or proteasome inhibitors, overcomes tumor resistance to single-agent therapies.[73] Combining TRAIL with chemotherapy, radiotherapy, targeted therapies, or immunotherapies significantly enhances treatment efficacy. For example, HDAC inhibitors increase DR5 expression, boosting TRAIL's antitumor effects; combining TRAIL with imatinib enhances the killing of chronic myeloid leukemia

(CML) cells; and TRAIL plus bortezomib overcomes MM drug resistance. Drugs like LY294002 and Wortmannin restore TRAIL-induced apoptosis by inhibiting the PI3K/Akt signaling pathway.[74] Moreover, advancements in nanotechnology have enabled the targeted delivery of TRAIL, increasing the tumor site concentration while reducing systemic toxicity.[75]

6.2. Nano-based gene and protein delivery systems

TRAIL's clinical application is limited by its poor pharmacokinetics and the challenges of targeted delivery. Gene therapy, particularly targeting localized TRAIL expression, offers a potential solution by generating a bystander effect. One promising strategy uses nanoparticles for TRAIL gene delivery, enabling precise targeting of tumor cells while addressing TRAIL resistance through combination therapy. Nanoparticles allow the delivery of TRAIL-encoding DNA directly into cancer cells, overcoming the limitations of recombinant TRAIL protein. In addition, the co-delivery of drugs that sensitize or regulate apoptotic pathways through gene delivery could further counteract TRAIL resistance, offering a more effective approach to cancer treatment.[76,77]

6.3. Targeted regulation of receptor expression

(1) Gene Editing Technology: CRISPR/Cas9 gene editing technology has been used to upregulate DR4 and DR5 expression, restoring sensitivity to TRAIL.[78]
(2) Epigenetic regulation: Studies have shown that HDAC inhibitors upregulate DR4 and DR5 expression, enhancing TRAIL-induced apoptosis.

6.4. Inhibitors of anti-apoptotic proteins

(1) c-FLIP is a crucial inhibitor of the extrinsic apoptotic pathway, preventing the homodimerization and autoactivation of pro-caspase 8 and pro-caspase 10, essential initiators of apoptosis. However, Yaacoub et al[79] challenged this view by showing that caspase 8 was simultaneously recruited to the DISC with c-FLIP(s/L). Based on this, molecular modeling and docking studies were conducted to create homology models of c-FLIP and caspase 8 with the goal of developing selective inhibitors that target unique sequences of c-FLIP without affecting caspase 8. This approach offers a more targeted method for modulating the apoptotic pathway.[79]
(2) Bcl-2 family inhibitors: BCL-2 inhibits apoptosis by blocking cytochrome c release from mitochondria. Venetoclax, a selective BCL-2 inhibitor, disrupts the interaction between BCL-2 and pro-apoptotic proteins (BAX, BAK, and BIM), promoting MOMP, cytochrome c release, caspase activation, and apoptosis. Venetoclax-based therapies have significantly improved the overall survival and complete remission rates in patients with AML across various subtypes and risk groups.[80,81]

6.5. Activation of the mitochondrial pathway

Mitochondria play a crucial role in death receptor-mediated apoptosis. In response to death receptor signaling, truncated BID activates the pro-apoptotic proteins, BAX and BAK, triggering MOMP. Lauterwasser et al[82] demonstrated that hexokinases 1 and 2 inhibit this process by retro-translocating truncated BID, BAX, and BAK from the mitochondria to the cytosol. This protection from TRAIL- and FasL-induced apoptosis relies on the localization of hexokinase to the mitochondria and its interaction with BCL-2 proteins, rather than glucose phosphorylation. Their study highlighted hexokinase-dependent retrotranslocation as a key regulatory mechanism in mitochondrial apoptosis.[82]

6.6. Chemical synthetic approaches to mimic the TRAIL

TRAIL has emerged as a promising target for cancer therapy because it induces apoptosis in cancer cells by binding to death receptors (DR4/DR5) while sparing most normal cells. Strategies mimicking TRAIL have been developed for various therapeutic purposes. Recombinant soluble TRAIL (rhTRAIL) and death receptor agonistic antibodies have been tested in preclinical and clinical trials, demonstrating their safety and tolerability. However, their clinical efficacy is limited. In addition to biotechnologically derived therapeutics, several chemically synthesized compounds have been identified as TRAIL mimics. Some of these compounds exhibit significant efficacy both *in vitro* and *in vivo*, offering the potential for further development.[83,84]

7. CONCLUSIONS

TRAIL, a protein with selective apoptosis-inducing activity, demonstrates significant potential for the treatment of hematopoietic and blood system tumors, especially lymphoma. Current research aims to enhance TRAIL's antitumor effects. Future directions include optimizing dosage and administration, developing novel delivery systems (eg, nanotechnology), applying precise gene editing, exploring additional combination therapies, and conducting biomarker research. These research endeavors promise to provide more therapeutic options and hope for patients with hematologic malignancies.

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