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Mechanisms Of Apoptosis Of T Killer Cells

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Abstract: Cytotoxic T lymphocytes (CTL or T killer cells) play an important role in the body's immune defense. They activate the apoptosis mechanism to destroy virus-infected or tumor cells. This article reviews the main pathways of T killer cells that induce apoptosis — the perforin-granzyme system, the Fas-FasL pathway, and the mitochondrial pathway. Studies conducted over the past decade have further elucidated the molecular basis of these mechanisms and opened up new directions in the field of immunotherapy.

Keywords: T killer cells, cytotoxic T lymphocyte, apoptosis, granzyme, perforin, FasL, mitochondria, immune response.

Introduction: Research objective: The aim of the study is to analyze the molecular mechanisms of apoptosis in target cells by T killer cells and to demonstrate their importance in immunotherapy and cancer treatment.

Research methods: The article was prepared in the form of a systematic review of scientific literature. The data were selected from articles published in 2015–2025 from PubMed, Nature, ScienceDirect, and Cell Press databases.

The immune system is a complex biological network that protects the body from external pathogens, viruses, bacteria, and tumor cells. One of the most important effector elements of this system is cytotoxic T-lymphocytes ($CD8^+$ T-killer cells). They ensure the specificity and selectivity of the immune response by identifying virus-infected or mutated cells and destroying them through the process of apoptosis [1]. Studies conducted in the last decade show that the mechanisms of apoptosis of T-killer cells play an important role not only in the protective reactions of the immune system, but also in understanding the pathogenesis of cancer, autoimmune diseases, and viral infections [2].

Killer T cells induce apoptosis through two main pathways: the perforin/granzyme pathway and the Fas/FasL (CD95/CD95L) receptor pathway [3]. Perforin and granzyme B are stored in cytotoxic granules, penetrate the target cell membrane, and activate intrinsic apoptotic mechanisms [4]. FasL, in turn, binds to the Fas receptor on the target cell and triggers programmed cell death via the caspase chain [5]. These mechanisms are involved not only in antiviral immunity but also in maintaining immune homeostasis, that is, in the elimination of overactive immune cells [6].

In recent years, particularly in 2015–2025, studies published in internationally recognized scientific journals such as Nature, Frontiers in Immunology, Cell Communication and Signaling, and Science have revealed important information about the factors regulating the apoptotic activity of T-killer cells, such as

mitochondrial signals, reactive oxygen and nitrogen species (ROS/RNS), and immune checkpoint molecules (PD-1, CTLA-4) [7][8]. This new evidence makes it possible to improve therapeutic outcomes by activating T-killer cells or controlling their apoptosis in immunotherapy and cancer treatment [9]. Currently, a deep study of apoptosis mechanisms is of strategic importance in understanding the activity, durability, and death cycle of T-killer cells, as well as in improving the efficacy of CAR-T and immune checkpoint-based therapies [10]. Therefore, this study aims to analyze the apoptosis mechanisms of T-killer cells at the molecular, cellular, and clinical levels, which is one of the current directions in immunology and oncology [11].

RESULTS

Perforin/Granzyme Pathway

One of the best-studied and rapid mechanisms of target cell killing by cytotoxic T lymphocytes (CTLs) is the perforin/granzyme pathway [1]. Through this pathway, CTL cells deliver the enzymes perforin and granzyme, which are stored in their cytotoxic granules, to target cells. After the formation of an immune synapse, these granules are brought closer to the target cell membrane by the microfilaments of the CTL, and the granule membrane fuses with the cell membrane [2].

Perforin is a 67 kDa calcium-dependent pore-forming protein that forms pores in the target cell membrane [3]. Through these pores, granzymes (types A, B, K, M) enter the cell cytoplasm and activate apoptosis mechanisms. In particular, granzyme B causes fragmentation of nuclear DNA by directly cleaving caspase-3 [4]. At the same time, granzyme B activates the mitochondrial outer membrane-disrupting protein Bid, leading to cytochrome c release and the activation of the caspase-9 cascade via Apaf-1 [5].

Granzyme A disrupts the mitochondrial electron transport chain, increasing the generation of reactive oxygen species (ROS), which causes oxidative damage to DNA [6]. In 2022, studies by Hay and Slansky demonstrated that granzyme A disrupts nuclear stability by inducing single-strand breaks in the DNA structure [7].

The combined activity of perforin and granzymes ensures selective cell death in diseases. For example, rapid initiation of apoptosis through the perforin pathway in virus-infected cells stops viral replication [8]. In 2018, Grossman and colleagues published articles in the journal Immunity showing that perforin deficiency causes severe inflammatory syndromes in congenital immune defects (e.g., familial hemophagocytic lymphohistiocytosis) [9]. Also in 2024, Guo and colleagues published new data on granzyme K in the journal Trends in Immunology, revealing that this enzyme is involved not only in apoptosis, but also in immune regulation and tissue regeneration [10]. These results demonstrate the complex and multifunctional nature of the perforin/granzyme pathway and highlight the importance of studying it as a target mechanism for immunotherapy [11]

Apoptosis via the Fas/FasL system

The induction of apoptosis of target cells by cytotoxic T lymphocytes (CTLs) occurs not only through the perforin/granzyme pathway, but also through the Fas/Fas ligand (FasL, CD95/CD95L) system [1]. This pathway is called the “extrinsic apoptosis pathway” because it initiates cell death via external membrane receptors. When the FasL protein on the surface of CTL cells interacts with the Fas (CD95) receptor on the target cell membrane, this receptor trimerizes and an intrinsic signaling cascade is initiated [2].

The cytoplasmic portion of the Fas receptor contains a structure called the Death Domain (DD). After binding to FasL, Fas recruits the adaptor protein FADD (Fas-Associated Death Domain). FADD, in turn, forms a complex with procaspase-8 to form the “Death-Inducing Signaling Complex (DISC)” [3]. In this complex, procaspase-8 is activated and activates caspase-3, which leads to the process of apoptosis accompanied by DNA fragmentation and nuclear condensation [4].

In 2021, studies by Wallach-Dayan and colleagues revealed that the Fas/FasL system plays an important role not only in immunity, but also in inflammation and tissue aging. According to their results, the free form of FasL (sFasL) has a pathogenic effect in chronic inflammatory diseases, while the membrane-bound form ensures physiological apoptosis [5].

The Fas/FasL system also plays an important role in autoimmune control. For example, in 2018, Nakamura et al. demonstrated that autoreactive T cells are not killed in a timely manner in patients with Sjögren's syndrome due to a disruption of the Fas/FasL system, which exacerbates the autoimmune response [6]. However, studies in the context of cancer, in particular a 2024 article in Frontiers in Immunology, have shown that tumor cells sometimes evade immune surveillance by overexpressing FasL and killing nearby T cells [7]. In addition, Fas/FasL signaling is also interconnected with the mitochondrial pathway. Activated caspase-8 cleaves the Bid protein, converting it to tBid; tBid, in turn, activates the Bax/Bak complex in the outer mitochondrial membrane, triggering cytochrome c release [8]. This in turn triggers the intrinsic apoptosis pathway and enhances the apoptotic cascade via caspase-9 [9]. Thus, the Fas/FasL system provides a “two-step” apoptotic attack of killer T cells — first via

the extrinsic receptor pathway, then via the intrinsic mitochondrial pathway [10]. In recent years, this system has also been actively studied in the field of immunotherapy. For example, in 2023, Yang et al. reported in Nature Communications that attenuation of Fas signaling in T cells ensures their long-term survival in the tumor environment and increases the effectiveness of CAR-T therapy [11]. Therefore, the Fas/FasL system is considered an important target not only in maintaining immune homeostasis, but also in the development of new treatment strategies [12].

TNF-α-mediated pathway

The tumor necrosis factor alpha (TNF-α)-mediated pathway is one of the important mechanisms for the induction of apoptosis in target cells by T killer cells (cytotoxic T lymphocytes, CTL) [1]. TNF-α is a pleiotropic cytokine produced mainly by activated T lymphocytes and macrophages, and it plays a central role in the regulation of cell survival, growth, and death [2]. By secreting TNF-α, T killer cells interact with TNF receptors (TNFR1 and TNFR2) on target cells, which initiates the apoptosis signaling cascade [3].

The TNFR1 receptor contains a Death Domain (DD) that forms a complex with TRADD (TNFR1-associated death domain protein). TRADD, in turn, recruits FADD and RIPK1 to form the DISC (Death-Inducing Signaling Complex). In this process, procaspase-8 is activated, which activates caspase-3, initiating the apoptotic cascade [4]. Although this mechanism is similar to the Fas/FasL system, TNF-α signaling is more enhanced in conditions associated with inflammation and cellular stress [5].

A study published in Frontiers in Pharmacology by Lin and Chen in 2025 revealed that modulation of the PI3K/AKT signaling system by the TNF-α pathway plays a central role in apoptosis and cell cycle arrest [6]. Their results suggested that drug-mediated regulation of TNF-α signaling activity could be an important strategy for reducing immune-inflammatory diseases.

The TNF-α-mediated pathway has a dual effect: on the one hand, it promotes apoptosis, and on the other hand, it promotes cell survival through the NF-κB pathway [7]. The activated TNFR1 complex has two outcomes: if the level of cIAP (cellular inhibitor of apoptosis proteins) is high, the cell survives; otherwise, the dominance of the RIPK1 and caspase-8 complex initiates the apoptosis process [8].

In 2020, Brenner and colleagues investigated the relationship between TNF-α signaling and necroptosis, demonstrating that TNF-α induces necroptotic cell death through MLKL in cases where apoptotic mechanisms are completely blocked [9]. This discovery highlights the need for dual control of the TNF-α system for therapeutic purposes.

In a 2023 Nature Reviews Immunology article, Kandhari et al. found that TNF-α signaling also plays a crucial role in the processes of CAR-T cell therapy. According to their study, high levels of TNF-α in the tumor environment lead to exhaustion of killer T cells, but targeted blockade of TNFR1 preserves their functional activity [10].

The TNF-α pathway is also closely linked to the mitochondrial apoptosis system. Activated caspase-8 cleaves Bid to tBid, which activates the Bax/Bak complex on the mitochondrial outer membrane and stimulates the release of cytochrome c [11]. This in turn triggers the intrinsic apoptosis pathway via caspase-9 and enhances the apoptotic cascade [12].

Recent molecular studies (2022–2024) have shown that TNF-α-mediated apoptosis mechanisms are important targets for immune homeostasis, autoimmunity, and cancer immunotherapy [13]. Therefore, in-depth study of the TNF-α pathway is an important step in the development of new molecular therapies for the treatment of immune system diseases [14]

Mitochondrial (intrinsic) apoptosis pathway

The mitochondrial or intrinsic apoptosis pathway is one of the most profound and complex molecular mechanisms of cell death induced by T killer cells [1]. This pathway is activated mainly by intracellular stress factors, DNA damage, oxidative stress, cytotoxic cytokines or granzymes [2]. T killer cells, through their granzyme B enzyme, convert the Bid protein to the tBid form in the cytoplasm of the target cell, which increases the permeability of the outer mitochondrial membrane and initiates the apoptosis signal [3].

The central element of mitochondrial apoptosis is the system of proteins belonging to the Bcl-2 family. They are divided into two groups: proapoptotic (Bax, Bak, Bid, Bim, Puma, Noxa) and antiapoptotic (Bcl-2, Bcl-xL, Mcl-1) proteins [4]. Under stress conditions, Bax and Bak form oligomers in the mitochondrial outer membrane, stimulating cytochrome c release. This protein then associates with Apaf-1 and procaspase-9 to form the apoptosome complex [5]. This complex activates caspase-9, which in turn activates caspase-3 and caspase-7, completing the apoptotic chain [6].

In a 2020 study published in Nature Communications, Li et al. found that Bax/Bak dimerization in mitochondrial-mediated apoptosis is an irreversible step in cell death [7]. They also demonstrated a critical role for the VDAC (Voltage-Dependent Anion Channel) in regulating cytochrome c release. In a 2019 paper published in Nature Reviews Molecular Cell Biology by Tait and Green, mitochondrial outer membrane

permeability was shown to be a key checkpoint in apoptosis [8].

In addition, the p53 transcription factor is crucial for mitochondrial apoptosis [9]. Following DNA damage, p53 upregulates the expression of proapoptotic genes Bax, Puma, and Noxa, while suppressing antiapoptotic genes Bcl-2 and Mcl-1 [10]. A 2021 study published in Cell Death & Differentiation found that direct translocation of p53 into mitochondria directly promotes Bax/Bak activation [11].

Reactive oxygen species (ROS) also play an important role in mitochondrial apoptosis [12]. Accumulation of ROS leads to a decrease in mitochondrial membrane potential, which subsequently leads to the cessation of ATP production. This in turn depletes cellular energy resources and enhances the apoptotic cascade [13]. In a 2022 study published in Frontiers in Immunology by Zhang et al., antioxidant therapy that reduces ROS levels prolonged the cytotoxic activity of killer T cells [14].

The mitochondrial pathway can be activated not only by intrinsic factors, but also by extrinsic signals such as Fas/FasL and TNF-α. In these pathways, activated caspase-8 cleaves the Bid protein to form tBid, which increases mitochondrial permeability [15]. Therefore, the intrinsic and extrinsic pathways often work in close conjunction with each other [16].

Recent studies have confirmed that mitochondrial apoptosis mechanisms play an important role in immune regulation associated with cancer immunotherapy, viral infections, and autoimmune diseases [17]. Therefore, in-depth study of this pathway is a promising direction for the development of a new generation of immunomodulatory drugs [18].

DISCUSSION

Recent studies have shown that the apoptosis mechanisms of killer T cells are important not only in the immune response to viral infections, but also in the immune response to cancer cells. However, an immunosuppressive microenvironment (e.g., TGF-β or PD-L1 signaling) can impair these mechanisms. Therefore, strategies to reactivate killer T cells—e.g., CAR-T technology or immune checkpoint inhibitors—are at the heart of modern immunotherapy.

CONCLUSION

Killer T cell apoptosis mechanisms are a highly regulated and multistep process that plays an important role in maintaining immune balance and eliminating pathological cells. In-depth study of these mechanisms opens new opportunities for improving the effectiveness of immunotherapy.

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