ОБЗОРЫ/REVIEWS

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DIFFERENTIATION AND FUNCTIONS OF CD8+ EFFECTOR T CELLS

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OBJECTIVE. Analyze Russian and foreign scientific literature reflecting the mechanisms of $CD8^+$ T-lymphocyte activation, lysis of infected cells, and the formation of possible immune dysfunctions.
MATERIALS AND METHODS. Recent Russian and international scientific literature from 1998 to 2025 on the biological features of $CD8^+$ T-lymphocyte activation was studied and analyzed. The primary sources were searched in the RINC, PubMed, Scopus, and Web of Science databases. The following combinations of keywords were used: T-lymphocyte subpopulations, cytotoxic T-lymphocytes, cytokines, granulins, perforin proteins, transcription factors, and hereditary mutations. A total of 49 articles were analyzed.
RESULTS. The differentiation of $CD8^+$ T cells depends on many factors, including $CD4^+$ T lymphocytes, without which the formation of effector $CD8^+$ T cells and memory T cells does not occur. Interleukins -2, -12, and IFN type I ensure the proliferation of $CD8^+$ T cells and their differentiation into cytotoxic lymphocytes. They stimulate the expression of transcription factors T-BET and BLIMP-1, which ensure the expression of perforin and granzymes. In chronic viral infections, T-cell differentiation is blocked by programmed cell death protein-1, as well as CTLA-4, TIM-3, LAG-3, and others. KIR receptors transmit inhibitory signals that prevent the destruction of uninfected cells by cytotoxic T lymphocytes. Thanks to the expression of NKG2D receptors, which recognize MHC-like class I molecules—MICA, MICB, and ULBP—that are expressed only by infected or transformed cells, "normal" cells and tissues are not damaged, activating nucleases in target cells.
DISCUSSION. Cytotoxic T lymphocytes initiate the destruction of microbial DNA, as well as the genome of the target cell, thereby eliminating potentially infectious DNA. The functioning of cytotoxic T lymphocytes is affected by hereditary mutations associated with perforin and occurring in genes encoding proteins involved in exocytosis.
CONCLUSION. CD8+ T lymphocytes proliferate and differentiate into CTLs containing cytotoxic granules, which enable them to lyse infected cells. Differentiation into CTLs is accompanied by the acquisition of mechanisms for destroying target cells and controlling various transcription factors. In the case of chronic antigen exposure (tumors, chronic viral infections), CD8+ T cells initiate a response and begin to express inhibitory receptors that suppress the immune response.

KEYWORDS: marine medicine, perforin proteins, lymphocytes, cytokines, granzymes, receptors, hereditary mutations, transcription factors, immune response

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ДИФФЕРЕНЦИРОВКА И ФУНКЦИИ CD8$^+$-ЭФФЕКТОРНЫХ Т-КЛЕТОК

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ЦЕЛЬ. Проанализировать отечественную и зарубежную научную литературу, отражающую механизмы активации CD8$^+$ Т-лимфоцитов, лизис инфицированных клеток и формирование возможных иммунных дисфункций.
МАТЕРИАЛЫ И МЕТОДЫ. Изучена и проанализирована современная отечественная и зарубежная научная литература за период 1998–2025 гг., посвященная биологическим особенностям активации CD8$^+$ Т-лимфоцитов. Поиск первоисточников проводился в базах данных РИНЦ, PubMed, Scopus и Web of Science. Использовали следующие сочетания ключевых слов: субпопуляции Т-лимфоцитов, цитотоксические Т-лимфоциты, цитокины, гранулизины, белки-перфорины, факторы транскрипции, наследственные мутации. Проанализировано 49 статей.
РЕЗУЛЬТАТЫ. Дифференцировка CD8$^+$ Т-клеток зависит от многих факторов, в том числе и от CD4$^+$ Т-лимфоцитов, при отсутствии которых не происходит образования эффекторных CD8$^+$ Т-клеток и Т-клеток-памяти. Интерлейкины (IL)-2, IL-12 и IFN I типа обеспечивают пролиферацию CD8$^+$ Т-клеток, их дифференцировку в цитотоксические лимфоциты. стимулируют экспрессию факторов транскрипции T-BET, BLIMP-1, обеспечивающих экспрессию перфорина, гранзимов. При хронических вирусных инфекциях имеет место блокировка дифференцировки Т-клеток, осуществляемая белком программируемой клеточной гибели-1, а также CTLA-4, TIM-3, LAG-3 и другими. KIR-рецепторы передают ингибирующие сигналы, препятствующие уничтожению неинфицированных клеток цитотоксическими Т-лимфоцитами. Благодаря экспрессии рецепторов NKG2D, распознающих MHC-подобные молекулы I класса — MICA, MICB и ULBP, которые экспрессируются только инфицированными или трансформированными клетками, не происходит повреждения «нормальных» клеток и тканей, активируя нуклеазы в клетках-мишенях.
ОБСУЖДЕНИЕ. Цитотоксические Т-лимфоциты инициируют разрушение микробной ДНК, а также генома клетки-мишени, тем самым устраняя потенциально инфекционную ДНК. На функционировании цитотоксических Т-лимфоцитов отражаются наследственные мутации, связанные с перфорином и происходящими в генах, кодирующих белки, участвующие в экзоцитозе.
ЗАКЛЮЧЕНИЕ. CD8$^+$ Т-лимфоциты пролиферируют и дифференцируются в CTL, содержащие цитотоксические гранулы, что обеспечивает лизис ими инфицированных клеток. Дифференцировка в CTL сопровождается приобретением механизмов для уничтожения клеток-мишеней и управления различными факторами транскрипции. В случае хронического воздействия антигена (опухоли, хронические вирусные инфекции) CD8$^+$ Т-клетки инициируют ответную реакцию и начинают экспрессировать ингибирующие рецепторы, супрессирующие иммунный ответ.

КЛЮЧЕВЫЕ СЛОВА: морская медицина, белки-перфорины, лимфоциты, цитокины, гранзимы, рецепторы, наследственные мутации, факторы транскрипции, иммунный ответ

Introduction. Historically and justifiably, the priority in studying T-lymphocyte population was given to CD4$^+$ T-lymphocytes [1–3]. It was believed that CD8$^+$ T-lymphocytes are cytotoxic effector cells (CTL), destroying pathogens, using an intracellular type of parasitism, which perform tumor cell eradication and play a crucial role in acute allograft rejection [4, 5]. However, there are a lot of peculiarities in all these processes, impacting on efficacy of cytotoxic mechanisms [6]. Studying these peculiarities is another very important contribution to the understanding of possible violation of immune homeostasis [7, 8]. CTL not only lyse infected and tumor cells, but also produce interferon-γ (IFN-γ), activating macrophages, and promote immune protection against many types of cancer [9]. CD8$^+$ T-cells recognize peptides, represented as molecules of the major histocompatibility complex (MHC) of class I, i. e. being MHC-restricted cells [10, 11]. Studying features of CD8$^+$-cell reactions, their clonal expansion after antigen activation and other signals will enable us to understand how naive CD8$^+$-cells without cytolytic effects differentiate into functional CTLs and how they lyse other cells [12–14].

Objective. Analyze Russian and foreign scientific literature reflecting the mechanisms of CD8+ T-lymphocyte activation, lysis of infected cells, and the formation of possible immune dysfunctions.

Materials and methods. We studied contemporary Russian and foreign scientific literature for the period 1998–2022 devoted to the biological features of CD8+ T-lymphocyte activation. The search for primary sources was conducted from May 2024 to April 2025, mainly in the PubMed,

Scopus, and Web of Science databases. The following combinations of keywords were used: T-lymphocyte subpopulations, cytotoxic T-lymphocytes, cytokines, granulin, perforin proteins, transcription factors, hereditary mutations. The works were filtered manually, and the study results were analyzed and discussed by all authors.

Results. The differentiation of $CD8^+$ T cells into effector cells is accompanied by the generation of a large pool of functional CTLs containing numerous modified lysosomes with perforin and granzyme proteins. The activation of naive $CD8^+$ T cells proceeds in stages, similar to the reactions of $CD4^+$ T cells, but has two unique features: it depends on cross-presentation of the antigen by a specialized subpopulation of dendritic cells (DC) and also requires the assistance of $CD4^+$ T cells. Antigens presented to $CD8^+$ T cells are localized in the cytosol of antigen-presenting cells (APC), since only cytosolic proteins are processed by proteasomes into molecules delivered to the endoplasmic reticulum for placement in the MHC class I molecule site. This function is primarily performed by classical dendritic cells (cDC). This process of cross-presentation is an important first step in the activation of naive $CD8^+$ T cells [15, 16].

In viral infections, APCs express costimulatory molecules of the B7 family, which interact with CD28 on naive T cells and provide the necessary second signals. However, in latent viral infections and tumor-associated reactions, innate immune responses are relatively weak because these viruses and tumor cells express low levels of molecules that activate receptors on cells involved in innate immune responses, or do not produce any of them at all. In these situations, secondary signals are provided by $CD4^+$ T cells. $CD4^+$ T cells activate naive $CD8^+$ T lymphocytes through several mechanisms. For example, $CD4^+$ T cells secrete cytokines that stimulate the differentiation of $CD8^+$ T cells. It is known that activated $CD4^+$ T cells express the CD40 ligand (CD40L), which binds to CD40 DCs containing antigen. This interaction activates APCs, making them more effective in stimulating $CD8^+$ T cell differentiation, partly by increasing the expression of costimulatory molecules. This process is called APC licensing [17–19].

The importance of $CD4^+$ T cells in the development of CTL responses is illustrated by studies in mice lacking $CD4^+$ T cells. In these mice, viral infections do not lead to the formation of effective CTLs or $CD8^+$ memory cells, and infected cells are not destroyed. The absence of the helper function of $CD4^+$ T cells explains the defects in CTL formation in individuals infected with human immunodeficiency virus (HIV), which lyses predominantly $CD4^+$ T cells. There is also evidence that $CD4^+$ T cells are more important for the generation of $CD8^+$ memory T cells than for the differentiation of naive $CD8^+$ T cells into effector CTLs. Effector cells (differentiated CTLs that lyse other cells) can be activated without costimulation and are capable of lysing any cell that expresses an antigenic protein in the cytosol and presents the corresponding peptide in MHC class I molecules [20, 21].

These processes are facilitated by interleukin (IL)-2 (IL-2), secreted by $CD8^+$ or $CD4^+$ T cells, which promotes the proliferation of $CD8^+$ T cells and their differentiation into CTLs and memory cells. $CD8^+$ cells express β and γ chains of the IL-2 receptor and can temporarily express high levels of α chains after activation. It has been established that IL-12 and type I IFN stimulate the differentiation of naive $CD8^+$ T cells into effector CTLs. These cytokines are secreted by various DC populations during the development of innate immune response mechanisms to viral and some bacterial antigens. It should be noted that these same cytokines are involved in the differentiation of $CD4^+$ T cells into Th1 cells. Thus, IL-12 and type I IFN promote the development of these two effector populations by stimulating the expression of related transcription factors T-BET (for both Th1 cells and CTLs) and eomesoderm (for CTLs — T-box brain protein 2; Tbr2, encoded by the EOMES gene). IL-15 is secreted by many cell types, including DCs, and ensures the survival of CD8+ memory T cells. Mice lacking IL-15 show a significant loss of $CD8^+$ memory T cells [22, 23].

The gene expression program during CTL differentiation is carried out by transcription factors: T-BET, eomesoderm, which is structurally related to T-BET; and BLIMP-1. The optimal expression of these transcription factors depends on IL-2, IL-12, type I interferons, and the JAK-STAT signaling pathways they activate. Cytokines interact with each other to promote the transcriptional program of CTL differentiation. Thus, IL-2-induced STAT5 together with IL-12-induced STAT4 are necessary for the expression of T-BET and BLIMP-1, which stimulate the expression of perforin, granzymes, and certain cytokines, especially IFN-γ [24, 25].

In many viral infections, $CD8^+$ T cells are suppressed, and the generation of CTL effector responses declines, resulting in T-cell exhaustion. The phenomenon of exhaustion occurs in chronic viral infections and is associated with prolonged viral persistence. A strong and persistent immune response to chronic infections can lead to severe tissue damage. Apparently, T-cell depletion has developed as a mechanism to limit the immunopathology associated with chronic infection. The same mechanism probably reduces the body's response to any chronic or persistent antigenic stimulus [26, 27].

Repeated stimulation leads to numerous functional impairments in T cells, including reduced proliferative capacity, decreased IFN-γ production, and weak cytotoxic activity, and thus $CD8^+$ cells are unable to fight infections or tumor processes. These defects are the result of blocked T-cell differentiation associated with increased expression of inhibitory receptors by repeatedly stimulated T cells. These inhibitory receptors include programmed cell death protein-1 (PD-1), as well as CTLA-4, TIM-3, LAG-3, and others. The important role of PD-1 as a mediator of exhaustion is evidenced by the change in the phenotype of $CD8^+$ cells obtained using monoclonal antibodies against PD-1. Studies in mice show that antigen recognition by $CD8^+$ memory T cells with simultaneous PD-1 signaling leads to irreversible shutdown (exhaustion) of the phenotype, while PD-1 blockade elicits effective responses by allowing memory cells to be activated into functional (non-exhausted) effectors. T-cell exhaustion in humans is observed in infections such as HIV and viral hepatitis C, as well as in the ability of some tumors to "evade" the immune response [28, 29].

CTL-mediated lysis involves specific recognition of target cells and delivery of proteins to the target cell, causing its death. CTLs lyse targets containing the same peptide antigen at MHC class I molecule sites, triggering the proliferation and differentiation of naive $CD8^+$ T cells into functional CTLs. Such lysis of CTL target cells is highly antigen-specific, so cells that do not contain the MHC-peptide complex are not damaged. The specificity of destruction is achieved by the formation of an immune synapse between the CTL and the antigen-expressing target cell. The molecules that actually carry out lysis are secreted into the synapse and do not diffuse into other nearby cells. Target cells die as a result of apoptosis, which does not cause intense inflammation. Thus, CTL-mediated lysis does not cause concomitant damage to neighboring normal tissues. CTL-mediated lysis of targets consists of antigen recognition, CTL activation, and lysis itself. Each of these stages is controlled by specific molecular interactions [30, 31].

CTLs use their antigen receptor, CD8 co-receptor, and adhesion molecules to bind to target cells. For effective recognition by CTLs, target cells must express the MHC class I complex, a peptide that acts as a ligand for the T-cell receptor (TCR). Signal transmission via TCR promotes the formation of a specialized immune synapse between TCR, signaling molecules, and the outer ring of integrins, in particular, antigen 1 associated with leukocyte function-associated antigen 1 (LFA-1), CTL, which binds to its ligand, intercellular adhesion molecule 1 (ICAM-1), or to the target cell. Inside the ring between the membranes of the two cells, there is a closed gap. Using immunofluorescence microscopy, individual sections of the CTL membrane can be observed inside the ring with a signaling section that includes TCR, CD8, signaling proteins (such as protein kinase C-Θ and tyrosine kinase LCK), and a secretory section that looks like a slit. The interaction of the TCR with the antigen triggers biochemical signals that activate the CTL, leading to the process of cell lysis. However, cytokines and costimulatory molecules expressed by DCs, as well as T cell support necessary for the differentiation of naive $CD8^+$ T cells into CTLs, are not essential for the generation of an effector CTL pool [29, 32].

CD8+ CTLs also express receptors similar to those expressed by natural killer (NK) cells, which contribute to both the regulation and activation of CTLs. Some of these receptors belong to the killer immunoglobulin receptor (KIR) family; they recognize MHC class I molecules on target cells but are not specific for a particular peptide-MHC complex. KIR receptors transmit inhibitory signals that prevent CTLs from destroying uninfected cells. In addition, CTLs express the NKG2D receptor, which recognizes MHC-like class I molecules — MICA, MICB, and ULBP — that are expressed by infected or transformed cells. The combined signaling effects and TCR antigen recognition enhance the killer effects of CTLs [33, 34].

The main mechanism of CTL-mediated destruction of target cells is the delivery of cy-

totoxic proteins from cytoplasmic granules to the target cell, thereby triggering its apoptosis within 2–6 hours. Recognition of the TCR CTL antigen leads to the reorganization of the actin cytoskeleton, during which the center of CTL microtubule organization moves to the cytoplasm region located near the contact with the target cell. CTL cytoplasmic granules are transported along microtubules and concentrated in the synaptic region, and the granule membrane fuses with the plasma membrane in the synaptic region. The fusion of membranes leads to the exocytosis of the contents of CTL granules into a limited space within the synaptic ring, between the plasma membranes of CTLs and target cells. The main proteins of CTL and NK cell granules that mediate cytotoxic effects are granzymes and perforins. Human CTLs have five different granzymes—A, B, H, K, and M—of which granzymes A, B, H, and K are secreted at high levels. All granzymes are serine proteases. Granzyme B cleaves proteins and thereby activates caspases, which induce apoptosis. The granules also contain the intracellular proteoglycan serglycin, which keeps granzymes and perforins in the granules in an inactive state [35, 36].

Perforin, a molecule homologous to complement component C9, disrupts the functioning of cell membranes. Its main function is to facilitate the delivery of granzymes into the cytosol of the target cell. However, how this is achieved is still not entirely clear. Perforin can polymerize and form pores in the plasma membrane of the target cell containing cholesterol, but these pores may be too small for granzymes to penetrate. According to one model, complexes of granzyme B, perforin, and serglycin are released from CTLs into the target cell, and the introduction of perforin into the target cell membrane triggers a membrane repair process that leads to the internalization of both perforin and granzymes into endosomes. In addition, perforin can act on the endosomal membrane, promoting the release of granzymes into the cytosol of the target cell. Once in the cytosol, granzymes cleave various substrates, including caspases, and initiate apoptotic cell death. Thus, granzyme B cleaves and activates caspase-3, as well as BCL-2, a member of the BID family that initiates the mitochondrial pathway of apoptosis. Granulysin, contained in the granules of human CTL and NK cells, damages membranes that are low in cholesterol, which is characteristic of bacteria but not mammalian cells. This ensures the delivery of granzymes, which induce the formation of active oxygen species that destroy intracellular parasitic microbes [36–38].

When activated, CTLs express a membrane protein called FAS ligand (FAS-L), which binds to the FAS receptor expressed by many cell types. This interaction also leads to the activation of caspases and apoptosis of targets expressing FAS. Studies with knockout mice lacking perforin, granzyme B, or FAS-L have shown that perforin and granzyme B are the main mediators of $CD8^+$ T cell lysis. After lysis, the CTL separates from the target cell, which usually occurs before the target cell dies. The CTLs themselves are not damaged during the destruction of target cells. Two mechanisms have been proposed to explain CTL protection. First, CTLs express the serine protease inhibitor Spi6 in the cytosol, which neutralizes granzymes, including granzyme B. Second, CTL granules contain the proteolytic enzyme cathepsin B, which is delivered to the surface of CTLs during granule exocytosis, where it destroys stray perforin molecules located near the CTL membrane. However, it is unknown how cathepsin B is delivered to the surface of CTLs rather than target cells [26, 28].

After activation, naive $CD8^+$ T cells differentiate not only into functional CTLs, but also into long-lived memory cells. Functionally, $CD8^+$ memory T cells are inactive and require antigen restimulation to differentiate into active effector CTLs. The general principles of $CD8^+$ memory T cell formation are similar to those for other T cells. Memory T cells that reside for long periods in non-lymphoid tissues without recirculation (tissue-resident memory T cells, or TRM) are also $CD8^+$ T cells. T cells secrete IFN-γ, which activates macrophages. In fact, the secretion of IFN-γ in response to specific peptides is an indicator of the differentiation of T lymphocytes into antigen-specific $CD8^+$ T cells. It is likely that both $CD4^+$ Th1 cells and $CD8^+$ T cells contribute to IFN-γ-induced phagocytosis. $CD8^+$ T cells are also involved in some cytokine-induced inflammatory reactions in hypersensitivity reactions, in which IFN-γ-secreting $CD8^+$ T cells appear even earlier than $CD4^+$ T cells and outnumber them. IL-17-producing $CD8^+$ T cells are abundant in some chronic inflammatory skin diseases (psoriasis) [37–39].

The role of CD8+ CTL is particularly important in cases where phagocytosis mechanisms are

ineffective against intracellular parasitic microorganisms. This occurs in the following situations: firstly, most viruses reproduce in cells in which oxygen-dependent and oxygen-independent phagocytosis mechanisms are ineffective. Second, even in phagocytes, some microbes can leave the phagolysosome and reside in the cytosol of the cell, where bactericidal mechanisms are ineffective. Mycobacterium tuberculosis and Listeria monocytogenes have such effects. Therefore, such infections can be neutralized primarily by $CD8^+$ CTL in adaptive immune responses. In addition, caspases, which are activated in target cells by granzymes and FAS-L, cleave many substrates and activate DNA-degrading enzymes, but they do not distinguish between host and microorganism molecules. Consequently, by activating nucleases in target cells, CTLs can initiate the destruction of microbial DNA as well as the target cell genome, thereby eliminating potentially infectious DNA. A massive increase in the number of $CD8^+$ T cells during infectious and inflammatory processes is necessary to combat these infections. Defects in CTL development and activity lead to increased susceptibility to viral and some bacterial infections and reactivation of latent viral infections (such as Epstein-Barr virus infection), which are normally controlled by virus-specific $CD8^+$ CTLs [40-43].

Discussion. Thus, as indicated by Russian and foreign scientists, the destruction of infected CTL cells is the cause of tissue damage in some infectious diseases [44, 45]. For example, when infected with hepatitis B viruses, infected liver cells die as a result of the reaction of CTL and NK cells of the host, rather than under the action of viruses [46]. These effects of CTL can contribute to the development of immunopathology associated with many other common viral infections, such as influenza. CTLs are also important mediators of tumor immunity. In addition to their protective role, $CD8^+$ CTLs contribute to tissue destruction in some autoimmune diseases and to tissue transplant rejection [47–49].

CTL function is affected by hereditary mutations associated with perforin and occurring in genes encoding proteins involved in exocytosis. This usually occurs in a rare familial form of the disease, hemophagocytic lymphohistiocytosis (HLH), associated with impaired macrophage activation. In HLH and other similar diseases CTL, activated by viral antigen, secrete IFN-γ, but do not lysis virus-infected cells due to ineffective microbicidal effects. As a result, there is persistence of viral antigen, chronic secretion of IFN-γ by $CD8^+$ T cells, and excessive activation of macrophages by IFN-γ. Severe and prolonged macrophage activation underlies disease manifestations associated with enlargement of the spleen caused by an increase in the number of activated macrophages (lymphohistiocytosis) phagocytizing and destroying normal erythrocytes (hemophagocytosis) [28, 40].

Conclusion. $CD8^+$ T-lymphocytes proliferate and differentiate into CTLs containing cytotoxic granules, which ensures their lysis of infected cells. Differentiation of $CD8^+$ T cells into functional CTLs and memory cells begins with recognition of antigen presented by dendritic cells, with signals from $CD4^+$ T cells and, in some situations, with costimulation and stimulatory effects of cytokines. Differentiation into CTL is accompanied by the acquisition of mechanisms for killing target cells and controlling various transcription factors. In the case of chronic antigen exposure (tumors, chronic viral infections), $CD8^+$ T cells initiate a response and begin to express inhibitory receptors that suppress the immune response. $CD8^+$ CTL lysed cells express cytosolic peptides presented at the sites of class I MNS molecules. CTL-mediated killing is mainly the result of exocytosis of secretory granules and the microbicidal effects of the perforin protein. Perforin also initiates apoptosis processes. The granulysin protein is also involved in the lysing effects. IFN-γ secretion by $CD8^+$ T-cells promotes macrophage activation, phagocytosis and development of delayed-type hypersensitivity reactions.

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