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CD8+ T Cells as Multitasking Cells in Immunotherapy: A Review Update

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Abstract

CD8+ T cells, referred to as cytotoxic T lymphocytes (CTLs), play a pivotal role in adaptive immunity, particularly in combating viral infections and malignancies. CD8 T cells, derived from bone marrow progenitors and matured in the thymus, play an essential role in immune defense through their cytotoxic activity. These cells are distinguished by their ability to recognize and eliminate cells that present specific antigens via the major histocompatibility complex (MHC) class I molecules. Upon activation by antigen recognition, they proliferate and differentiate into effector cells capable of eliminating infected or abnormal cells.CD8+ T cells develop in the thymus and express the CD8 co-receptor, which interacts specifically with MHC class I molecules. When a naïve CD8+ T cell encounters an antigen-presenting cell (APC) displaying an antigen bound to MHC class I, it undergoes activation, clonal expansion, and differentiation into cytotoxic effector cells. The primary function of these cells is to eliminate infected or malignant cells by inducing apoptosis through the release of cytotoxic granules containing perforin and granzymes or by engaging death receptors on target cells. Over the past few decades, CD8+ T cells have garnered significant attention for their potential in immunotherapy, particularly in cancer treatment. This review highlights the multifaceted roles of CD8+ T cells in immunotherapy, their mechanisms of action, and the challenges associated with harnessing their full potential.

Keywords: *CD8+ T cells; viral immunotherapy; cancer immunotherapy*

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Introduction

Conventional T cells play a critical role in the immune system, primarily consisting of CD4 and CD8 T cell subtypes, each with distinct functions in responding to pathogens. CD4 T cells, often termed helper T cells, are essential in orchestrating the immune response by interacting with professional antigen-presenting cells (APCs) that present antigenic peptides through MHC class II molecules. On the other hand, CD8 T cells, which recognize antigens displayed by MHC course I particles, serve a more coordinate part, essentially in their capacity to induce cytotoxicity, focusing on and killing contaminated or unusual cells such as those in tumors or viral contaminations. It has been well established that the CD8 cells can differentiate and mature in a well guided pathway. Determined from lymphoid progenitor cells in the bone marrow, CD8 T cells move to the thymus, where they develop undergo selection processes to become fully functional T cells.1 These develop CD8 T cells, regularly alluded to as naïve CD8 T cells, circulate in the periphery, anticipating actuation. Activation happens upon experiencing their particular antigen displayed by an MHC course I particle, regularly amid an resistant challenge such as an contamination or tumor presence[1-2]. Naïve CD8 T cells have gathered expanding consideration for their phenotypic and useful differing qualities, which uncovers a already

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underappreciated heterogeneity inside this population[3]. Whereas customarily seen as a uniform bunch prepared for enactment, later thinks about recommend that indeed inside the naïve CD8 pool, there exist subpopulations with distinctive capacities for multiplication, survival, and effector capacities, such as the capacity to react more energetically to contaminations. The cytotoxic role of CD8 T cells was originally recognized in the study of infectious diseases. When naïve CD8 T cells encounter a pathogen, they become activated, rapidly proliferating and differentiating into effector cells. These effector CD8 T cells are vital for selectively eliminating infected cells, thus safeguarding the host from severe infections. Their cytotoxic activity involves the release of molecules such as perforin and granzymes, which trigger apoptosis in target cells. The swift response of effector CD8 T cells is essential for controlling acute infections, limiting the spread and severity of the disease[4-5].

After the pathogen is eliminated, not all effector CD8 T cells are destroyed. Some of these cells transition into memory CD8 T cells, which are long-lived and remain dormant until they encounter the same antigen again. These memory CD8 T cells are a key feature of immunological memory, allowing the immune system to mount a faster and stronger response during future encounters with the same pathogen6. This capacity for "immunological recall" ensures that secondary infections are often controlled more effectively and rapidly than the initial exposure[4]. However, the chronic presence of an antigen can lead to a detrimental state known as T cell exhaustion. This marvel is especially watched in incessant viral contaminations and cancer, where CD8 T cells are ceaselessly uncovered to antigens without accomplishing total pathogen or tumor clearance.

Over time, these T cells continuously lose their effector capacities, counting cytokine generation and cytotoxicity, and enter a state of weariness characterized by the up-regulation of inhibitory receptors such as PD-17. Exhausted CD8 T cells have a diminished capacity to control infections and tumors, presenting a major barrier to effective management of infectious diseases and progress in cancer immunotherapy. These cells typically lose their ability to proliferate, produce cytokines, and kill infected or cancerous cells. The state of exhaustion in CD8 T cells is often caused by chronic exposure to antigens, as seen in persistent infections or tumors. Prolonged stimulation in these conditions can impair their function, leading to reduced effectiveness in controlling the disease. Comprehending the mechanisms that lead to T cell exhaustion is vital for creating therapeutic strategies to restore T cell function. Contributing factors include the upregulation of inhibitory receptors such as PD-1, LAG-3, and TIM-3, as well as changes in metabolism and transcriptional profiles. Therapeutic interventions, like checkpoint inhibitors like PD-1/PD-L1 inhibitors, seek to reverse exhaustion by blocking these inhibitory pathways, effectively reinvigorating T cell responses. By targeting these components, it may be possible to enhance the effectiveness of T cells in combating chronic infections and tumors. Current inquires about endeavors center on mediations such as resistant checkpoint inhibitors, which square the inhibitory signals that contribute to weariness, subsequently reestablishing CD8 T cell work and improving the resistant system's capacity to clear diseases or tumors[8-9].

Mechanisms of Action

CD8+ T cells employ several mechanisms to eliminate target cells:

Cytotoxic Granules: Once activated, CD8+ T cells release perforin, which forms pores in the target cell membrane, allowing entry of granzymes that trigger apoptosis. This granule-mediated killing is critical in controlling infections and tumor progression5.

Fas-FasL Interaction: CD8+ T cells can also induce apoptosis via the Fas (CD95) pathway. The engagement of Fas ligand (FasL) on T cells with Fas on the target cell surface triggers a cascade of signals leading to cell death[4-6].

Cytokine Production: Activated CD8+ T cells secrete pro-inflammatory cytokines, such as interferon-gamma (IFN-γ), which enhances their cytotoxic activity and modulates the tumor microenvironment to promote immune cell infiltration and anti-tumor immunity[10].

Viral Immunotherapy

There are several viral immunotherapies among which CD8 T cells play the central role which is implemented to kill and destroy virus-infected cells. By overcoming challenges such as T cell depletion and utilizing techniques like checkpoint inhibitors, receptive T cell treatment, and restorative immunizations, immunotherapy looks for to tackle the full potential of CD8 T cells to treat incessant viral diseases and related maladies. It is well established that CD8+ T cells can

destroy the cancer cells; furthermore, these cells can be used for controlling viral diseases. They recognize viral peptides displayed by tainted cells and kill these cells to avoid viral replication. This highlight has been tackled in viral vector-based antibodies and treatments, where CD8+ T cells are prepared to recognize and target cells contaminated with particular infections. CD8 T cells has potent cytotoxic ability which is implemented by targeting and eliminating virus infected cells and this can be used as viral immunotherapy. Their inclusion in immunotherapy points to upgrade or reestablish the resistant system's capacity to control viral contaminations, especially incessant or diligent ones like HIV, hepatitis B (HBV), and hepatitis C (HCV), as well as infections related with cancers, such as Epstein-Barr infection (EBV) or human papillomavirus (HPV)[11].

Activation and Cytotoxic Function: CD8 T cells are central to viral immunotherapy due to their capacity to recognize and devastate the infected cells. Upon experiencing an infection, antigen-presenting cells (APCs) show viral peptides on MHC course I particles. This actuates naïve CD8 T cells, which multiply and differentiate into effector T cells able of killing infected cells. These effector CD8 T cells create particles such as perforin and granzymes, which initiate apoptosis in the target cell, viably restricting viral replication[4-6]. In the context of viral immunotherapy, strategies often focus on enhancing the initial activation and expansion of virus-specific CD8 T cells. This is crucial because many viruses, especially chronic ones like HIV and HBV, have evolved mechanisms to evade immune detection or suppress the activity of CD8 T cells, allowing them to persist in the host[10].

Overcoming T Cell Exhaustion: One of the primary challenges in viral immunotherapy is T cell exhaustion. In chronic viral infections, CD8 T cells are repeatedly exposed to viral antigens, leading to a state of dysfunction characterized by reduced cytokine production, impaired proliferation, and the up regulation of inhibitory receptors like PD-1[11]. Exhausted T cells lose their capacity to control viral replication effectively, making it difficult for the immune system to clear the infection. To combat this, immune checkpoint inhibitors (ICIs), such as anti-PD-1 antibodies, have been developed. These drugs block inhibitory signals that prevent T cell activity, effectively "reawakening" exhausted CD8 T cells[12]. By removing these brakes, ICIs can restore the effector functions of CD8 T cells, improving their ability to attack and clear infected cells. This approach has shown promise not only in cancer immunotherapy but also in viral infections, where it helps reinvigorate virus-specific CD8 T cell responses.

Adoptive T Cell Therapy: Adoptive T cell therapy is another innovative strategy in viral immunotherapy. This involves isolating virus-specific CD8 T cells from a patient, expanding them in vitro, and re-infusing them back into the patient to boost the immune response. In the case of viral infections associated with cancer, such as EBV-driven lymphomas, adoptive transfer of virus-specific T cells has demonstrated significant therapeutic benefits[13]. These therapies provide a direct boost of functional CD8 T cells that can target and eliminate virus-infected or cancerous cells.

Vaccine-Based Approaches: Therapeutic vaccines are another method to harness the power of CD8 T cells. Unlike preventive vaccines, therapeutic vaccines aim to stimulate a robust CD8 T cell response in individuals already infected with a virus. These vaccines deliver viral antigens to the immune system in a way that promotes the activation and expansion of virus-specific CD8 T cells, potentially controlling or even clearing the infection[14]. A notable example is the success of vaccines against human papillomavirus (HPV), which prevent cervical cancers by eliciting strong CD8+ T cell responses against viral oncoproteins[15]. Similarly, CD8+ T cells are involved in the control of chronic viral infections like HIV, where they contribute to the elimination of infected cells despite the presence of latent reservoirs that remain a challenge in developing a cure.

Cancer Immunotherapy

CD8 T cells are central to the success of cancer immunotherapy due to their potent cytotoxic functions, enabling them to directly recognize and eliminate cancerous cells. Often referred to as "killer" T cells, CD8 T cells play a critical role in the body's immune surveillance system, constantly patrolling for abnormal or infected cells. In the context of cancer, immunotherapy strategies aim to harness or enhance the ability of these cells to target and destroy tumor cells effectively.

Activation of CD8 T Cells in Cancer Immunity: CD8 T cells are activated through a series of interactions with antigen-presenting cells (APCs), particularly dendritic cells. These APCs present tumor-specific antigens on major histocompatibility complex (MHC) class I molecules, which are

recognized by the T cell receptor (TCR) on CD8 T cells4. This recognition, combined with co-stimulatory signals and cytokine support (notably from IL-2, IL-12, and IFN-γ), leads to the activation, proliferation, and differentiation of naïve CD8 T cells into effector T cells. Once activated, effector CD8 T cells migrate to the tumor site, where they recognize and bind to cancer cells displaying the same antigen16. Their cytotoxic activity is then unleashed, involving the release of perforin and granzymes. Perforin creates pores in the target cell membrane, allowing granzymes to enter and induce apoptosis, effectively killing the cancer cel[16].

Overcoming Tumor-Induced Immune Suppression: A significant challenge for CD8 T cells in cancer is overcoming the immunosuppressive tumor microenvironment (TME). Tumors employ several strategies to evade immune detection and suppress the activity of cytotoxic T cells. These include: Immune checkpoint pathways; Treg and MDSCs; Metabolic competition. Immune checkpoint pathways: Tumors often express ligands like PD-L1, which bind to inhibitory receptors such as PD-1 on CD8 T cells[11]. This interaction dampens the T cell response, reducing their ability to kill cancer cells. This immune suppression is particularly pronounced in "exhausted" T cells, which have been chronically exposed to tumor antigens. Treg and MDSCs: Tumor-associated regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) release immunosuppressive cytokines, such as IL-10 and TGF-β, which inhibit CD8 T cell function. Tregs also compete for IL-2, reducing the availability of this growth factor for effector T cells[17]. Metabolic competition: Tumor cells can create a nutrient-deprived environment by consuming glucose and other vital resources needed by CD8 T cells for optimal function[18]. Additionally, they produce immunosuppressive molecules like adenosine and lactate, which further inhibit T cell activity[19]. To counteract these suppressive mechanisms, cancer immunotherapy strategies aim to reinvigorate CD8 T cell function and enhance their persistence in the TME.

Immune Checkpoint Inhibition: One of the most significant advancements in cancer immunotherapy is the development of immune checkpoint inhibitors (ICIs). These therapies target inhibitory pathways, such as PD-1/PD-L1 and CTLA-4, which are exploited by tumors to suppress CD8 T cell function. PD-1/PD-L1 inhibitors: These drugs block the interaction between PD-1 (expressed on T cells) and PD-L1 (expressed on tumor cells), preventing the "off" signal that inhibits T cell activity. By blocking this pathway, checkpoint inhibitors can restore the cytotoxic function of exhausted CD8 T cells, enabling them to attack and destroy cancer cells[20]. CTLA-4 inhibitors: CTLA-4 is another inhibitory receptor on T cells that competes with the co-stimulatory receptor CD28 for binding to B7 molecules on APCs. By blocking CTLA-4, these therapies promote a stronger activation signal, enhancing CD8 T cell proliferation and function. Checkpoint inhibitors have shown remarkable success in treating various cancers, including melanoma, non-small cell lung cancer, and renal cell carcinoma[21]. They represent a powerful tool in restoring the anti-tumor activity of CD8 T cells.

Adoptive T Cell Therapy: Adoptive T cell therapy (ACT) is a form of personalized cancer immunotherapy that involves extracting T cells from a patient, engineering or expanding them ex vivo, and reinfusing them back into the patient. The most prominent form of ACT is chimeric antigen receptor (CAR) T cell therapy, in which CD8 T cells are genetically modified to express receptors specific to antigens on cancer cells[22]. CAR T cell therapy. This approach enhances the ability of CD8 T cells to recognize and attack cancer cells. By introducing a synthetic receptor that recognizes a specific tumor antigen, CAR T cells can bypass the need for MHC-mediated antigen presentation. CAR T cell therapy has been particularly effective in treating certain hematological cancers, such as B-cell leukemias and lymphomas[22-24]. TIL therapy: Tumor-infiltrating lymphocyte (TIL) therapy is another form of ACT, where CD8 T cells are isolated from the patient's own tumor, expanded in large numbers, and reinfused to bolster the immune response against the tumor. TIL therapy has shown promise, particularly in melanoma, where durable responses have been observed[25].

Cancer Vaccines and CD8 T Cell Stimulation: Therapeutic cancer vaccines aim to stimulate the immune system, particularly CD8 T cells, to recognize and attack tumor cells. These vaccines introduce tumor-associated antigens (TAAs) to the immune system, promoting the activation and expansion of CD8 T cells capable of targeting the tumor. By presenting these antigens in conjunction with immune-stimulatory adjuvants, cancer vaccines can enhance the CD8 T cell response, improving tumor control. While challenges remain, such as selecting the most effective antigens and overcoming the

immunosuppressive TME, therapeutic cancer vaccines are an emerging area of research with the potential to significantly boost the role of CD8 T cells in cancer immunotherapy[26].

The Future of CD8 T Cells in Cancer Immunotherapy:
As our understanding of CD8 T cell biology and tumor immunology deepens, the role of CD8 T cells in cancer immunotherapy will continue to expand. Researchers are exploring ways to enhance the persistence, specificity, and cytotoxic function of CD8 T cells in the TME. Combining immunotherapies, such as checkpoint inhibitors with CAR T cells or therapeutic vaccines, represents a promising approach to achieve more robust and durable anti-tumor responses. CD8 T cells are fundamental to the success of cancer immunotherapy, and strategies that enhance their function or overcome tumor-induced suppression hold immense promise for improving cancer treatment outcomes. Through immune checkpoint inhibitors, adoptive T cell therapies, and therapeutic vaccines, the role of CD8 T cells in fighting cancer is being harnessed to transform the landscape of oncology[26].

Challenges and Limitations

While CD8+ T cells hold immense promise in immunotherapy, several challenges remain. One major limitation is T cell exhaustion, a state where prolonged antigen exposure as seen in chronic infections or tumors leads to a loss of function. Exhausted T cells express inhibitory receptors like PD-1, TIM-3, and LAG-3, which dampen their effector functions[11]. While ICIs can reinvigorate these cells, not all patients respond to such therapies, and resistance mechanisms often develop. Additionally, tumor microenvironments can be immunosuppressive, hindering T cell infiltration and activation. Tumors may evade immune detection through loss of antigen presentation machinery or secretion of immunosuppressive cytokines, making it difficult for CD8+ T cells to mount an effective response.

Future Perspectives

To maximize the therapeutic potential of CD8+ T cells, ongoing research is exploring combination therapies. Combining ICIs with CAR-T therapy or other agents that modulate the tumor microenvironment could enhance the efficacy of T cell-based immunotherapies. The development of novel CAR constructs and the identification of new tumor-specific antigens are also promising strategies to overcome current limitations. Moreover, harnessing CD8+ T cells for infectious diseases remains a burgeoning area of interest, particularly in developing vaccines that generate robust and long-lasting cytotoxic responses against intracellular pathogens.

Conclusion

CD8+ T cells have emerged as a crucial element in the landscape of immunotherapy due to their capacity for targeted cytotoxicity and adaptability in combating malignancies and infections. Their ability to identify and destroy infected or malignant cells through antigen-specific mechanisms, coupled with their capacity for memory formation, positions them as versatile multitasks in immune responses. Advancements in adoptive T cell therapy, checkpoint inhibitors, and chimeric antigen receptor (CAR) T cell engineering have underscored their therapeutic potential. However, challenges such as tumor microenvironment-induced dysfunction, exhaustion, and the need for personalized approaches in targeting heterogeneous tumors still need to be addressed. Future innovations are likely to focus on enhancing the durability of CD8+ T cell responses, overcoming immunosuppressive barriers, and improving the precision of antigen targeting. By optimizing their activation, persistence, and resilience, CD8+ T cells can become even more powerful allies in the fight against cancer and other diseases. Continued research will be critical in realizing their full potential, offering hope for more effective and personalized immunotherapies. CD8+ T cells are versatile and potent components of the immune system with significant potential in immunotherapy. Their ability to directly eliminate infected or malignant cells makes them attractive targets for therapeutic interventions in cancer and viral infections. However, overcoming challenges such as T cell exhaustion and tumor evasion will be critical for fully harnessing their therapeutic potential in the future.

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Jahan T, Munshi SU conceived and designed the study, and wrote up the draft manuscript. Both authors have read and approved the final

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Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

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