Exploration of Key Steps and Mechanisms in the Development of Thymic T Cells

Zixin Zhang

***Abstract*—The development of T cells undergoes a series of finely regulated stages and selections in the thymus. This paper aims to delve into the key steps and mechanisms of this process. Through a detailed analysis of the DN, DP, and SP stages of T cell development, as well as discussions on the mechanisms of positive and negative selection, we reveal the complexity of T cell development. Additionally, this paper highlights the structural features, generation process, and gene rearrangement mechanisms of the T cell receptor (TCR), emphasizing the importance of TCR in T cell diversity and immune response.**

***Index Terms*—Thymus, T cell development, immune system, immune response.**

I. Introduction

In the immune system, T-cell development is a critical process that undergoes complex and sophisticated selection and regulation within the thymus to ensure the production of an efficient and diverse T-cell population[1]. These T cells will perform important immune functions in the body, including fighting infections, clearing tumour cells and maintaining immune homeostasis. The process of T cell development involves several key factors and regulatory mechanisms. This developmental process includes both positive and negative selection, by which the thymus balances the antigen recognition ability and self-tolerance of T cells. Dendritic cells play a crucial role in this process, acting as specialised antigen-presenting cells that initiate T cell development and function by presenting antigens[2]. Of particular note, CD4+ and CD8+ T cell subsets play distinct but equally important roles in the immune system[3]. CD4+ T cells play a key role in coordinating and regulating the immune response, whereas CD8+ T cells are directly involved in the clearance of infected and tumour cells[4]. An in-depth understanding of the development and functional characteristics of these T-cell subpopulations will help us to better understand their roles in different disease contexts and provide a theoretical basis for the design of more targeted immunotherapeutic regimens with fewer side effects.

In cancer treatment, the development of immunotherapy has attracted much attention. Removal of tumour cells by exploiting the immune function of T cells has emerged as a potential therapeutic strategy. For example, Inman et al. explored the functions and interactions of immune cells in pancreatitis and pancreatic cancer, as well as the potential for targeting pancreatic cancer using immune response-assisted immunotherapies[5]. Heuvers et al. emphasised the critical role of the immune system in tumour development and treatment by investigating the complex role of immune cells in the tumour microenvironment during the later stages of non-small cell lung cancer[6]. Bitsouni et al. used mathematical and computational methods to explore the complex interactions between newly identified tBregs cells and immune cells in breast cancer, and investigated the potential therapeutic effects of rituximab in this process [7]. However, in the cancer microenvironment, T cell function may be inhibited, limiting their effective action against tumours[8]. Therefore, in-depth study and understanding of T cell function is crucial for the development of more effective immunotherapeutic strategies[9-11].

Despite our understanding of some of the basic steps and mechanisms of T cell development, many details and complexities remain to be explored in depth. In-depth analyses of the key factors and regulatory mechanisms during T cell development can help to better understand the role of T cells in the immune system. In particular, insights into the developmental and functional characteristics of CD4+ and CD8+ T cell subsets will help us to better understand their role in responding to infections, tumours and autoimmune diseases. By delving into the mechanisms of T cell development in this paper, we can provide an important reference for the future development of new immunotherapeutic approaches and disease prevention strategies. A full understanding of T-cell development and function will provide a theoretical basis for designing more targeted immunotherapeutic regimens with fewer side effects, contributing to the health and well-being of mankind.

II. T Cell Development Process

T cell development in the thymus is divided into three phases involving two selections. The three stages are DN (double negative phase), DP (double positive phase), and SP (single positive phase). Negative and positive here represent CD4 and CD8 cells. If both are absent, it is called the double-negative phase; if both are present, it is called the double-positive phase; and if there is only one of these species, it is called single-positive stage. The two selections are positive and negative selection.

The development of T cells in the thymus is shown in the figure, starting with precursor T cells (Pre-T), which enter the cortex. This is the stage when there are neither CD4 nor CD8 cells, so it is the DN stage, i.e. double negative stage. From the DN-DP process, CD4 cells as well as CD8 cells will slowly grow. A positive selection, the DP-SP process, is performed immediately afterward. During this selection, some cells are eliminated, and if CD8 is selected, it is the CD8 monopositive phase (CD8 SP) if CD8 is selected, and

Manuscript received April 15, 2024
Zixin Zhang, Tiangong University/ School of Mathematical Sciences, Tianjin, China,

vice versa for CD4 single-positive phase (CD4 SP). Finally undergoing a negative selection, CD4 SP (CD8 SP) cells become mature CD4 T cells (CD8 T cells).

III. T Cell Activation

T cells play a crucial role in the cellular immune response. The first step in the cellular immune response is the activation of T cells. T cell activation is divided into CD4+ T cell activation and CD8+ T cell activation.

A. Antigen processing and presentation

There are two types of antigen-presenting cells:

(1) Specialized APC: continuously express MHC-II molecules. Examples include DCs (dendritic cells), macrophages, and B cells

(2) Non-specialized APC: can express MHC-II-like molecules under specific conditions. Examples include endothelial cells, epithelial cells Almost all nucleated cells can express MHC-I class I molecules on their surface.

During the DP-SP phase of T cell activation, the antigen-presenting cells undergoing positive selection are endothelial cells in the thymus, which can express both MHC-II and MHC-II molecules. cells, which can express both MHC-I and MHC-II molecules, but not all endothelial cells can express both MHC-II molecules. cells, but not all endothelial cells can express both MHC molecules.

B. Recognize

The most important thing in this process is to have the formation of immune synapses. The molecules are rearranged in this process - the molecules with recognition function are aggregated, and the other adhesion molecules are dispersed, forming a concentric circle structure with the TCR complex-pMHC as the center and the adhesion molecules dispersed to the left and right. This enhances the recognition function of the TCR and makes the binding more stable.

T cell activation is a two-signal process.

(1) The first signal is a recognition signal: TCR, CD4+ T cells bind to peptide complexes.

(2) The second signal is the co-stimulatory signal: the common co-stimulatory pairs are B7 and CD28. these two signals are known as the two conditions for T cells to be activated.

IV. CTL Killing Mechanism

Tumor cells become cancerous and undergo self-proliferation while infecting normal cells, eliciting a cellular immune response. Tumor cells are transduced and translated inside the cell to form tumor proteins, which are processed and presented as antigens by antigen-presenting cells (dendritic cells) to T cells to transmit signals. Dendritic cells stimulate the activation of helper T cells and killer T cells in response to IL-12. Helper T cells mediate the activation of killer T cells in the presence of IL-12, and killer T cells kill cancer cells in the direct or indirect presence of granzymes, perforin, the Fas-FasL pathway, and cytokines.

In this immunotherapy process, there are very many cells and cytokines that act to enhance the killing effect. Three types of cells are involved: NK cells, NK T cells, and CTL cells.

A. NK cells

NK cells (natural killer cells) are able to recognize the target cells and kill the mediators. They are derived from bone marrow lymphoid stem cells. NK cells, unlike T and B cells, are a class of lymphocytes that can kill tumor cells and virus-infected cells non-specifically without prior sensitization.

NK cells have a neutral affinity receptor for IL-2 and can undergo a value-added response to IL-2 stimulation. Activated NK cells can produce IFN-γ, TNF-α, and TNF-β. IL-2, IL-12, IFN-α, and TNF-α have positive regulatory effects on NK cell activation and differentiation of NK cells.

B. NK T cells

NK T cells have both TCR and NK cell receptors on their surface, which can produce cytokines in large quantities and exert cytotoxic effects similar to those of NK cells.

NK T cells can secrete large amounts of IL-4, IFN-γ, GM-CSF, IL-13 and other cytokines and chemokines in response to TCR stimulation, playing an immunomodulatory role, and NK T cells are one of the bridges linking intrinsic immunity and acquired immunity. NK T cells have NK cell-like cytotoxic activity after activation, and they can dissolve the target cells that are sensitive to NK cells, and the main effector molecules are perforin, Fas ligands, and IFN-γ. IL-12 induces the NK T cells to produce IFN-γ.

C. CTL cells (mainly mature CD8+ T cells)

Effector CD8+ T cells in the tumor microenvironment produce IL-2, IL-12, and IFN-γ, which enhances the cytotoxicity of CD8+ T cells. Activated CD8+ T cells also produce a variety of cytokines that contribute to host defense, such as TNFα. In addition, the cells produce molecules involved in cytolysis (e.g., granzyme B and perforin).

V. Cytotoxic Effect

In the process of cytotoxic action, it is the granzyme that really plays a "killing" role, and perforin only plays a transportation role. At the same time, the cytotoxin is taken only through the target cell membrane damage, resulting in the death of the target cell lysis. As shown in Fig. 2.

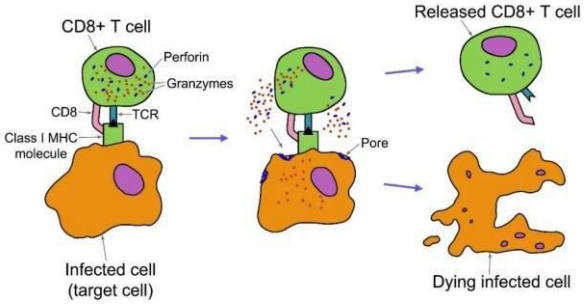

Fig.1. Cytotoxic killing of target cells

It takes only half an hour for a killer T cell to kill a target cell after coming into contact with it. But it does not mean that this requires large amounts of perforin and granzyme. Instead, CTLs use relatively small amounts of perforin and granzyme in each attack to accomplish their goals. Cytotoxic T-cells, after lysing and killing a target cell, repeat their action on another target cell. Therefore, a single CTL can fight multiple infected target cells. In the case of

an invasion so that thousands of cells may be infected, in order to amplify the killing capacity, CTLs proliferate once they arrive at the battlefield.

Another important feature of the cytotoxic mechanism of action is targeting; CTL cells lysed target cells in a targeted manner, and neither the perforin and granzyme mixture before or after killing affects the surrounding normal cells. There are two reasons for this.

(1) After the CTL recognizes the target cell, the CTL organelles are rearranged so that the perforin and granzyme mixture is close to the target cell and will act directly on the target cell after release;

(2) The target cell is killed by apoptosis and his contents are encapsulated by vesicles, which are later phagocytized by phagocytes and do not cause damage to normal cells in the environment.

VI. Membrane Molecules

Membrane molecules refer to FasL receptors on the surface of cytotoxic T cells and Fas receptors on the surface of target cells.

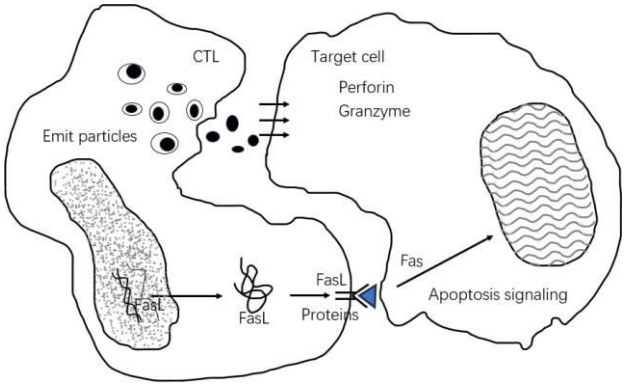

Fig.2. Rarget cell apoptosis

The mechanism of action of membrane molecules is shown in Fig 2. First is recognition. First FasL and Fas receptor have to bind, then adhesion molecules on the cell surface immobilize the target cell. This process is dependent on mg+ ions. Then transmit apoptotic signals. the FasL gene on the CTL chromosomal DNA is transcriptionally translated with the Fas gene on the putative cell chromosomal DNA. The mechanism of target cell killing by membrane molecules works in parallel with the killing mechanism by cytotoxins. Both require contact with the target cell.

VII. Cytokines

A. *Interferon*

Interferon is a glycoprotein produced by viruses or other interferon-inducing agents that stimulate humans or animals, and has a variety of effects including antiviral, antitumor, and immunomodulation. Macrophages, lymphocytes, T cells can produce interferon. type I interferon, antiviral effect is stronger than immunomodulatory effect; type II interferon, immunomodulatory effect is stronger than antiviral effect.

(1) Activated CD4 T cells secrete interferon, and IFN-α and IFN-β increase the expression of MHC I molecules in various cell types, whereas IFN-γ increases the expression of MHC I and MHC II in specific types of cells (usually referred to as antigen-presenting cells-macrophages, B-lymphocytes, dendritic cells). expression.

(2) Binds to interferon receptors on the cell surface, activates downstream signalling pathways, and induces cells to produce antiviral proteins to exert antiviral effects. Interferon is released and spreads quickly after synthesis, which can both interrupt the virus infection of infected cells and limit the spread of the virus, and has a certain inhibitory effect on most viruses.

B. *Cytokine TNF*

(1) Change the stability of target cell lysosomes, resulting in a variety of hydrolytic enzymes leakage;

(2) affect the cell membrane phospholipid metabolism;

(3) Alter target cell glucose metabolism to reduce pH in tissues;

(4) As well as activation of target cell nucleic acid endonuclease, degradation of genomic DNA and thus cause programmed cell death and other mechanisms to kill target cells.

The process of TNF-induced cell death is significantly slower than that of perforin cell lysis.

VIII. Conclusion

The key steps and mechanisms of thymic T cell development are crucial for the normal functioning of the immune system. Through a deeper understanding of T cell development details, we can better understand the regulatory mechanisms of immune responses, providing new insights and approaches for the prevention and treatment of related diseases.

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