

The Analogy between the Immune System and Human Life

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Abstract

The immune system operates as a complex organization with distinct roles and functions. Excitingly we recognized the similarities between the cellular dynamics of the immune system and our lives, activities, and behaviors. Observing the immune system can guide how to respond to various daily situations, including when to react, tolerate, or ignore. Recognizing this analogy between our lives and the immune system should motivate us to adopt a wisdom-based approach when investigating the mechanisms and future discoveries related to this system and to deepen our understanding of this complex system with newfound respect. In this context, the present review examines several integral biological processes of the immune system by drawing parallels between them and human life, activities, and behaviors to learn how we must behave based on the insights offered by this complex organization. The literature search was conducted in international databases such as PubMed/MEDLINE and Google Scholar search engine using English equivalent keywords from 1998 up to April 2023. The search strategy used the following subject heading terms: Immune system, analogy, human life, cellular dynamics, memory, tolerance, and ignorance. In conclusion, the immune system is a complex organization comprising various cells interacting within specific sites and networks, communicating, drawing experiences, and learning how to tolerate certain conditions that make it share certain similarities with human life.

Keywords

Immune System, Analogy, Memory, Tolerance, Ignorance

1. Introduction

The immune system works as a complex organization consisting of organs, cells, receptors, and proteins that are born and developed to work together by using

advanced biological network connections, and therapy to protect us from self and outside dangers, which is surprisingly quite similar to our own human lives in several aspects. The purpose of this article is to review the major integral mechanisms of the immune system in an analogous way to human life's behaviors and activities, as they are very similar in nature, and style of response, we will discuss these observations throughout the journey of the immune system from birth to death. Our main aim is to keep learning from our own self-immune system how to behave and react to promote both physical and well-being health.

2. Methods

This review aimed to review the significant integral mechanisms of the immune system in an analogous way to human life's behaviors and activities. Similarities and disparities in the existing evidence and literature were examined to obtain conclusive results. An electronic literature search was employed, including Pub Med (National Library of Medicine) and Google Scholar search engine for studies published between 1998 and 2024. The keywords operated for the search were "Immune system" OR "Immunity" AND "analogy" AND "ignorance" AND "human life" AND "tolerance" AND "cellular dynamics" AND "memory." A manual search for specified references from included studies, appropriate reviews, and gray literature was conducted for additional relevant studies not encountered in the database search. This review included original observational research that included cohort, case-control, cross-sectional studies, case reports, case series, and reviews published in English. In addition, non-relevant articles and studies that did not fulfil the eligibility criteria were excluded.

3. Origin and Population

Human beings originated from a single ancestor and, over time, have diversified into different lineages and populations, eventually migrating worldwide. With regard to cells, hematopoietic stem cells (HSCs) originate from the aorta-gonad-mesonephros region during embryonic development and can differentiate into all hematopoietic lineages, including erythrocytes, leukocytes, and platelets [1]. HSCs are located in the fetal liver and, subsequently, the bone marrow (Figure 1) [2] [3]. Leukocytes (neutrophils, basophils, eosinophils, lymphocytes, monocytes, and macrophages) constitute the cellular components of the immune system, and are akin to the citizens of a country, as they coexist, collaborate, and interact with each other dependently and independently, and similar to good citizens, surveil, maintain the homeostasis of, and protect their homeland. Each leukocyte type possesses different morphologies and functions. The immune system comprises two major branches: innate and adaptive [4] [5]. The innate immune system serves as the first line of defence of the human body, and includes, alongside physical and anatomical barriers, effector cells, antimicrobial peptides, soluble mediators, and cell receptors, which function as border soldiers that identify threats and foreign entities and either destroy or report them to higher authorities (the

adaptative immune system) [6].

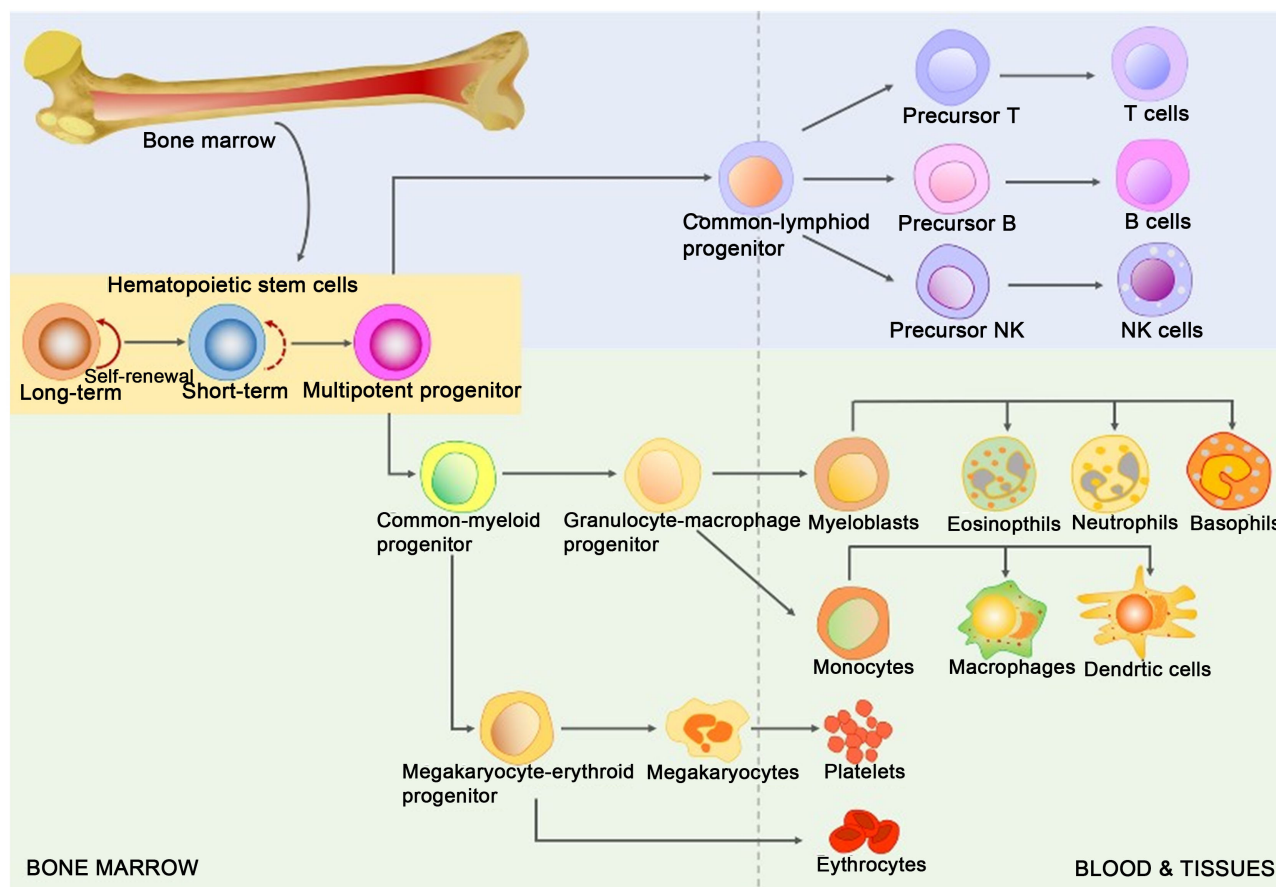


Figure 1. The hierarchical system model of hematopoietic stem cell (HSC) self-renewal and differentiation. HSCs are positioned at the top of the hematopoietic hierarchy. Multipotent progenitors can differentiate into all lineages [7].

4. Residence and Transportation

Immune cells are located throughout the human body and ensure the safety, security, and well-being of all bodily systems, protect against infectious hazards, and continuously monitor abnormal cells and cell growth. These roles of the immune system, along with the unique functions of different immune cells, necessitate specific sites of residence and modes of transportation. Immune cells originate from the bone marrow and subsequently migrate into the bloodstream before eventually settling in specialized tissues, namely, the thymus, lymph nodes, mucus membranes, and spleen [8]. Lymph nodes are distributed throughout the body at distinct locations, such as the tonsils, which are located near an opening of the body. Lymph nodes are interconnected via a special transportation network, the lymphatic system, which comprises a complex network of vessels that form pathways through which immune cells are transported throughout the body. The lymphatic system ensures safe and rapid antigen and immune cell transport and drainage of the lymph nodes, where immune actions and responses occur [9]. Lymph nodes contain the main immune cells, T and B cells, which are responsible for the most

integral aspects of the adaptive immune response: antigen presentation, functional cell differentiation, and cloning and production of specific immunoglobulins, depending on antigen types. T and B cells function as command centres or police stations where antigen-presenting cells (APCs) present antigens to T cells in a manner akin to victims being brought to a station, where a police officer examines the case and directs specific and appropriate actions (Figure 2).

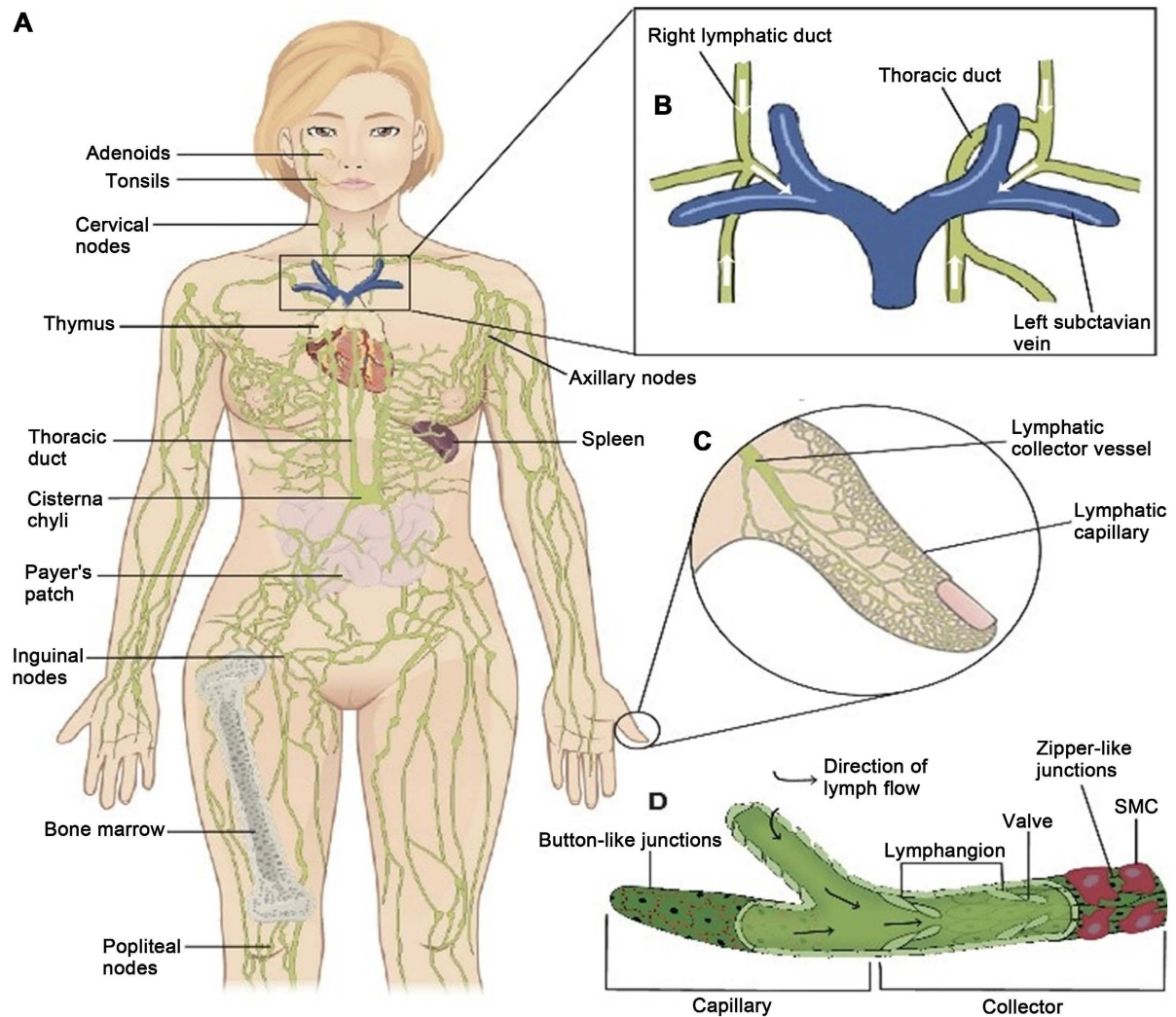


Figure 2. Anatomy of the lymphatic system [10].

5. Language and Communication

The immune system is a complex organization that requires a means of communication to connect all cell systems and orchestrate the complex operations of cellular immune interactions. [11] Similar to how languages have words for coding and decoding items, immune cells communicate via proteins called cytokines, which are secreted by activated immune cells. Cytokines function as chemical messengers, similar to the words in a language, and exert their effects by binding to the receptors of target cells, which decode the message and subsequently

transmit signals to the cell nuclei via multilevel pathways involving regulatory protein and molecule complexes. The ultimate outcome of these complex interactions is the encoding of new proteins or messengers (cytokines) necessary for subsequent cellular communication and actions.

Cytokines include chemokines, interferons, interleukins (ILs), lymphokines, and tumour necrosis factors, each of which belongs to a distinct family of cytokines with distinct classifications and roles. Two ILs, IL-1 and IL-2, were first named at the Second International Lymphokine Conference [12].

Examples of some cytokines and their actions [13]:

IL-1 Co-stimulation, cell activation, inflammation, fever, acute phase reactant

IL-2 Cell growth/activation

IL-4 Th2 differentiation, cell growth/activation, IgE isotype switching

IL-5 Cell growth/activation

IL-6 Co-stimulation, cell growth/activation, acute phase reactant

IL-10 Inhibits antigen-presenting cells, inhibits cytokine production

IL-12 Th1 differentiation

IL-18 Cell growth/activation, inflammation

IL-21 Cell growth/activation, control of allergic responses and viral infections

IL-23 Chronic inflammation, promotes Th17 cells

IFN- α Anti-viral, enhances MHC expression

IFN- γ Cell growth/activation, enhances MHC expression

TGF- β Inhibits cell growth/activation

TNF- α Co-stimulation, cell activation, inflammation, fever, acute phase reactant

6. Learning from Previous Experiences (Memory)

In the early 17th century, scientists discovered that the initial infection was the most severe, with subsequent infections being noticeably milder. It was speculated that the body's defence mechanism learns from previous infections, and trials based on the implementation of this theory were conducted.

Variolation was a method wherein a person was deliberately infected with particles from the sores of patients with smallpox, with the aim of inducing a milder form of the disease [14]. Although variolation was not entirely safe, it represented a novel scientific approach at the time for observing disease outbreaks and searching for a cure. In the 18th century, Edward Jenner noticed that milkmaids exposed to cowpox appeared to be immune to smallpox. Leveraging his knowledge of variolation, Jenner successfully vaccinated a child against smallpox using cowpox sores from an infected milkmaid [15]. This concept was of the human defence system keeping information on previous infections.

Similar to humans, one of the most notable functions of the human immune system is its ability to retain information regarding previously encountered challenges. In the case of the immune system, information on previously encountered infectious antigens, abnormal cells, signals, or stimuli is stored by its memory

system, which functions in a manner similar to a defence agency that keeps criminal records, enabling the immune system to respond more rapidly and effectively when encountering the same or similar threat a second time. This mechanism whereby the immune system recalls previous encounters with antigens is referred to as immunological memory [16]. Following exposure to a new antigen, immune cells differentiate and multiply to become memory T and B cells.

Over time, our understanding of immunological memory has led to the development and remarkable advancement of vaccination techniques [17].

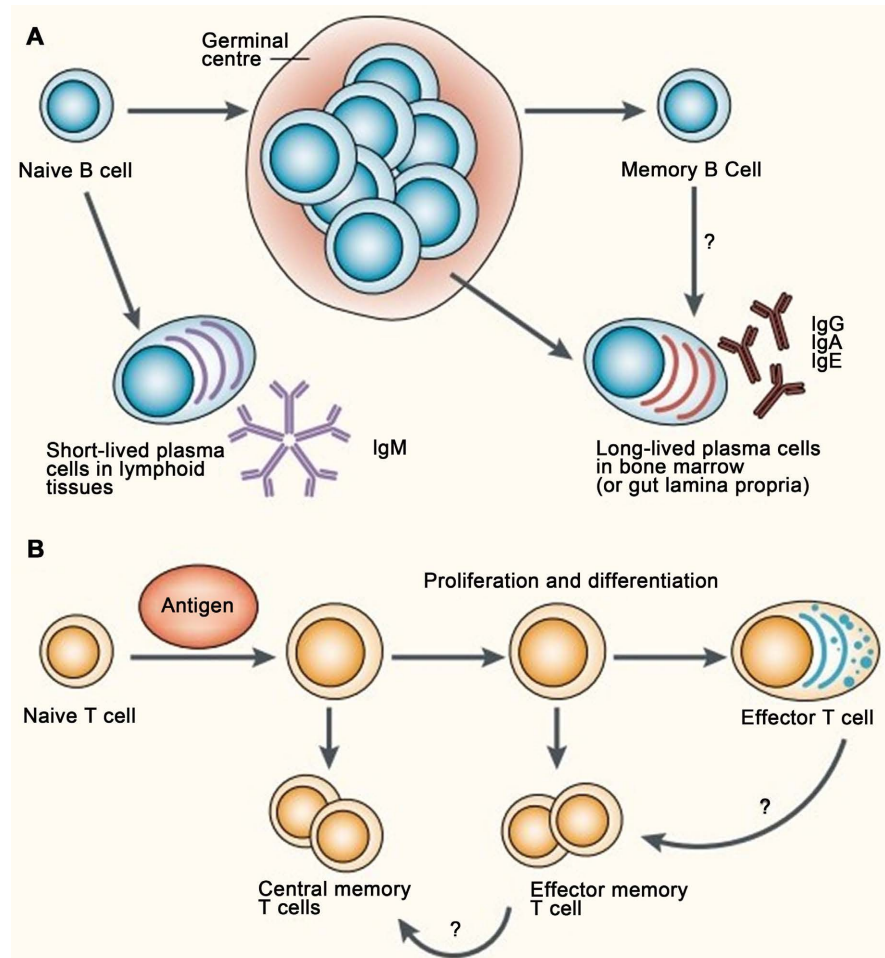


Figure 3. Naïve T and B cells differentiate to give rise to memory T and B cells [18].

7. School System and Graduation

The naïve cells of the immune system that are destined for leadership roles must undergo a preparatory phase, akin to attending a specialized school. In this regard, the thymus can be considered the primary school of immunity. The role of the thymus was discovered in 1961 [19], and what was considered an insignificant organ was found to be the most important component of the entire immune system. The function of the thymus was discovered during work on virus-induced leukemia [19]. He observed that the removal of the thymus from a neonate mouse

rendered it more susceptible to illnesses compared to non-thymectomized mice. Additionally, he observed that neonatally thymectomized mice did not reject foreign skin grafts transplanted from other mice. This research subsequently revealed the crucial role of the thymus in educating naïve T lymphocytes that originate from the bone marrow and then travel to the thymus. The thymus, where markers from nearly all human body tissues are presented through the autoimmune regulator gene within the thymic tissues, can be likened to a school, wherein T cells that recognize self-antigens graduate as normal and subsequently enter the workplace [20]. The role of the thymus will be discussed further in the section “Central tolerance” (Figure 3).

8. Leadership and Collaborative Teamwork

In 1968, two scientists, Miller and Mitchell, found that T cells assisted B cells, leading to the term “T helper cells” being coined [21]. The collaboration between T and B cells is orchestrated by T cells via a complex process that begins with the stimulus signals being recognized by APCs such as dendritic cells and B cells [22], and then being presented to T cells through a series of co-stimulation/inhibition cell receptor interactions, which ultimately results in the production of effector T and B cells [23]. Plasma cells (effector B cells) produce antibodies, including immunoglobulin IgA, IgE, and IgG. Although B cells can produce immunoglobulins independent of T cells, those antibodies (IgM), while important for a rapid immune response, are less effective and short-lived. Working as a team is always more effective than working alone, even if it requires more time and communication. The co-stimulation and -inhibition mechanisms of the immune system have inspired the discoveries of therapeutic biological agents that target receptors, which has led to the development of revolutionary cancer treatments and successful organ transplants.

Such collaborative teamwork from the immune system serves as a model for how effective leadership and proper assistance and support from team members can help humans organize themselves [24] [25].

9. Balance of Response

Immune system responses mirror human responses in various aspects because of the diversity of people worldwide and the differences in their personalities. While certain situations may result in conflict or fighting, tolerance or ignoring is sometimes the healthiest response in others [26]. Accordingly, the immune response can be likened to when humans decide to fight, tolerate, or ignore an event. In some situations, humans may show a lack of interest or energy to fight (anergy), whereas in other situations where no solution is available and there are risks of leaving threats unaddressed, it becomes necessary to encircle the threats and contain them to mitigate the danger posed. Granulomas formed by the immune system can be considered a jail wherein bacteria are contained within a wall of immune cells that limit their growth and spread, such as in the case of *Mycobacterium tuberculosis*

[27] [28]. However, if problems persist and there is no means to resolve or heal them, if the ability to tolerate such conditions is lost, or if exposed to dangerous, overreactive people, humans may become aggressive and harm themselves. With regard to the immune system, these are the main reasons for autoimmunity [29].

10. Tolerance (Mind of the Immune System)

The immune system must recognize self-antigens before recognizing non-self-antigens [30]. “Immune tolerance” is defined as a state wherein the immune system is unresponsive to foreign and self-antigens [31]. Immune tolerance is vital for the suppression of self-reactivity and the prevention of autoimmunity. There are two types of immune tolerance: central and peripheral. Central immune tolerance occurs in T cells during the thymic stage of development. T cell receptors bind to thymic self-expressed antigens to learn to recognize self-antigens and receive survival signals to exit the thymus as healthy, normal cells [32]. However, if a T cell binds to a self-expressed antigen abnormally, it will not receive a survival signal and subsequently undergo apoptosis [33]. These processes are referred to as positive and negative selection, respectively. Some T cells may escape negative selection in the thymus and become autoreactive (Figure 4). Such autoreactive T cells play a major role in autoimmunity; for example, if T cells that inappropriately bind to the expressed insulin-secreting tissues escape apoptosis during their development in the thymus, they will become the main mediators of β -insulin cell death in type 1 diabetes [34].

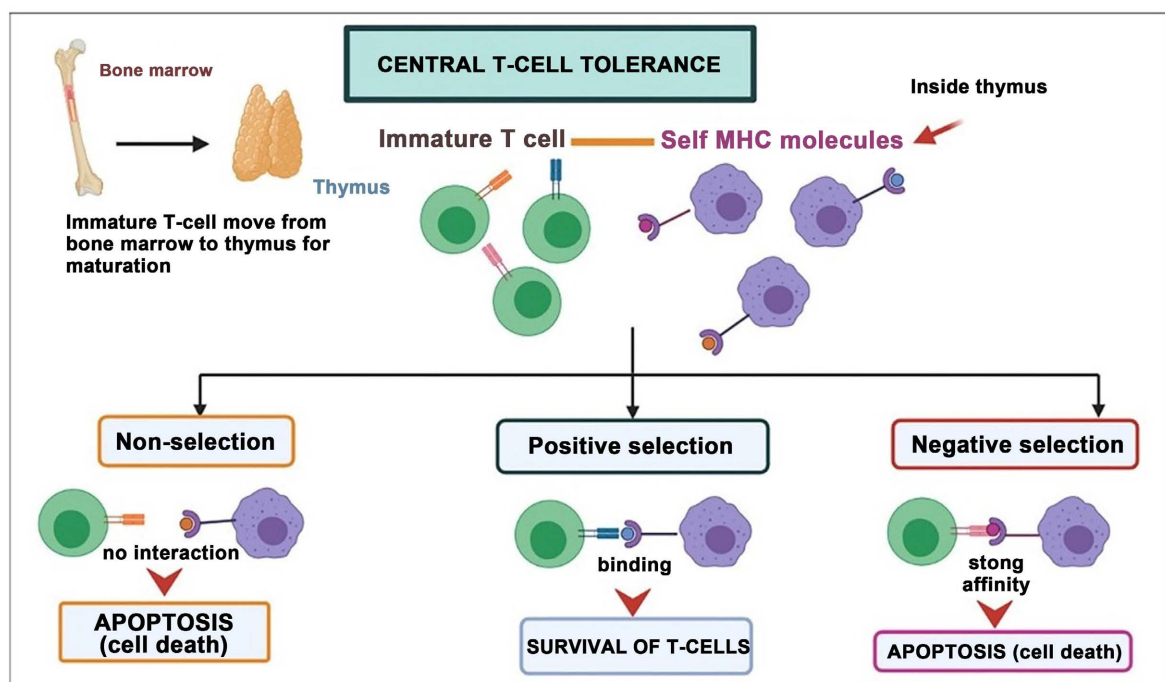


Figure 4. Central T cell tolerance mechanism. T cells mature in the thymus by attaching to self-major histocompatibility complex (MHC) molecules. If the interaction is not strong, the T cell survives in a process termed “positive selection”. If the interaction is overly strong, it leads to programmed cell death via “negative selection” [35].

Considering the potential for some autoreactive T cells might escape central immune tolerance and become risk factors for the development of autoimmune disorders, another immune tolerance mechanism serves as a crucial backup mechanism. Peripheral immune tolerance comprises several mechanisms that prevent inappropriate T-cell activation, including mechanisms of antigen ignorance and anergy (lack of reaction). Additionally, T regulatory cells offer regulatory safeguard mechanisms. In certain conditions, programmed death provides an alternative solution [36].

Ignorance of the immune system is another important strategy for preventing the unnecessary activation of the immune response when encountering certain undesirable stimuli. Immune cells can ignore antigens either by choosing not to bind to them or by binding to them with low affinity and not initiating a response [37] [38]. This approach offers a valuable lesson for certain human conditions, emphasizing that sometimes ignorance can be beneficial.

Anergy is another notable response that resembles human reactions when a response can prove harmful. Anergy of immune cells is a programmed response that prevents the activation of lymphocytes when they encounter certain antigens, which renders the lymphocytes hyporesponsive. Intrinsically, cell growth is arrested, and cell differentiation is suppressed [39]. This state of anergy may be life-long or reversed upon contact with certain stimuli [40].

Apoptosis is an integral aspect of human biology and represents the cessation of life. Cells can die naturally via necrosis, a process triggered by disease, toxic stimuli, or abnormal growth [41]. Alternatively, cell death can be a genetically programmed mechanism of cellular suicide in response to certain conditions to ensure normal homeostasis and integrity of the multicellular system by eliminating unwanted cells [42].

11. Regulation (T Regulatory Cell)

The immune system is a powerful defensive system with complex activation processes. It is essential to understand how the suppressive and regulatory tolerance functions of this system operate, along with how efficient immune cellular activation maintains homeostasis and prevents auto-reaction toward self-antigens and beneficial microbes. The contrasting functions of the immune system require cells that are specialized for this regulatory role; these cells were discovered in the mid-1990s as suppressive T cells and are referred to as T regulatory cells (Tregs) [43]. The genetic transcription factor of Tregs is Foxp3, which is specifically expressed in Treg cells. Ablation of Foxp3-positive Tregs leads to the induction of fatal autoimmune disorders [44]. Tregs play a major role in maintaining immune tolerance and sustaining normal immune system function by eliminating autoreactive T cells, inducing self-tolerance, and restraining inflammatory response cascades [45]. Prominent immune mediators of Tregs mediate their roles via specific cytokines (transforming growth factor- β and interleukin-10) that are known to be involved in immune system suppressive functions [46].

12. Conclusion

The immune system shares certain similarities with human life. It is a complex organization comprising various immune cells that engage in interactions within specific sites and networks, communicate via distinct languages, draw from their previous experiences, learn how to tolerate certain conditions, graduate as safe and healthy, and ignore some situations. We interchangeably learn from each other.

Author Contribution

Gassem Gohal did the study design, review literature, manuscript writing, editing, and revision, approved the final manuscript, and was responsible for the integrity of the research.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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