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UNRAVELING THE SHIELDS AND SWORDS: THE DUEL OF INNATE AND ADAPTIVE IMMUNITY AGAINST FILARIAL INVADERS

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Abstrak

The immune system, comprising innate and adaptive components, is crucial for defending the human body against various infectious agents, including filarial parasites. Filariasis, caused by thread-like nematodes, poses a significant health risk in tropical and subtropical regions, affecting over 120 million people worldwide. Understanding the immune response to filarial infection is essential for developing effective treatments and preventive strategies. A comprehensive literature review was conducted, focusing on the human immune response to filarial infections, particularly the roles of the adaptive and innate immune systems. Systematic searches of databases such as PubMed, Scopus, Web of Science, and Google Scholar were carried out, with search terms including "lymphatic filariasis," "immune response to filariasis," and others. The immune response to filarial infection involves complex interactions between the innate and adaptive immune systems. The skin and mucous membranes act as the first line of defense, while specific immune cells and cytokines play crucial roles in the inflammatory response and parasite elimination. The adaptive immune response, particularly the Th2 response, is critical for clearing microfilariae from the bloodstream. However, the immune system's ability to effectively deal with filarial infections varies due to factors such as genetic susceptibilities, infection severity, and environmental exposures.

Keywords*: Filarial Infections, Immune Response, Adaptive Immunity, Innate Immunity, Lymphatic Filariasis*

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INTRODUCTION

Antimicrobial and infectious microorganisms, including viruses and bacteria, typically activate the immune system, the body's innate defense mechanism. In contrast to other body systems confined to a single organ or a small area, the immune system is a network of various cells, tissues, and organs dispersed throughout the body. It is tasked with defending against different infectious agents and is one of the most complex systems in the human body. As one of the most interconnected systems in the body, it is additionally engaged in relational functions with other bodily systems. Integervented and adaptive immune systems are the two primary components of the immune system. It contains all multicellular organisms and is inherited according to the genetic sequence. The innate immune system is the initial defense against infectious organism invasion. The adaptive immune system is activated approximately 96 hours following the initial invasion of an organism through infection. It identifies and retains particular antigens and proteins transferred to foreign germ cells within the body. Vaccination is built upon the adaptive immune system as well. The human body is exceptionally resistant to infections, particularly in comparison to other organisms, due to the integration of its two immune systems. Infection caused by the filariasis-causing pathogen is a health danger that human bodies continue to encounter despite this capability.[1,2]

METHOD

This literature review is conducted to enhance current knowledge on the human immune response to filarial infections, specifically focusing on the roles of the adaptive and innate immune systems. Systematic database searches were conducted to identify pertinent studies encompassed PubMed, Scopus, Web of Science, and Google Scholar. The search criteria comprised the following: "lymphatic filariasis," "filarial infection," "immune response to filariasis," "innate immunity," and "adaptive immunity." To achieve this, the search was restricted to English-language articles published between January 2010 and the present to incorporate the most recent advancements in the discipline. In this investigation, both research and review articles were included. Deliberations revolved around the immune mechanisms employed to combat filariasis, encompassing molecular and cellular components. The functions of various immune cells (including dendritic cells, NK cells, eosinophils, and basophils), cytokine profiles, and the progression of humoral responses were explicitly highlighted. Further attention was devoted to comprehending how immune responses can differ due to environmental exposures, genetic susceptibilities, and infection severity. A critical review was conducted on the gathered data to assess the present knowledge regarding immune mechanisms that respond to filarial infections. This evaluation emphasized the complex interaction between the host's innate and adaptive immune systems, which are engaged in combating these parasitic infections.

LITERATURE REVIEW

Overview of the Immune System

Designed to safeguard the body against infection, the immune system is intricate and highly developed. Protecting the body from a diverse array of pathogenic microorganisms and toxic substances, including helminths, it comprises a complex network of cells, proteins, tissues, and organs. Implementing an integrated defense strategy that incorporates both innate and adaptive immune responses, it has developed to protect against parasites, bacteria, viruses, and fungi. The immune system is complicated and highly developed. Organs, tissues, and cells that form an intricate network to defend the body against various pathogenic organisms and toxic substances are integrated into this system. Its purpose is to prevent infection. The innate and adaptive immune systems constitute the system's two primary components. Comprising intact epidermis, mucous membranes, cilia, commensal flora, and gastric acid, the innate immune system is the initial defense against infection. It consists of biochemical, physical, and mechanical defenses.[3]

Furthermore, overarching pathogen-associated molecular patterns (PAMPs) prevalent across sizable groups of pathogens can be recognized by the cells and proteins comprising the innate immune system, such as complement proteins, natural killer (NK), macrophages, and dendritic cells. Throughout an individual's lifetime, the acquired or adaptive immune system develops. It can identify a diverse array of antigens as a defense mechanism. Having a memory for the microorganisms, the adaptive immune system provides sustained protection against future infections by selectively targeting pathogens. In

addition to physical barriers, antigenic variation, and immune suppression, each immune system component possesses methods to circumvent its function and continue protecting the body from infection. To fully comprehend the immune response to filariasis and other parasitic diseases, the specifics of these methods may be pivotal.[4]

Understanding Filariasis Infection

In tropical and subtropical regions across the globe, filariasis is a debilitating and disfiguring illness. A third of the global population is at risk of contraction, which impacts more than 120 million individuals in these regions. Feline parasitosis, caused by thread-like nematodes on a microscopic scale, is transmitted via mosquito bites. Black flies, biting notes, midges, and mosquitoes are vectors for the diffusion of these nematodes. While uncommon symptoms are associated with the infection, certain cases may present with signs such as intense lymph node enlargement, lymphangitis, or fever.[5]

Innate Immune Response

Physical barriers, including mucous cell membranes and the epidermis, furnish the initial line of defense for the Innate Immune Response system. Pathogen entry into the human body is a formidable challenge that these physical barriers vigorously oppose. It is difficult for pathogens to penetrate the epidermis due to its composition of multiple layers of densely packed cells. Should they even penetrate, sebaceous and sweat secretions contain naturally occurring antimicrobial peptides that inhibit bacterial proliferation on the human epidermis. Humid due to fluid mucus, mucous membranes constitute the second physical barrier. Other organisms, including viruses, are prevented from entering various organ systems by mucus. On the contrary, a greater focus on the skin and its function in preventing filarial infections reveals that the epidermis is the primary entry point for filarial larvae into the human body. The successful establishment of the parasite is unattainable in the absence of larval entrance into the site. Female mosquitoes serve as vectors for injecting filarial larvae into the host's body; however, the subcutaneous layer of humans is the most commonly targeted host site.[1]

Role of Skin and Mucous Membranes

Numerous intrinsic protective mechanisms are present at the skin's surface. Obstacles to pathogen entry are significantly diminished by physical factors such as the stratum corneum's robust barrier and the rapid cell turnover at the skin's surface. Keratin, the protein that comprises most stratum corneum cells, is particularly resistant to enzymatic and chemical degradation. The epidermis harbors resident bacteria that resist numerous pathogens and function as a barrier. Obstetric conjunctiva, gastrointestinal, and respiratory tracts are among the bodily regions where mucous membranes act as barriers. Enzymes and mucus secreted by these secrete pathogen entrapment and growth inhibition or destruction of pathogens, including lysozyme, lactoferrin, and lactoperoxidase.[6]

Phagocytosis and Natural Killer Cells

An intricate network of proteins, fluids, and cells constitutes the immune system, which functions as a secondary line of defense when microorganisms breach our external defenses. White blood cells, produced in the bone marrow and vital to the immune system's operation, are its principal cellular components. Phagocytes and lymphocytes are the two variations of white blood cells. Lymphocytes generate proteins known as antibodies, which react against the pathogenic microorganisms, while phagocytes ingest and degrade them. The fundamental operational mechanism of lymphocytes underpins the two subdivisions of the immune system—innate and adaptive responses. Since it is not pathogen-specific, the natural system serves as the initial barrier. Phagocytic entrapment and subsequent elimination of the pathogen occur at the attachment site. Pathogen-specific humoral and cellular responses comprise the remainder of the adaptive response. These responses are more complex.[7]

Adaptive Immune Response

Effector B and T cells begin to perish rapidly within days of a primary immune response, successfully eradicating the infection. Memory cells result from an immediate immune response and comprise a minute fraction of cells, typically in both the B and T cell populations. Survival of the host following reinfection depends on the presence of memory cells. These memory cells can mount a focused and accelerated secondary immune response. Secondary immunity swiftly mobilizes anti-viral IgG antibodies upon pathogen invasion to impede the dissemination of replicating viruses within 18 hours of infection. Additionally,

the infection's resolution occurs before the onset of clinical symptoms, as this accelerated and targeted immune response shortens the duration of viral dissemination.[8,9]

B Cells and Antibodies

According to a whole cell-mediated cell immunity precisely tailored to its targets, bone marrow generates B cells upon demand. If they remain in the absence of a soluble substance for two days after activation, they will endure apoptosis and cease expressing the antibody. The cause of cell death is unknown. Antigen presentation by interfollicular dendritic cells and membrane-bound B cell membrane-bound Bcl-2 are remarkably correlated, according to a recent study by Itano et al. (2003). However, the answer to this question remains unknown. The authors observed apoptotic cells responding to active antigen growth stimuli by employing immunofluorescence microscopy to deliver native antigens to follicular and interfollicular B cells.[4,10]

T Cells and Cell-Mediated Immunity

T lymphocytes, which participate in cell-mediated immune responses, will be the subject of this section. Cells, their effector and memory status, cytokine production, and the fundamental functions these cells perform in host defense must be discussed once more, as in the preceding section. It is imperative to elucidate the potential modulation of these cells to prevent collateral inflammation, which may result in many immunological symptoms, including those associated with chronic disease.[4,9]

Adaptive and innate immunity's interaction

Identifying and binding antigens by T-cells is a crucial phase in the immune response. Antigens necessitate prior processing before their presentation in complex with major histocompatibility complex (MHC) molecules. T cells of the immune system in humans express two distinct categories of MHC molecules: classes I and II. Antigen-presenting cells (antigen-presenting cells), including dendritic cells (DCs), macrophages, and B cells, are the only cells that express MHC class II molecules; these molecules deliver processed peptides to CD4+ helper T cells. MHC class I molecules are present on the surface of nearly all nucleated cells. Due to the T-cell receptor's (TCR) ability to identify minor peptides within the context of MHC molecules, the interaction between T cells and antigen-presenting cells is always specific. Furthermore, the interaction between CD40 on antigen-presenting cells and its ligand CD40 on the T cell typically provides the costimulatory signal necessary for T-cell activation. In initiating and maintaining the immune response, T cells secrete cytokines that affect responding cells once primed.[11,12]

Mechanisms of T Cell Activation and Antigen Presentation

In summary, upon activating CD4+ T lymphocytes or CD8+ T cells by the foreign antigen on the MHC II molecule, CD4+ and CD8+ T cells gage in interactions with B cells and killer cells, which are specific for the antigen. In Figure 6, the antigen presentation process is illustrated. This process involves the presentation of foreign antigens in the form of MHC II molecules by CD4+ T lymphocytes and MHC I molecules by CD8+ T lymphocytes.[1,4]

Communication among Immune Cells and Cytokines

Cytokines are signaling proteins secreted by immune cells to regulate and mediate cell development, differentiation, and effector functions. Cytokines typically affect cells by activating a signal transduction cascade, culminating in a cellular response by binding to receptors on the target cell's surface. Interferons, interleukins, chemokines, and molecules resembling tumor necrosis factor (TNF) are a few of the subclasses into which cytokines can be classified broadly. Moreover, numerous cell types within the immune system secrete additional cytokine-like mediators, such as lymphokines and growth factors, which are produced, for instance, by transformed cells or fibroblasts. Assistance from T-helper cells, which secrete particular cytokines to stimulate B cells or CD8+ T cells, is frequently necessary for the costimulation of T cells. These cytokines are crucial for host defense.[1,13]

Filariasis Infection-Induced Immune Response

Through cellular injury linked to the movement of larvae and the localization of adult worms, infection with the filariasis worm stimulates the innate immune system. Circumnavigating the lymphatic system, there is an accumulation of eosinophils and mast cells. These innate immune cells can induce extensive tissue damage near the obstructed lymphatic system due to the degranulation and release of

toxic granular contents (e.g., eosinophil peroxidase, a major essential protein). Antigen-specific responses that are thought to be down-regulatory in the host, thereby aiding the parasite's survival within the host, have been linked to CD4 Th2 responses, particularly in the lymphatic system. Filariasis's clinical ramifications center on the host's immune response towards adult worm microfilaria; infected humans' sensitivity to antigens can differ substantially between life stages. The host's immune system typically does not react to adult worms in the lymphatic system; instead, the immune response is elicited when microfilaria invade the vascular system. The tissue may sustain injury due to this heightened immunoreactivity. The immune system is believed to develop a tolerance to helminths. Wolbachia, an endosymbiotic bacterium, is hypothesized to be produced by adult filarial worms and to provide the nutrients that the adult worms require. An individual chronically infected with filarial worms may develop 'endotoxin tolerance' via mechanisms mediated by regulatory T cells. Macrophage-killing mechanisms could disarm this tolerance if Wolbachia, a potent stimulatory component of B7 of the host's immune system, is linked to the response to toll-like receptors.[4]

Parasite Identification in Filariasis

Different molecules, including cytokines and antigen-presenting molecules, are stimulated when L3 filamentous worms bind to their respective cell surface receptors, such as C-type lectins and TLRs. Furthermore, several of these molecules are up-regulated in infected tissues due to the activation of numerous cell types, including dendritic cells, macrophages, and granulocytes. Alphabeta, NK T cells, and various variants thereof are also stimulated. As evidence of the host's adaptive immune response to all parasites, these alterations in infected tissues and vessels that facilitate the digestion, elimination, and binding of mature worms and their byproducts form the foundation for clinically observable phenomena like lymphangitis.[3,5]

Immune Cells and Inflammatory Response

As the filarial infection progresses, the immune system detects and initiates a local inflammatory response against circulating microfilariae and developing larval stages (Figure 3). Diverse soluble mediators, including histamine, leukotrienes, prostaglandins, and pro-inflammatory cytokines; endothelial receptors, including ICAM-1, VCAM-1, L-selectins; and cytokine-stimulated tissue responses; in addition to tissue monocytes, macrophages, dendritic cells, and dendritic cells; and innate immune system components, including mast cells, eosinophils, neutrophils, tissue monocytes, and dendritic cells;[12]

Filariasis Elimination via Adaptive Immunity

The human immune response to lymphatic filariasis concludes with the Th2 response. Microfilaria removal from the bloodstream is essential during both the onset of an infection when the parasites are still in the blood and can be captured by mosquitoes, and chronic infections when mature microfilariae are released. Because it operates via eosinophils, the Th2 response lacks potent microfilaricidal capability. It is conceivable that eosinophil and IgE responses do not function as effective clearance mechanisms for patients due to their limited microfilaricidal capacity against other filarial infections. Within the context of a research investigation, it was observed that seven out of eight asymptomatic individuals who tested positive for microfilariae had IgE levels surpassing the mean of those who tested negative for microfilariae; this finding indicates that these individuals possessed a persistently elevated and responsive anti-filaria IgE. Individuals who were asymptomatic and exhibited elevated levels of IgE and IL5 also had filarial antigens (www.journals.plos.org), indicative of immune recognition upon exposure. Constant responses from the populace are observed. Clearance of microfilariae likely requires Th2 responses. For CD4 cells to function as a protective mechanism against this infection, it is critical to identify the stimuli that activate a Th2 response that may include microfilaricidal activity.[2,4]

CONCLUSION

Filarial nematode parasites are transmitted to humans via mosquitoes, resulting in human lymphatic filariasis (LF). Enhanced lymphodema, hydrocoele, and extremity enlargement result from the migration to the lymphatic system. LF is a significant public health concern as a debilitating human disease. The assessment provides an opportunity to examine the intermediate evolution process in individuals who resist worms or fall prey to them. Understanding the mechanisms by which the immune system can alter the course of a disease is significantly advanced by research into the function of these cellular and immune

responses. In the same way that immunosuppression will promote the prolongation of parasite persistence and the spread of the disease, immune research has confirmed that persistence is a critical disease threshold. Undoubtedly, it will be the top focus of forthcoming research, instilling optimism regarding the development of potentially practical therapeutic approaches. As demonstrated by the findings of this study, the immune system significantly contributes to the filarial parasite's expanding attacks, which is particularly pronounced during the pre-patent infection phase. Some of the productive immune mechanisms may now be advantageously utilized in some of the essential treatments, notwithstanding the ongoing debates regarding the role of immunity in defense and the pathogenesis of human LF.

REFERENCE

1. Sibi JM, Mohan V, Munisankar S, Babu S, Aravindhan V. Augmented Innate and Adaptive Immune Responses Under Conditions of Diabetes–Filariasis Comorbidity. Front Immunol. 2021 Sep;12.
2. Harker J. Insights into the life cycle of filarial parasites. IRD J Club. 2016 Mar;
3. Ton TGN, Mackenzie C, Molyneux DH. The burden of mental health in lymphatic filariasis. Infect Dis poverty. 2015;4:34.
4. Babu S, Nutman TB. Immunology of lymphatic filariasis. Parasite Immunol. 2014 Aug;36(8):338–46.
5. Cross JH. Filarial Nematodes. In: Baron S, editor. Medical Microbiology. 4th ed. Galveston (TX): NIH; 1996.
6. Hesthammer JE, Olteanu C, Rao J. A review on oral supplements and herbal remedies in the treatment of Acne vulgaris. 50 ~ Int J Herb Med. 2021;9(6):50–4.
7. Hirayama D, Iida T, Nakase H. The Phagocytic Function of Macrophage-Enforcing Innate Immunity and Tissue Homeostasis. Int J Mol Sci. 2017 Dec;19(1).
8. Tippalagama R, Chihab LY, Kearns K, Lewis S, Panda S, Willemsen L, et al. Antigen-specificity measurements are the key to understanding T cell responses. Front Immunol. 2023;14:1127470.
9. Corthay A. How do regulatory T cells work? Scand J Immunol. 2009 Oct;70(4):326–36.
10. Alberts B, Johnson A, Lewis J. The Adaptive Immune System. In: Molecular Biology of the Cell. 4th ed. New York: Garland Science; 2002.
11. Long H, Liao W, Wang L, Lu Q. A Player and Coordinator: The Versatile Roles of Eosinophils in the Immune System. Transfus Med Hemother. 2016 Mar;43(2):96–108.
12. Mogensen TH. Pathogen recognition and inflammatory signaling in innate immune defenses. Clin Microbiol Rev. 2009 Apr;22(2):240–73, Table of Contents.
13. Bouchery T, Kyle R, Ronchese F, Le Gros G. The Differentiation of CD4(+) T-Helper Cell Subsets in the Context of Helminth Parasite Infection. Front Immunol. 2014;5:487.