Research Output Journal of Public Health and Medicine 4(3):42-46, 2024

ROJPHM

ISSN ONLINE: 1115-9715
ISSN PRINT: 1115-6147

https://rojournals.org/roj-public-health-and-medicine/

https://doi.org/10.59298/ROJPHM/2024/434246

Interleukin-17 in Health and Disease: A Double-Edged Sword in Immunity

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ABSTRACT

Interleukin-17 (IL-17), a key pro-inflammatory cytokine primarily produced by T-helper 17 (Th17) cells, plays a crucial role in immune regulation and host defense, particularly against extracellular pathogens such as bacteria and fungi. As part of the IL-17 family of cytokines, IL-17A and IL-17F are the most well-characterized members, essential for recruiting neutrophils and promoting the production of antimicrobial peptides. However, IL-17's potent inflammatory effects make it a double-edged sword in immunity, contributing not only to protective immune responses but also to chronic inflammation and autoimmunity when dysregulated. IL-17 is implicated in the pathogenesis of various autoimmune and inflammatory diseases, including rheumatoid arthritis (RA), psoriasis, multiple sclerosis (MS), inflammatory bowel disease (IBD), and systemic lupus erythematosus (SLE). In these conditions, IL-17 promotes the production of other pro-inflammatory cytokines and matrix metalloproteinases, driving sustained inflammation and tissue damage. This dual role of IL-17—protective in infection but harmful in chronic inflammation—highlights its complexity in immune regulation. The therapeutic targeting of IL-17 has led to the development of biologics such as secukinumab and ixekizumab, which have shown significant efficacy in treating autoimmune diseases like psoriasis and ankylosing spondylitis. However, the use of IL-17 inhibitors presents challenges, particularly in balancing infection control with immune modulation. This review examines the biology of IL-17, its role in health and disease, and the potential therapeutic implications of modulating its activity in clinical settings.

Keywords: Interleukin-17 (IL-17), Th17 cells, Autoimmunity, Chronic inflammation, Biologic

INTRODUCTION

The immune system is a highly complex and adaptive network that protects the body from infections, cancers, and other harmful threats. It is composed of diverse immune cells and signaling molecules that work in concert to recognize and eliminate pathogens while preserving the integrity of the body's own tissues [1]. Cytokines, small protein messengers, are essential for this communication, regulating immune responses by influencing the activity of immune cells [2]. Among the many cytokines involved in immune regulation, interleukin-17 (IL-17) has garnered considerable attention for its crucial role in inflammation and immunity. IL-17 is a pro-inflammatory cytokine produced primarily by T-helper 17 (Th17) cells, a subset of CD4+ T cells. The IL-17 family consists of six members: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F, with IL-17A and IL-17F being the most widely studied [3]. IL-17A, often simply referred to as IL-17, is the prototype and most well-characterized member of this family. It plays a pivotal role in host defense, particularly against extracellular bacteria and fungi, by stimulating the production of chemokines and pro-inflammatory cytokines that promote the recruitment of neutrophils to infection sites [4]. In mucosal tissues, such as the gastrointestinal and respiratory tracts, IL-17 helps maintain barrier integrity by inducing the production of antimicrobial peptides [5].

In the context of infection, IL-17 is a vital component of the immune response, especially in cases of bacterial and fungal pathogens like Staphylococcus aureus and Candida albicans. Its ability to rapidly recruit neutrophils and other immune cells to the site of infection helps contain and clear the invading microorganisms, preventing their spread and reducing tissue damage [6,7]. Deficiencies in IL-17 signaling can lead to increased susceptibility to

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infections, as seen in individuals with chronic mucocutaneous candidiasis or hyper-IgE syndrome, both of which are characterized by impaired Th17 cell function and recurrent fungal or bacterial infections [8]. However, IL-17's role in immunity is not without drawbacks. Its potent pro-inflammatory properties, while essential for pathogen clearance, can also lead to tissue damage if not properly regulated. This is particularly evident in chronic inflammatory and autoimmune diseases, where an overactive IL-17 response contributes to sustained inflammation and tissue destruction. Elevated levels of IL-17 have been implicated in diseases such as rheumatoid arthritis (RA), psoriasis, multiple sclerosis (MS), inflammatory bowel disease (IBD), and systemic lupus erythematosus (SLE)[9]. In these conditions, IL-17 promotes inflammation by inducing the production of other pro-inflammatory cytokines (e.g., tumor necrosis factor-alpha [TNF-α], interleukin-1β [IL-1β]), matrix metalloproteinases (MMPs), and chemokines that recruit additional immune cells, perpetuating a cycle of chronic inflammation and tissue damage [10,11].

This paradoxical role of IL-17 as both a defender and a destroyer underscore its dual nature in immunity, earning it the reputation of a "double-edged sword." On one hand, IL-17 is indispensable for mounting effective immune responses against pathogens and maintaining mucosal barrier function [12]. On the other hand, its dysregulation can lead to the development and exacerbation of autoimmune diseases, where it contributes to the pathological inflammation of otherwise healthy tissues [8]. Given the prominent role of IL-17 in both protective immunity and the pathogenesis of inflammatory diseases, it has become a prime target for therapeutic intervention. Biologic drugs designed to block IL-17 or its receptor have shown promise in treating several autoimmune diseases, particularly psoriasis and ankylosing spondylitis. However, the therapeutic use of IL-17 inhibitors also presents challenges, particularly in balancing the need to control inflammation while preserving the cytokine's essential role in defending against infections [13]. In this review, we will explore the biological functions of IL-17 in normal immune responses, its contribution to the development and progression of inflammatory and autoimmune diseases, and the therapeutic implications of targeting IL-17. By understanding the dual nature of IL-17 in health and disease, we can better appreciate its role in immunity and the potential benefits and risks of modulating its activity for therapeutic purposes.

The Biology of IL-17

IL-17 Family and Receptors

IL-17 refers to a family of cytokines that includes six distinct members: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), and IL-17F [3]. Among these, IL-17A and IL-17F are the most studied due to their overlapping and potent pro-inflammatory effects. IL-17A, often simply referred to as IL-17, is the prototype of the family and is closely related to IL-17F in structure and function [14].

IL-17 family members signal through the IL-17 receptor family, which consists of five receptor subunits: IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE. IL-17A and IL-17F signal predominantly through a receptor complex formed by IL-17RA and IL-17RC [15]. Upon ligand binding, the IL-17 receptor complex activates downstream signaling pathways, including the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), mitogen-activated protein kinase (MAPK), and C/EBP pathways, leading to the production of pro-inflammatory mediators such as cytokines, chemokines, and matrix metalloproteinases (MMPs) [15,16].

Production of IL-17

IL-17 is primarily produced by a specialized subset of CD4+ T cells known as Th17 cells. Th17 differentiation is driven by a unique combination of cytokines, including IL-6, TGF-β, IL-1β, and IL-23. These cytokines activate key transcription factors such as RORγt, which promotes the differentiation and function of Th17 cells [17]. Although Th17 cells are the main producers of IL-17, other immune cells such as γδ T cells, innate lymphoid cells (ILCs), natural killer (NK) cells, and neutrophils can also produce IL-17 in response to infection or inflammation, underscoring the importance of this cytokine in various immune contexts [18].

IL-17 in Health: Essential for Host Defense

Role in Antimicrobial Immunity

IL-17 plays a critical role in defending the host against extracellular pathogens, particularly bacteria and fungi. It promotes the recruitment of neutrophils to sites of infection by inducing the production of chemokines such as CXCL1, CXCL2, and IL-8[19]. Neutrophils are essential for the clearance of pathogens, and their accumulation at infection sites is a hallmark of IL-17-mediated responses. One well-documented example of IL-17's protective function is its role in defending against Staphylococcus aureus infections. Mice deficient in IL-17 signaling are highly susceptible to *S. aureus* infections, demonstrating that IL-17 is crucial for neutrophil-mediated bacterial clearance [20]. Similarly, IL-17 plays a pivotal role in defending against fungal infections such as *Candida albicans*, where it drives neutrophil recruitment and activation, facilitating the clearance of fungal pathogens [21].

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Role in Mucosal Immunity

In addition to its role in controlling bacterial and fungal infections, IL-17 is vital for maintaining mucosal barriers, particularly in the respiratory and gastrointestinal tracts. At mucosal surfaces, IL-17 induces the production of antimicrobial peptides such as defensins and S100 proteins, which directly kill pathogens [22]. This protective role is evident in patients with chronic mucocutaneous candidiasis, a condition characterized by recurrent fungal infections due to defects in IL-17 production or signaling.

IL-17 in Disease: A Driver of Chronic Inflammation and Autoimmunity

While IL-17 is essential for protective immunity, its dysregulated production can contribute to chronic inflammation and autoimmunity. Elevated levels of IL-17 have been implicated in the pathogenesis of several autoimmune and inflammatory diseases.

Rheumatoid Arthritis (RA)

In rheumatoid arthritis, IL-17 plays a key role in driving inflammation within the synovial joints. IL-17 promotes the production of pro-inflammatory cytokines, such as TNF-α and IL-1β, and induces the expression of matrix metalloproteinases (MMPs), which degrade cartilage [23]. In addition, IL-17 stimulates osteoclastogenesis, contributing to bone erosion. Clinical trials of IL-17 inhibitors, such as secukinumab and ixekizumab, have demonstrated efficacy in reducing inflammation and joint damage in RA patients, highlighting the pathogenic role of IL-17 in this disease [24].

Psoriasis

IL-17 is a key driver of inflammation in psoriasis, a chronic inflammatory skin disease characterized by hyperproliferation of keratinocytes and the infiltration of immune cells into the skin. IL-17 stimulates keratinocytes to produce pro-inflammatory cytokines and chemokines, perpetuating a cycle of inflammation and tissue remodeling[25]. Targeting IL-17 with monoclonal antibodies like secukinumab and brodalumab has shown significant clinical benefits in psoriasis patients, leading to the clearance of psoriatic plaques and reducing skin inflammation [26].

Multiple Sclerosis (MS)

In multiple sclerosis, an autoimmune disease characterized by the destruction of myelin in the central nervous system (CNS), IL-17 contributes to disease pathology by promoting the recruitment of inflammatory cells into the CNS. Studies in animal models of MS, such as experimental autoimmune encephalomyelitis (EAE), have demonstrated that Th17 cells and IL-17 are crucial for the initiation and progression of CNS inflammation [27]. Elevated levels of IL-17 have been detected in the cerebrospinal fluid of MS patients, and targeting IL-17 in preclinical models has shown promise in reducing disease severity [19].

Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, is another condition where IL-17 plays a dual role. While IL-17 contributes to maintaining mucosal integrity and defending against microbial invasion, its overproduction can exacerbate intestinal inflammation [28]. IL-17 promotes the production of pro-inflammatory cytokines and chemokines, leading to the infiltration of immune cells and tissue damage in the gut[18]. However, IL-17 inhibitors have shown mixed results in IBD, with some studies reporting worsening of symptoms, highlighting the complexity of IL-17's role in gut immunity.

Systemic Lupus Erythematosus (SLE)

In systemic lupus erythematosus, a chronic autoimmune disease characterized by the production of autoantibodies and widespread tissue inflammation, IL-17 has been implicated in promoting the production of pathogenic autoantibodies by B cells. Elevated levels of IL-17 have been detected in the serum and affected tissues of lupus patients, and preclinical studies suggest that targeting IL-17 may reduce disease severity [29]. However, the exact role of IL-17 in lupus pathogenesis remains under investigation.

IL-17 as a Therapeutic Target

Given IL-17's central role in promoting inflammation and tissue damage in autoimmune diseases, therapeutic strategies aimed at blocking IL-17 signaling have gained traction. Several IL-17-targeting biologics have been developed and are approved for the treatment of autoimmune conditions. Secukinumab, a monoclonal antibody that neutralizes IL-17A, has been approved for the treatment of psoriasis, ankylosing spondylitis, and psoriatic arthritis, and has shown significant efficacy in reducing disease activity [30]. Similarly, ixekizumab targets IL-17A and has been approved for the treatment of psoriasis. Brodalumab, another IL-17-targeting therapy, binds to the IL-17 receptor, preventing IL-17 signaling and has demonstrated efficacy in treating psoriasis [31]. While IL-17 inhibitors have shown great promise in treating certain autoimmune diseases, their use is not without challenges. As IL-17 plays a critical role in host defense against infections, particularly fungal infections, patients receiving IL-17 inhibitors are at an increased risk of developing infections such as candidiasis. Therefore, careful monitoring of patients undergoing IL-17-targeted therapies is essential to balance the benefits of reducing inflammation with the potential risk of infection.

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CONCLUSION

Interleukin-17 (IL-17) is a critical cytokine with dual roles in health and disease, acting as both a promoter of protective immunity and a contributor to inflammatory pathology. While it is essential for combating infections and maintaining tissue homeostasis, its overexpression is linked to various autoimmune and chronic inflammatory conditions. Understanding the complex signaling pathways and regulatory mechanisms of IL-17 is crucial for developing targeted therapies. Future research should focus on balancing IL-17's protective and pathogenic effects to harness its benefits while mitigating its harmful consequences, ultimately leading to more effective treatment strategies for autoimmune diseases and related disorders.

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CITE AS: Ssenkayi Julius. (2024 Interleukin-17 in Health and Disease: A Double-Edged Sword in Immunity. Research Output Journal of Public Health and Medicine 4(3):42-46. https://doi.org/10.59298/ROJPHM/2024/434246

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