Temporal dynamics of Th17 responses to Candida albicans in rheumatoid arthritis: Implications for immunity and treatment

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by symmetrical polyarthritis and systemic inflammation. Recent studies have highlighted the critical role of the Th17/IL-17 axis in RA pathogenesis, with elevated Th17 cell frequencies and IL-17 production contributing to disease progression. Candida albicans, a commensal fungus residing in mucocutaneous surfaces, relies on Th17-mediated immunity for protection against mucocutaneous candidiasis. However, RA patients exhibit impaired Th17 responses, increasing their susceptibility to C. albicans infections. This review examines the temporal dynamics of Th17 responses to C. albicans in RA patients, analysing the expression trends of Th17 and regulatory T cells (Tregs) over 12, 24, and 48 hours. Findings indicate that RA patients have a diminished initial Th17 response, inadequate IL-17 production at peak activity, and sustained immune dysfunction, leading to compromised fungal clearance. Additionally, biologic therapies targeting the Th17/IL-17 pathway, while effective for RA symptom management, may exacerbate infection risks. Understanding these dynamics is crucial for developing strategies that enhance antifungal immunity without aggravating RA symptoms. Further research is essential to optimize treatment protocols that balance antifungal defenses and autoimmune regulation.

Keywords: Rheumatoid arthritis, Th17 cells, Candida albicans, immune response, IL-17, cytokines, fungal infections, biologics, autoimmunity.

Introduction

Rheumatoid arthritis (RA) is a long-term autoimmune disorder marked by symmetrical polyarthritis and widespread inflammation throughout the body. Increasing research suggests that the cytokine interleukin (IL)-17 and CD4+ T-helper type (Th)17 cells play a crucial role in the development of RA (Gaffen, 2009b; McInnes & Schett, 2007).

IL-17 is a proinflammatory cytokine that not only induces but also works together with tumor necrosis factor (TNF) alpha to stimulate the production of IL-1β and IL-6 in target cells. This process leads to the creation of factors like matrix metalloproteinases and reactive oxygen species, which contribute to the development of erosive arthritis (Gaffen, 2009a).

In line with the role of the Th17/IL-17 axis in RA pathogenesis, patients with severe RA show higher frequencies of Th17 cells. Additionally, clinical responses to TNFα inhibitors in individuals with autoimmune conditions have been linked to decreases in circulating Th17 cells (Chen et al., 2011; Zaba et al., 2007).

Candida albicans is a commensal fungus that inhabits mucocutaneous surfaces such as the oral cavity, tracheobronchial tree, and the gastrointestinal and genitourinary tracts. The Th17/IL-17A axis is crucial for protective immunity against mucocutaneous candidiasis, with the majority of Candida-responsive T cells being of the Th17 phenotype (Acosta-Rodriguez et al., 2007; Vautier et al., 2010).

Individuals with impaired Th17 cell induction (due to mutations in genes such as STAT1, STAT3, or CARD9) or defects in IL-17A signaling (from mutations in IL17RA or IL17F) are highly susceptible to chronic mucocutaneous candidiasis. This condition is also observed in patients with circulating antibodies against Th17 cytokines, as seen in autoimmune polyendocrinopathy syndrome-1 or certain thymomas. Interestingly, Candida infections are not commonly reported in RA patients; however, recent epidemiological data from those with inflammatory bowel disease indicate that TNFα inhibitors increase the risk of oropharyngeal candidiasis (OPC) at rates comparable to mycobacterial infections (Ford & Peyrin-Biroulet, 2013; Huppler et al., 2012; Puel et al., 2010; Strangfeld & Listing, 2006).

This review examines the relationship between RA and susceptibility to Candida albicans infections, emphasizing the impaired Th17 responses and the impact of new biologic treatments targeting this pathway.

Th17 Cells and Their Role in Autoimmunity and Fungal Immunity

Th17 cells are a subset of T-helper cells known for producing IL-17, a cytokine crucial for neutrophil recruitment and antifungal defense. Th17 cells play a pivotal role in mucosal immunity and are essential for controlling fungal pathogens such as C. albicans. Th17 cells play a crucial role in maintaining mucosal immunity, but their pathogenicity in autoimmunity, cancer, and HIV infection requires further exploration and novel therapeutic interventions (Wacleche et al., 2017). However, their pro-inflammatory nature also implicates them in autoimmune diseases, including RA. In RA, the dysregulated Th17 pathway can contribute to both disease pathology and an increased risk of infections.

Rheumatoid arthritis (RA) and Increased Susceptibility to Candida albicans

Rheumatoid arthritis patients exhibit impaired oral immune responses to the fungus Candida albicans, despite elevated baseline IL-17A production (Bishu et al., 2014). Patients with RA are more susceptible to infections, including those caused by C. albicans, due to both the underlying autoimmune condition and the immunosuppressive treatments commonly used. These treatments, while effective in controlling RA symptoms, can impair the immune response, particularly the Th17 pathway, thereby increasing the risk of opportunistic infections.

Temporal Dynamics of Th17 Responses to C. albicans

The temporal dynamics of Th17 responses to Candida albicans in rheumatoid arthritis (RA) patients provide critical insights into the immune deficiencies associated with this autoimmune condition. By examining Th17 activity at various time points—12, 24, and 48 hours—we can better understand how these responses influence susceptibility to fungal infections and the potential implications for treatment strategies.

Th17 and Treg Expression Dynamics

Studies investigating the expression levels of regulatory T cells (Tregs) and Th17 cells in different contexts can shed light on similar patterns observed in RA patients. For instance, in a study on acute gouty arthritis, it was found that Treg and Th17 levels in the spleen varied significantly over time post-treatment. At 12 hours, both Treg and Th17 expression were significantly higher in the ATP-treated group compared to the control and BBG groups, with the control group showing higher levels than the BBG group. However, by 72 hours, these differences were no longer significant (Dai et al., 2018).

Applying these findings to RA, we can infer that early immune responses to C. albicans involve a dynamic interplay between Treg and Th17 cells. Initially, there may be a robust Th17 response, as seen in the increased levels of Th17 cells at 12 and 24 hours. This heightened response is crucial for the effective recruitment of neutrophils and the control of fungal infections. However, in RA patients, this response might be blunted due to the chronic inflammatory environment and immunosuppressive therapies, leading to impaired fungal clearance.
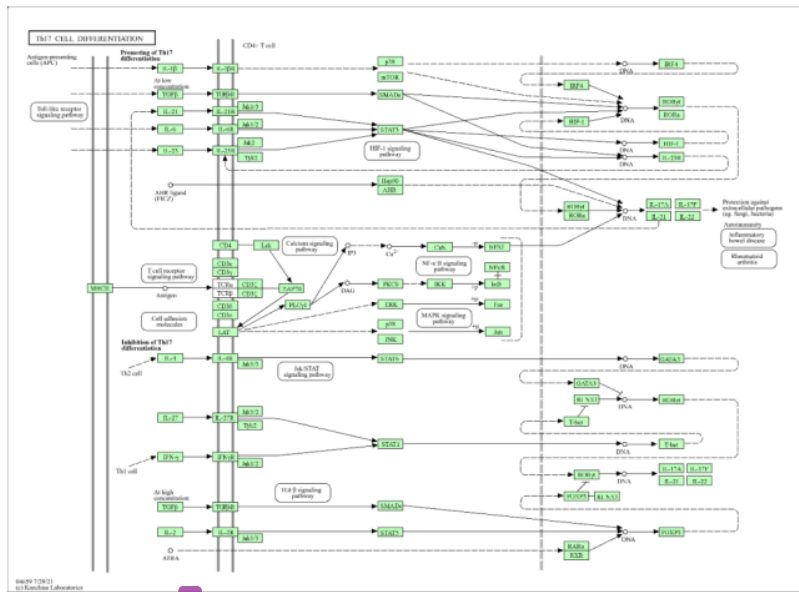

Figure 1: Th17 Cell Differentiation Pathway in Homo sapiens

Interleukin (IL)-17-producing helper T (Th17) cells represent a subset of CD4+ T cells intricately involved in orchestrating immune responses against extracellular microbes,

particularly through interactions with epithelial cells and neutrophils. Additionally, they play pivotal roles in the pathogenesis of autoimmune diseases. In vivo, the differentiation of Th17 cells necessitates antigen presentation and co-stimulation, triggering the activation of antigen-presenting cells (APCs) to secrete a milieu of cytokines including transforming growth factor-beta (TGF-beta), interleukin-6 (IL-6), interleukin-1 (IL-1), interleukin-23 (IL-23), and interleukin-21 (IL-21). This initial activation cascade leads to the upregulation of signaling molecules such as STAT3, ROR(gamma)t, and other transcriptional factors in CD4+ T cells. These factors subsequently bind to the promoter regions of genes encoding IL-17, IL-21, and IL-22, ultimately inducing their expression. Conversely, the differentiation of Th17 cells and their subsequent IL-17 expression are negatively modulated by factors such as interleukin-2 (IL-2), the Th2 cytokine interleukin-4 (IL-4), interleukin-27 (IL-27) and the Th1 cytokine interferon-gamma (IFN-gamma). These inhibitory signals activate STAT5, STAT6, and STAT1, respectively. Moreover, retinoic acid and the combination of IL-2 and TGF-beta can upregulate the expression of the transcription factor Foxp3, which in turn downregulates the production of cytokines such as IL-17 and IL-21. Such fine-tuning mechanisms serve as a protective strategy to prevent excessive inflammation by regulating the expression of IL-17. Thus, the balanced differentiation of Th cells, including Th17 cells, is indispensable for maintaining immune homeostasis and ensuring host protection.

Temporal Expression Trends

The expression trends of Treg and Th17 cells over different time points further elucidate the immune dynamics in RA. For example, Treg levels increase at 6 hours but decrease at 12 and 24 hours before rising again at 48 hours. Th17 levels, on the other hand, increase at 6, 12, and 24 hours but decrease at 48 and 72 hours. These trends suggest a complex regulation of immune responses over time, with potential implications for how RA patients handle C. albicans infections (Dai et al., 2018). In RA, the initial increase in Th17 cells might be insufficient or poorly sustained, leading to inadequate antifungal defenses. By 48 hours, when the immune response should be resolving the infection, RA patients may still struggle with fungal clearance due to an impaired or dysregulated Th17 response.

Treg/Th17 Ratio

The ratio of Treg to Th17 cells is also a critical factor in understanding immune responses. In the gouty arthritis model, this ratio decreased in the first three time points but increased at 48 and 72 hours. A lower Treg/Th17 ratio indicates a stronger pro-inflammatory response, which is necessary for combating acute infections. However, in RA patients, this ratio might be imbalanced due to the disease pathology and treatments, leading to either excessive inflammation or inadequate immune activation.

At 12 hours, a lower Treg/Th17 ratio in RA patients might reflect an initial attempt to mount a strong antifungal response. However, if this ratio is not properly regulated over time, it could lead to either persistent infection or exacerbation of RA symptoms.

Implications for RA and C. albicans Susceptibility

Understanding the temporal dynamics of Th17 responses in RA patients highlights the challenges in managing fungal infections like those caused by C. albicans. Impaired early responses and dysregulated Th17 activity can lead to increased susceptibility and chronic infection. Additionally, treatments targeting the Th17/IL-17 pathway, such as TNFα inhibitors, must be carefully managed to balance controlling RA symptoms and maintaining effective antifungal immunity.

The insights gained from temporal studies in other inflammatory models, like acute gouty arthritis, emphasize the need for time-specific interventions that can enhance Th17 responses without exacerbating RA. Further research should focus on optimizing therapeutic strategies that consider the dynamic nature of immune responses in RA patients, particularly in the context of opportunistic

The impaired Th17 response to Candida albicans in RA patients is a critical factor in their increased susceptibility to fungal infections. By examining the temporal dynamics of Th17 activity, we can better understand the deficiencies in the immune response and develop more effective treatment strategies. These findings underscore the importance of a balanced Th17 response in maintaining both antifungal immunity and control over autoimmune inflammation. Further research is essential to optimize treatment regimens that enhance antifungal defenses while managing RA symptoms effectively.

1. 12-Hour Response: Initial Immune Activation

In the early stages of infection (within 12 hours), the immune system typically activates innate immune cells, leading to the production of cytokines that drive Th17 differentiation. Healthy individuals exhibit robust IL-6 and IL-23 production during this phase, promoting Th17 cell development. However, in RA patients, these cytokines may be inadequately produced due to underlying immune dysregulation and the effects of immunosuppressive drugs. This insufficient cytokine milieu results in a poor initial Th17 response, which is critical for early fungal control.

2. 24-Hour Response: Peak Th17 Activity

By 24 hours, Th17 cells should reach their peak activity, marked by substantial IL-17 production, which recruits neutrophils to the site of infection. In healthy individuals, this leads to effective fungal clearance. In contrast, RA patients often exhibit reduced IL-17 levels during this critical period. This impaired response is due to the chronic inflammatory state of RA, which can skew cytokine production and Th17 cell function. Additionally, RA treatments targeting TNF-α and other cytokines might inadvertently suppress Th17 responses, compromising the body's ability to combat C. albicans.

3. 48-Hour Response: Sustained Immunity and Resolution

At 48 hours, the immune response should be resolving the infection, with decreasing inflammatory signals as the pathogen is controlled. In healthy immune systems, Th17 cells

help maintain a balanced inflammatory response, ensuring fungal clearance without excessive tissue damage. However, RA patients may experience prolonged or inadequate fungal clearance due to sustained or unresolved Th17 dysfunction. Persistent low-level fungal infections can contribute to chronic inflammation, exacerbating RA symptoms and complicating disease management.

Implications of Biologic Therapies Targeting the Th17 Pathway

The advent of biologics targeting the Th17/IL-17 pathway, such as secukinumab and ixekizumab, offers new treatment options for RA but also raises concerns about increased infection riskcod(Codreanu, 2018). These therapies can significantly reduce IL-17 levels, potentially compromising antifungal defenses. Thus, while these biologics can effectively control RA symptoms, clinicians must balance the benefits with the potential for increased susceptibility to C. albicans and other opportunistic infections.

Conclusion

The studies discussed shed light on the intricate relationship between rheumatoid arthritis (RA) and susceptibility to Candida albicans infections, particularly focusing on the temporal dynamics of Th17 responses. RA patients exhibit impaired Th17 responses, characterized by diminished initial activation, inadequate IL-17 production, and sustained immune dysfunction. These deficiencies contribute to increased susceptibility to C. albicans infections and highlight the importance of understanding the immune dysregulation in RA.

Furthermore, the findings underscore the challenges in managing fungal infections in RA patients, especially considering the potential exacerbation of symptoms by biologic therapies targeting the Th17/IL-17 pathway. Balancing antifungal defenses with autoimmune regulation poses a significant clinical challenge.

Moving forward, optimizing treatment protocols is paramount, requiring a nuanced approach that enhances antifungal immunity while mitigating autoimmune pathology. Further research is essential to elucidate the underlying mechanisms driving Th17 dysregulation in RA and to develop targeted interventions that address both autoimmune inflammation and fungal susceptibility. Ultimately, a comprehensive understanding of the immune dynamics in RA will facilitate the development of personalized treatment strategies aimed at improving patient outcomes and quality of life.

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