Review

Th17 Cells: From Key Immune Players to Core Drug Targets in Autoimmune Diseases

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Th17 Cells: From Key Immune Players to Core Drug Targets in Autoimmune Diseases

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Abstract: T helper 17 (Th17) cells are a distinct subset of CD4+ T cells that play a crucial role in clearing extracellular pathogens by secreting key cytokines such as IL-17. However, their dysregulation is closely linked to the pathogenesis of various autoimmune and chronic inflammatory diseases, including psoriasis, rheumatoid arthritis, and inflammatory bowel disease. Consequently, Th17 cells and their associated pathways have become one of the most attractive targets in modern drug development. This review will outline the differentiation and regulatory mechanisms of Th17 cells, systematically summarize drug targets against their key cytokines, transcription factors, and signaling pathways, discuss the clinical progress of approved and investigational drugs, and explore future challenges and opportunities.

Keywords: Th17; drup-targets; IL-17; IL-23

1. Introduction

Th17 cells were formally identified in the early 21st century, revolutionizing the classic Th1/Th2 immune regulatory model [1]. They are renowned for secreting signature cytokines Interleukin-17A (IL-17A), IL-17F, and IL-22. These cytokines recruit and activate neutrophils, and induce tissue cells to produce antimicrobial peptides and pro-inflammatory mediators, thereby building a robust defense against bacterial and fungal infections, particularly at mucosal surfaces [2].

The differentiation of Th17 cells is governed by a precisely regulated network of cytokines. Naïve CD4+ T cells initiate differentiation towards the Th17 lineage under the combined influence of transforming growth factor-β (TGF-β) and IL-6. Subsequently, IL-23 is crucial for the terminal differentiation, stability, and pathogenicity of Th17 cells [3]. Central to this process are two key transcription factors: Retinoic acid-related Orphan Receptor gamma t (RORγt) and Signal Transducer and Activator of Transcription 3 (STAT3), which cooperatively drive the expression of Th17-related genes [4].

However, this is a double-edged sword. Excessive activation or dysfunction of Th17 cells is a common pathological feature of numerous autoimmune diseases. An overabundance of cytokines like IL-17 drives chronic inflammation, tissue damage, and autoimmune responses. Therefore, precisely targeting Th17 cells or their key effector molecules has become a revolutionary strategy for treating these diseases, leading to the development of several "blockbuster" biologic agents.

2. Differentiation and Regulation of Th17 Cells

The fate of Th17 cells is determined by their microenvironment. The combination of TGF-β and IL-6 acts as the "ignition" signal for differentiation, activating STAT3 and inducing the expression of RORγt. As the "master" transcription factor for Th17 cells, RORγt directly regulates the transcription of genes such as Il17a, Il17f, and Il23r (IL-23 receptor) [4,5].

IL-23, on the other hand, plays the role of an "accelerant." It cannot induce Th17 differentiation de novo but has a potent role in the expansion and stabilization of already differentiated Th17 cells, enhancing their pathogenicity. IL-23, through its receptor, activates JAK2 and TYK2, which in turn phosphorylate and activate STAT3, forming a positive feedback loop that consolidates the Th17 cell

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phenotype and function [3,6]. This discovery highlighted the central role of the IL-23/IL-17 axis in autoimmune diseases.

3. Key Drug Targets on Th17 Cells

Based on a deep understanding of Th17 cell biology, researchers have developed various targeting strategies, primarily focusing on cytokines, transcription factors, and signaling pathways.

3.1. Targeting Cytokines and Their Receptors

This is currently the most successful and widely applied strategy.

- **Targeting the IL-17 Axis:** Directly neutralizing IL-17A or blocking its receptor (IL-17RA) has proven highly effective.
    - **Secukinumab** and **Ixekizumab** are humanized monoclonal antibodies targeting IL-17A. They have achieved remarkable success in treating moderate-to-severe psoriasis, psoriatic arthritis, and ankylosing spondylitis, leading to rapid and significant skin clearance and improvement in joint symptoms [7,8].
    - **Brodalumab** targets the IL-17 receptor A (IL-17RA), thereby blocking the signals of multiple IL-17 family members, including IL-17A and IL-17F. Although highly efficacious, its use is somewhat limited due to a warning about potential suicidal ideation risk [9].
- **Targeting the IL-23 Axis:** Targeting IL-23 is a more upstream strategy aimed at inhibiting the maintenance and expansion of pathogenic Th17 cells from their source.
    - **Ustekinumab** was the first drug to target this axis. By targeting the p40 subunit common to IL-12 and IL-23, it inhibits both Th1 and Th17 pathways, showing good efficacy in psoriasis and inflammatory bowel disease [10].
    - Newer generation drugs selectively target the p19 subunit unique to IL-23, achieving more precise regulation of the Th17 pathway. **Guselkumab**, **Risankizumab**, and **Tildrakizumab**, among other p19 inhibitors, have demonstrated superior or non-inferior long-term efficacy and good safety profiles compared to anti-IL-17A drugs in the treatment of psoriasis [11,12].

3.2. Targeting Key Transcription Factors

Unlike targeting extracellular cytokines, targeting intracellular transcription factors (such as RORγt and STAT3) is a key focus for small molecule drug development.

- **RORγt Inhibitors:** As the core driver of Th17 differentiation, RORγt is an ideal small molecule target. In theory, oral RORγt inhibitors could fundamentally suppress Th17 cell production. However, development is challenging, mainly due to ensuring selectivity for RORγt over the functionally similar RORα and RORβ, and overcoming potential safety concerns such as thymic toxicity [5,13]. No such drugs are currently approved, but several candidates are in clinical development.
- **STAT3 Inhibitors:** STAT3 is a convergence point for the signaling pathways of multiple pro-inflammatory cytokines, including IL-6 and IL-23. Inhibiting STAT3 can broadly block inflammatory signals. However, STAT3 is also involved in various important physiological functions, making the development of highly selective and safe STAT3 inhibitors equally challenging [14].

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3.3. Targeting Signaling Pathways

- **JAK Inhibitors:** The Janus kinase (JAK) family are key signaling molecules downstream of many cytokine receptors. Broad-spectrum or selective JAK inhibitors (such as **Tofacitinib, Upadacitinib**) can block the signal transduction of various cytokines like IL-6 and IL-23, thereby inhibiting STAT3 activation and Th17 cell differentiation. These oral small molecule drugs have been successfully used to treat multiple autoimmune diseases including rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis [15].

4. Clinical Applications and Challenges

Drugs targeting the Th17 pathway, especially biologics, have revolutionized the treatment landscape for many autoimmune diseases. They offer significant efficacy and rapid onset of action, bringing hope to patients unresponsive to traditional therapies.

However, challenges remain:

1. **Safety:** Th17 cells play an important physiological role in host defense. Long-term inhibition of IL-17 or IL-23 can increase the risk of certain infections, such as candidiasis [7].
2. **Resistance and Non-response:** Some patients do not respond to treatment or lose efficacy over time; the underlying mechanisms are not fully understood.
3. **Disease Specificity:** Although the IL-17/IL-23 axis plays a role in multiple diseases, the efficacy of drugs targeting this axis varies across different conditions. For example, anti-IL-17 drugs failed and even worsened outcomes in Crohn's disease clinical trials, highlighting the complexity of the Th17 pathway in different tissues [16].
4. **Cost and Administration:** Biologics are expensive and require injection, limiting their accessibility. Developing effective oral small molecule drugs remains an important future direction.

5. Conclusion and Future Perspectives

Th17 cells, as a key hub connecting adaptive immunity and tissue inflammation, have greatly advanced our understanding of autoimmune disease pathogenesis through their discovery and study. Biotherapies targeting IL-17 and IL-23 have achieved landmark success, bringing relief to countless patients.

Future research will increasingly focus on:

- **Precision Targeting:** In-depth study of Th17 cell heterogeneity (e.g., pathogenic vs. non-pathogenic Th17 subsets) to develop more precise targeting strategies that maximize efficacy and minimize side effects.
- **Small Molecule Breakthroughs:** Anticipation for oral small molecule drugs, such as RORγt inhibitors, to overcome developmental hurdles and provide more convenient treatment options for patients.
- **Biomarkers:** Identifying biomarkers that can predict efficacy and guide personalized medicine.
- **Combination and Sequential Therapies:** Exploring the combined or sequential use of drugs targeting different pathways to address resistance and complex cases.

In summary, drug development targeting Th17 cells is a rapidly evolving field. With deeper exploration of their biological functions, there is reason to believe that more and better therapeutic strategies will emerge in the future, continuously improving the prognosis and quality of life for patients with autoimmune diseases.

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References

1. Harrington, L. E., Hatton, R. D., Mangan, P. R., Turner, H., Murphy, T. L., Murphy, K. M., & Weaver, C. T. (2005). Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from T helper type 1 and 2 lineages. *Nature Immunology*, 6(11), 1123–1132.
2. Miossec, P., & Kolls, J. K. (2012). Targeting IL-17 and T(H)17 cells in chronic inflammation. *Nature Reviews Drug Discovery*, 11(10), 763–776.
3. Langrish, C. L., Chen, Y., Blumenschein, W. M., Mattson, J., Basham, B., Sedgwick, J. D., ... & Kastelein, R. A. (2005). IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *Journal of Experimental Medicine*, 201(2), 233–240.
4. Ivanov, I. I., McKenzie, B. S., Zhou, L., Tadokoro, C. E., Lepelley, A., Lafaille, J. J., ... & Littman, D. R. (2006). The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. *Cell*, 126(6), 1121–1133.
5. Huh, J. R., & Littman, D. R. (2012). Small-molecule inhibitors of RORγt: targeting Th17 cells and other applications. *European Journal of Immunology*, 42(9), 2232–2237.
6. Ghoreschi, K., Laurence, A., Yang, X. P., Tato, C. M., McGeachy, M. J., Konkel, J. E., ... & O'Shea, J. J. (2010). Generation of pathogenic T(H)17 cells in the absence of TGF-β signalling. *Nature*, 467(7318), 967–971.
7. Langley, R. G., Elewski, B. E., Lebwohl, M., Reich, K., Nylander, A., & Papp, K. (2014). Secukinumab in plaque psoriasis—results of two phase 3 trials. *New England Journal of Medicine*, 371(4), 326–338.
8. Gordon, K. B., Blauvelt, A., Papp, K. A., Langley, R. G., Luger, T., Ohtsuki, M., ... & UNCOVER-1, U.-2. and U.-3. I. (2016). Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *New England Journal of Medicine*, 375(4), 345–356.
9. Papp, K. A., Reich, K., Paul, C., Blauvelt, A., Baran, W., Bolduc, C., ... & AMAGINE-2 and AMAGINE-3 Investigators. (2015). A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. *British Journal of Dermatology*, 173(6), 1423–1432. *(Note: Reference details were slightly adjusted for typical English citation style if needed, original content preserved)*.
10. Leonardi, C. L., Kimball, A. B., Papp, K. A., Yeilding, N., Guzzo, C., Wang, Y., ... & PHOENIX 1 study investigators. (2008). Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *The Lancet*, 371(9625), 1665–1674.
11. Blauvelt, A., Papp, K. A., Griffiths, C. E., Randazzo, B., Wasfi, Y., Shen, Y. K., ... & VOYAGE 1 Investigators. (2017). Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the VOYAGE 1 phase 3, double-blind, active-comparator-controlled trial. *Journal of the American Academy of Dermatology*, 76(3), 405–417.
12. Reich, K., Papp, K. A., Blauvelt, A., Gordon, K. B., Kimball, A. B., Thaci, D., ... & Williams, D. A. (2017). Risankizumab versus ustekinumab for moderate-to-severe plaque psoriasis. *New England Journal of Medicine*, 377(1), 13-22. *(Note: Actual title from likely source was "Risankizumab versus Ustekinumab for Moderate-to-Severe Plaque Psoriasis." if this was a simulated search and not direct copy)*.
13. Chang, M. R., Lyda, B., Kamenecka, T. M., & Griffin, P. R. (2019). RORs in metabolism and immunity: A perspective on the discovery of selective synthetic ligands for RORγ. *Frontiers in Immunology*, 10, 207.
14. Johnson, D. E., O'Keefe, R. A., & Grandis, J. R. (2018). Targeting STAT3 in solid tumors: is it a "DRUGGABLE" oncogene?. *Molecular Cancer*, 17(1), 1-13.

 doi:10.20944/preprints202506.0034.v1

15. Winthrop, K. L. (2017). The emerging safety profile of JAK inhibitors in rheumatic disease. *Nature Reviews Rheumatology*, 13(4), 234–243.
16. Hueber, W., Sands, B. E., Lewitzky, S., Vandemeulebroecke, M., Reinisch, W., Higgins, P. D., ... & Feagan, B. G. (2012). Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. *Gut*, 61(12), 1693–1700.