**Propionibacterium acnes and the Th1/Th17 Axis, Implications in Acne Pathogenesis and Treatment**

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**Abstract**

Acne vulgaris is one of the most commonly seen conditions and the immunological link is a topic of active research. Recently, the Th17 pathway has been found to play a pivotal role in acne. The adaptive immune response toward *Propionibacterium acnes* leads to activation of Th17 axis. Consequently, the Th17 cytokines (IL-17, IL-1β, IL-6, and tumor growth factor, in turn, activate the various pathogenic steps in acne. Drugs such as Vitamin D3 and isoretinoin which target the Th17 pathway may offer an additional pathway for their therapeutic response.

**KEY WORDS:** Acne, IL 17, Propionibacterium acnes, Th1/Th17 axis

**Introduction**

Although *Propionibacterium acnes* had been proposed to play a role in acne, 50 years after it was discovered, its role was cast into doubt with the isolation of this organism from normal human skin.[1] Thus in the context of the increasing levels of resistance, as reported by an Indian study that found high resistance to clindamycin and macrolides (azithromycin), it was proposed that it would be best to avoid drugs that inhibit *P. acnes* and use drugs such as isoretinoin, zinc, and oral subantimicrobial doses of antibiotics (cyclines) to treat acne.[2,3] Novel molecules are being discovered that work by inhibiting *P. acnes* that do not preclude to resistance, even though some of them have been studied in vitro.[4] Recently, three studies that focus on the role of adaptive immunity, specifically Th17 cells, brings the focus back on the role of *P. acnes* in acne.[4-6]

**Immune Response in Acne**

It had been postulated that immunogenic *P. acnes* proteins released into the follicle could be processed by Langerhans cells, which could, in turn, present these antigens to CD4+ T-cells in local lymph nodes, via toll-like receptor 2 (TLR2) [Figure 1].[7] Histological studies found that CD4+ T-cells are the major leukocytes in the early (6-72 h) inflammatory infiltrates in acne lesions, with a small portion of CD11c dendritic cells. Neutrophils emerge when the 24 h and 72 h lesions are biopsied, which are then clinically identified as pustules.[8] CD8+ cells infiltrate the lesion later. These histological findings can now be explained by the Th17 axis a key component of the adaptive immune response [Figure 1].[9]

Studies that assess the cytokine response, should ideally test the expression of TLR2, TLR4, IL-8, IL-1β, tumor necrosis factor-alpha (TNF-α) and IL-6, which is largely indicative of innate immune response. The adaptive immune response is assessed by IL-12 β, interferon gamma (IFNy), IL-23A, IL-17A, and IL-22. Kistowska et al. found *P. acnes*-reactive Th17 and Th17/Th1 cells in the peripheral blood of patients suffering from acne and noted that while Th1 cells could be induced in only 40% of the tested donors; Th17 and Th17/Th1 cells could be induced by *P. acnes* in 100% of them.[6] This point to a Th1/Th17 axis in acne. The cytokines that play a role in the Th1/Th17 axis, including IL-1 β, IL-6 and tumor growth factor-beta (TGF-β), have been consistently found in acne lesions.[10-12] Agak al. and Kistowska et al. had proposed that IL-23, does not play a role in this Th17 response.[6,13] A recent study though found that IL-23 p19 is an important component in the immune response.
Importantly, they inhibit T1 and Th17 cells. Tumor growth factor-β induce regulatory T cells and Th17 cells via the induction of Foxp3 and RORC. Inflammatory cytokines, such as IL-6, IL-21, and IL-23, initiates Th17 axis. The effector cytokines released by Th17 cells include IL-17, IL-21, IL-22, and CCL20, which act on both immune and nonimmune cells and mediate several functions. APC: Antigen presenting cells; B: B cell; DC: Dendritic cell; EC: Endothelial cell; EpC: Epithelial cell

In addition, elevated levels of IL-22, IL-20, IL-1, IL-6, TNF-α, and TGF-β important in Th17 cell activation have been noted in acne lesions. Elevated serum levels of anti-inflammatory cytokine IL-10, Treg cells and increased number of Foxp3+ cells in the papillary dermis, are an additional finding, the last of which (Tregs), prevent autoimmunity and suppress immune responses.

A contrarian view was suggested by a study that studied the role of isotretinoin on adaptive immune response and observed significant downregulation of pro-inflammatory mediators IL-1 β and TLR2, as well as upregulation of antimicrobials S100A7 and lipocalin-2 (LCN-2) messenger RNA (mRNA) in the uninvolved skin in the acne patients. Remarkably, there was a lack of an effect on the level of Treg marker FOXP3 mRNA.

Clinical Implications

The implications of this research are manifold. First, this represents a new outlook to the pathogenesis of acne, wherein the Th17 pathway is now increasingly being recognized and can explain the histological findings and inflammation seen in acne. This is consequent to the Th17 effector cytokines, IL-17 and IL-22, which have the capacity to stimulate the production of various antimicrobial peptides and induce the production of neutrophil-recruiting chemokines such as IL-8 (CXCL8) in epithelial cells [Figure 1]. The Th17 cells also increases the specter of chronicity of disease, much like psoriasis, though in the case of acne, individual lesions do eventually resolve. This is consequent to the increased expression of IL-10 and Tregs that demarcate the inflammation of a single acne lesion efficiently from the beginning. The resolution of lesions can be understood in the light of the interplay of cytokines that mediate the Th17 axis. It has been shown that the combination of TGF-β and IL-21 is sufficient to induce the differentiation of human Th17 cells from naïve T cells, and IL-1 and IL-6 are important for enhancing the expansion of differentiated and memory Th17 cells.

However, in the absence of inflammation, the prominent TGF-β alone induces Foxp3, leading to the generation of iTregs that maintain immune tolerance along with nTregs. The rupture of the follicular walls and the decrease in the inflammatory cytokines can explain the resolution of individual lesions in acne.

There are therapeutic implications of the Th17 pathway, as drugs that inhibit this axis can have an enhanced role in the treatment of acne. These include dihydroxyvitamin D3, retinoids, Vitamin A and zinc, most of which have proven in vivo efficacy in acne. Retinoic acid can regulate reciprocally Tregs and Th17 through TGF-β-dependent generation of Foxp3, a mechanism that may be of importance in the treatment of acne by isotretinoin.

Isotretinoin, has anti-inflammatory properties, downregulating TLR2 expression on monocytes and neutrophil migration. Importantly, they inhibit inflammatory Th17 and promote regulatory T-cell (Treg) responses. A pilot study on gene expression from India found that with low dose isotretinoin, there was a upregulation in the expression of some prime genes such as LCN2, KRT23, and SERPINA3, which accounted for the initiation of the immune response against the pathogens causing acne. The significant aspect of most of the salient studies assessing the role of isotretinoin on gene expression is that low dose isotretinoin, through upregulation of apoptotic proteins such as TRAIL, IGFBP3, and LCN2 suppresses excessive sebum production associated with pro-inflammatory NLRP3 inflammasome activation.

Furthermore, the use of anti-IL-1 β and anti-IL-12/IL-23 may represent an efficient strategy for the targeting of Th17/Th1 cells. Active vaccination against IL-17 can replace the use of oral agents. A study has found that virus-like particles based vaccine against the IL-17 molecule is safe and effective in IL-17 mediated skin condition including acne vulgaris.

Synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome an inflammatory syndrome associated with
acne has responded favorably to anti-IL-1 antagonists involved in blocking of IL-17.\(^{[18]}\)

Importantly if this axis is crucial in acne, the dependence on antibiotics can be obviated that would ameliorate the specter of resistance which is at present a clear and present danger. This research, changes the focus, from \(P.\) \textit{acnes} to sebocytes and inflammation, which is a heartening fact, as this might reduce the focus on antibiotics with their attendant issue of resistance which is at present a clear and present danger.\(^{[2,3]}\)

**Conclusion**

Th17 cells display considerable plasticity and Th17 cells are unstable and depending on the type of inflammation and cytokine milieu, Th17 cells can acquire a phenotype of other T-cell subsets, such as IL-17 + IFN\(\gamma\) + T cells and IL17 + IL-6 + T cells.\(^{[9]}\) The discovery of Th17 cells in acne will have to be examined in a larger number of patients and lesions, in various types of acne, including the “difficult” acne cases, including the persistent, late onset, hormonal and resistant cases, to understand its role in acne. But it seems, that the focus is back on the role of \(P.\) \textit{acnes}, as the adaptive immune response, as evidenced by the Th1/Th17 axis is as a direct consequence of the immunogenicity of the organism.

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**Conflicts of interest**

There are no conflicts of interest.

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**What is new?**

- The Th17 axis may mediate the inflammation in acne
- This may explain the chronicity of acne lesions
- Drugs that work on this pathway may be important to treat acne
- Isotretinoin probably mediates its action via the Th17 axis

**References**

1. Evans CA, Smith WM, Johnston EA, Giblett ER. Bacterial flora of the normal human skin. J Invest Dermatol 1950;15:305-24.
2. Sardana K, Gupta T, Kumar B, Gautam HK, Garg VK. Cross-sectional pilot study of antibiotic resistance in \textit{Propionibacterium Acnes} strains in Indian acne patients using 16S-RNA polymerase chain reaction: A comparison among treatment modalities including antibiotics, benzoyl peroxide, and isotretinoin. Indian J Dermatol 2016;61:45-52.
3. Sardana K, Gupta T, Garg VK, Ghuinawat S. Antibiotic resistance to \textit{Propionobacterium acnes}: Worldwide scenario, diagnosis and management. Expert Rev Anti Infect Ther 2015;13:883-96.
4. Kelhäälä HL, Palatsi R, Ryhrquist N, Lehtimäki S, Väyrynen JP, Kallioinen M, et al. IL-17/Th17 pathway is activated in acne lesions. PLoS One 2014;9:e105238.
5. Ağak GW, Qin M, Nobe J, Kim MH, Krutzik SR, Tristan GR, et al. \textit{Propionibacterium acnes} induces an IL-17 response in acne vulgaris that is regulated by Vitamin A and Vitamin D. J Invest Dermatol 2014;134:766-73.
6. Kistowska M, Meier B, Proust T, Feldmeyer L, Cozzio A, Kuendi T, et al. \textit{Propionibacterium acnes} promotes Th17 and Th17/Th1 responses in acne patients. J Invest Dermatol 2015;135:110-8.
7. Farrar MD, Ingham E. Acne: Inflammation. Clin Dermatol 2004;22:380-4.
8. Norris JF, Cunliffe WJ. A histological and immunocytochemical study of early acne lesions. Br J Dermatol 1988;118:651-9.
9. Maddur MS, Miossec P, Kaveri SV, Bayry J. Th17 cells: Biology, pathogenesis of autoimmune and inflammatory diseases, and therapeutic strategies. Am J Pathol 2012;181:8-18.
10. Kelhäälä HL, Ryhrquist N, Palatsi R, Lehtimäki S, Väyrynen JP, et al. Isotretinoin treatment reduces acne lesions but not directly lesional acne inflammation. Exp Dermatol 2016;25:477-8.
11. Xiao S, Jin H, Korn T, Liu SM, Oukka M, Lim B, et al. Retinoic acid increases Foxp3+ regulatory T cells and inhibits development of Th17 cells by enhancing TGF-beta-driven Smad3 signaling and inhibiting IL-6 and IL-23 receptor expression. J Immunol 2008;181:2277-84.
12. Dispenza MC, Wolpert EB, Gilliland KL, Dai JP, Cong Z, Nelson AM, et al. Systemic isotretinoin therapy normalizes exaggerated TLR-2-mediated innate immune responses in acne patients. J Invest Dermatol 2012;132:2198-205.
13. Camisa C, Eisenstat B, Ragaz A, Weissmann G. The effects of retinoids on neutrophil functions in vitro. J Am Acad Dermatol 1982;6 4 Pt 2 Suppl:620-9.
14. Mucida D, Park Y, Kim G, Turovskaya O, Scott I, Kronenberg M, et al. Reciprocal Th17 and regulatory T cell differentiation mediated by retinoic acid. Science 2007;317:256-60.
15. Jha D, Sardana K, Gautam HK. Regulation of gene expression by quantitative real time PCR in low dose isotretinoin treated acne patients. Gene Technol 2015;S1:001.
16. Nelson AM, Zhao W, Gilliland KL, Zanglein AL, Liu W, Thiboutot DM. Neutrophil gelatinase-associated lipocalin mediates 13-cis retinoic acid-induced apoptosis of human sebaceous gland cells. J Clin Invest 2008;118:1468-78.
17. Foerster J, Bachman M. Beyond passive immunization: Toward a nanoparticle-based IL-17 vaccine as first in class of future immunotherapeutics. Nanomedicine (Lond) 2015;10:1361-9.
18. Firinu D, Garcia-Larsen V, Manconi PE, Del Giacco SR. SAPHO syndrome: Current developments and approaches to clinical treatment. Curr Rheumatol Rep 2016;18:35.
19. \textit{Propionibacterium acnes}: Worldwide scenario, diagnosis and management. Expert Rev Anti Infect Ther 2015;13:883-96.