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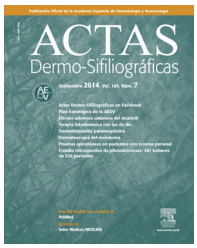

OPINION ARTICLE

Cytokine Pathways and the Role of Dysbiosis in Psoriasis, Psoriatic Arthritis, and Crohn Disease☆

Psoriasis, artritis psoriásica y enfermedad de Crohn: circuitos de citocinas y papel de la disbiosis

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Psoriasis, psoriatic arthritis, and other spondyloarthropathies such as those associated with inflammatory bowel disease (IBD) and IBD itself (Crohn disease being the paradigm), share many pathogenic features. The first characteristic to be identified, and one that was key for defining the concept of immune-mediated inflammatory disease (IMID), was the response of all these conditions to biologic agents that block tumor necrosis factor (TNF). However, there are subtle differences in the pattern of response that are worthy of comment. Examples include the lack of efficacy of etanercept in Crohn disease[1] (which has never been satisfactorily explained),[2] the fact that ustekinumab is only effective in Crohn disease after prior failure of at least one other anti-TNF agent,[3] and clinical worsening in patients treated with interleukin (IL) 17A inhibitors,[4] whose spectacular efficacy in psoriasis confirms the fundamental pathogenic role of IL-17A in this disease.[5]

Another feature common to IMIDs is the appearance of paradoxical manifestations during treatment with anti-TNF agents. Explanations have been proposed for this contradictory behaviour, such as the activation of alternative cytokine pathways. For example, TNF blockade through treatment might induce an increased production of interferon alpha by plasmacytoid dendritic cells, which in turn may then activate production of IL-17A (sustained by IL-23) and IL-22 by the corresponding T-cell subpopulations, as well as expression of IL-22 receptors in keratinocytes.[6] This would explain the onset of paradoxical psoriasis in some patients (for example patients with Crohn disease) who receive anti-TNF agents. These patients may have a certain genetic predisposition due to uncommon alleles of the IL23R gene and respond to treatment with ustekinumab,[7,8] whereas activation of another feedback circuit in which the cytokines IL-17C and IL-36γ participate may go some way towards explaining the activation of keratinocytes in paradoxical psoriasis. These observations may provide a basis for a new therapeutic approach to this disease[9] and perhaps to other pustular dermatoses.

With regards to the counterproductive effect of IL-17A blockade in Crohn disease, it has been observed that patients with active disease have lower circulating CD45RO + CD4+ T helper (Th) 17 cell levels than those present when the disease is controlled with adalimumab; the lymphocyte count inversely correlates with mucosal inflammation estimated from the levels of fecal calprotectin.[10]

This apparent paradox requires an explanation, given that IL-23 (which in principle can expand Th17 cell populations and is able to activate tissue-resident IL-17A–producing Tγδ cells) has a fundamental role in autoimmune intestinal inflammation in murine models of

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IBD.[11] There are probably different types of Th17 cells, able to produce different combinations of cytokines that determine a relatively specific antimicrobial action, and the imbalanced intestinal microflora in Crohn disease, and certain Gram+ bacteria in particular—segmented filamentous bacteria—may play a key role in differentiation of Th17 cells and induction of colitis in murine models of IBD.[11]

The levels of IL-22 produced by type 3 innate lymphoid cells in the intestine are critical for maintaining intestinal barrier function, and in absence of IL-22, overgrowth of segmented filamentous bacteria may occur, along with an increase in the number of Th17 cells both in the mucosa and the corresponding lymph nodes.[12,13] Inhibition of IL-17A, one of the cytokines produced by Th17 cells, exacerbates intestinal disease in some patients with Crohn disease, thus suggesting a protective role of IL-17A, consistent with the observations in some murine models of colitis.[14] Although a pathogenic role has been proposed for IL-17F and IL-25 in IBD,[15] treatment with brodalumab has not proved effective.[2] On the other hand, it has been postulated that exacerbations observed in patients treated with IL-17A inhibitors may be related to altered intestinal mycological flora.[16]

Currently, it is accepted that a disturbed immune response to an altered intestinal microbiome at the mucosal interface has a fundamental role in the pathogenesis of Crohn disease and ulcerative colitis in individuals with a certain genetic predisposition.[17] The microbiome is the set of commensal bacteria associated with each individual, located in the skin, vagina, oral cavity, and principally (70%), the gastrointestinal tract. The dominant phyla are *Bacteroidetes* and *Firmicutes*. The intestinal microbiome contributes to digestion of fiber and polyphenols, the production of certain vitamins, and maintenance of epithelial barrier integrity, regulating homeostasis of the host immune system.[18] Taxonomic alterations or imbalances in the intestinal microbiome (dysbiosis) have been associated with a range of conditions, including obesity, colorectal cancer, liver diseases, irritable colon, IBD, and other IMIDs.[19] Both in IBD and spondyloarthritis, disturbances in the intestinal microbiome have been reported, with a decrease in the number of *Firmicutes*, which may indicate another common pathogenic mechanism,[20] and the existence of analogous disturbances (relative decrease of *Coprococcus* and other beneficial taxa) in psoriatic arthritis.[21]

Numerous studies have shown that the intestinal microbiome may have an impact on Th17/Treg balance in the lamina propria, and that intestinal Th17 cells may be responsible for the onset of arthritis in experimental models. The activation of Toll-like receptors plays a key role in the differentiation of Th17 cells in the lamina propria and in the induction of autoimmune arthritis; possible mechanisms include cross-recognition of bacterial and endogenous antigens, migration of Th17 cells of intestinal origin to the joints, and an alteration in the microenvironment of cytokines that may stimulate differentiation of autoreactive Th17 cells.[22]

Although this mechanism may provide a plausible explanation for the role of a possible dysbiosis in the pathogenesis of psoriasis and psoriatic arthritis, in the case of psoriasis, more attention has been paid to possible alterations in the skin microbiome, by analogy with atopic dermatitis.[23]

The pathogenic role of intestinal dysbiosis, that is, disturbed immunologic tolerance of intestinal microflora, would seem an important and common feature of different IMIDs. Some physicians, however, may be reluctant to explore the possible therapeutic implications (fecal transplantation) of this mechanism. They may prefer an alternative explanation involving alteration in the skin microbiome, which may have a similar role (alternative or complementary) to intestinal dysbiosis in psoriasis[24] and psoriatic arthritis.[25]

In conclusion, psoriasis, psoriatic arthritis, and Crohn disease share common pathogenic features, but they also show differences that may help elucidate the complete inflammatory cycles implicated and so develop new therapeutic approaches.

Conflicts of Interest

L. Puig has received consultancy and/or speaker fees, and has participated as an investigator in clinical trials sponsored by AbbVie, Amgen, Janssen, Lilly, Novartis, and Pfizer.

References

1. Rutgeerts P, Vermeire S, van Assche G. Biological therapies for inflammatory bowel diseases. Gastroenterology. 2009;136:1182–97.
2. Kaser A. Not all monoclonals are created equal - Lessons from failed drug trials in Crohn's disease. Best Pract Res Clin Gastroenterol. 2014;28:437–49.
3. Sandborn WJ, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, et al., CERTIFI Study Group. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med. 2012;367:1519–28.
4. Hueber W, Sands BE, Lewitzky S, Vandemeulebroecke M, Reinisch W, Higgins PD, et al., Secukinumab in Crohn's Disease Study Group. 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. 2012;61:1693–700.
5. Reich K, Papp KA, Matheson RT, Tu JH, Bissonnette R, Bourcier M, et al. Evidence that a neutrophil-keratinocyte crosstalk is an early target of IL-17A inhibition in psoriasis. Exp Dermatol. 2015;24:529–35.
6. Grine L, Dejager L, Libert C, Vandenbroucke RE. An inflammatory triangle in psoriasis: TNF, type I IFNs and IL-17. Cytokine Growth Factor Rev. 2015;26:25–33.
7. Puig L, Morales-Múnera CE, López-Ferrer A, Geli C. Ustekinumab treatment of TNF antagonist-induced paradoxical psoriasis flare in a patient with psoriatic arthritis: Case report and review. Dermatology. 2012;225:14–7.
8. Tillack C, Ehmann LM, Friedrich M, Laubender RP, Papay P, Vogelsang H, et al. Anti-TNF antibody-induced psoriasiform skin lesions in patients with inflammatory bowel disease are characterised by interferon-γ-expressing Th1 cells and IL-17A/IL-22-expressing Th17 cells and respond to anti-IL-12/IL-23 antibody treatment. Gut. 2014;63:567–77.
9. Friedrich M, Tillack C, Wollenberg A, Schauber J, Brand S. IL-36γ sustains a proinflammatory self-amplifying loop with IL-17C in anti-TNF-induced psoriasiform skin lesions of patients with Crohn's disease. Inflamm Bowel Dis. 2014;20:1891–901.
10. Dige A, Støy S, Rasmussen TK, Kelsen J, Hvas CL, Sandahl TD, et al. Increased levels of circulating Th17 cells in quiescent versus active Crohn's disease. J Crohns Colitis. 2013;7:248–55.

11. Burkett PR, Meyer zu Horste G, Kuchroo VK. Pouring fuel on the fire: Th17 cells, the environment, and autoimmunity. J Clin Invest. 2015;125:2211–9.
12. Hepworth MR, Monticelli LA, Fung TC, Ziegler CG, Grunberg S, Sinha R, et al. Innate lymphoid cells regulate CD4+ T-cell responses to intestinal commensal bacteria. Nature. 2013;498:113–7.
13. Hepworth MR, Fung TC, Masur SH, Kelsen JR, McConnell FM, Dubrot J, et al. Immune tolerance. Group 3 innate lymphoid cells mediate intestinal selection of commensal bacteria-specific CD4 T cells. Science. 2015;348:1031–5.
14. O'Connor W Jr, Kamanaka M, Booth CJ, Town T, Nakae S, Iwakura Y, et al. A protective function for interleukin 17A in T cell-mediated intestinal inflammation. Nat Immunol. 2009;10:603–9.
15. Xu XR, Liu CQ, Feng BS, Liu ZJ. Dysregulation of mucosal immune response in pathogenesis of inflammatory bowel disease. World J Gastroenterol. 2014;20:3255–64.
16. Colombel JF, Sendid B, Jouault T, Poulain D. Secukinumab failure in Crohn's disease: The yeast connection? Gut. 2013;62:800–1.
17. Boyapati R, Satsangi J, Ho GT. Pathogenesis of Crohn's disease. F1000Prime Rep. 2015;7:44.
18. Zhang YJ, Li S, Gan RY, Zhou T, Xu DP, Li HB. Impacts of gut bacteria on human health and diseases. Int J Mol Sci. 2015;16:7493–519.
19. Wright EK, Kamm MA, Teo SM, Inouye M, Wagner J, Kirkwood CD. Recent advances in characterizing the gastrointestinal microbiome in Crohn's disease: A systematic review. Inflamm Bowel Dis. 2015;21:1219–28.
20. Gill T, Asquith M, Rosenbaum JT, Colbert RA. The intestinal microbiome in spondyloarthritis. Curr Opin Rheumatol. 2015;27:319–25.
21. Scher JU, Ubeda C, Artacho A, Attur M, Isaac S, Reddy SM, et al. Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease. Arthritis Rheumatol. 2015;67:128–39.
22. Rogier R, Koenders MI, Abdollahi-Roodsaz S. Toll-like receptor mediated modulation of T cell response by commensal intestinal microbiota as a trigger for autoimmune arthritis. J Immunol Res. 2015;2015:527696.
23. Muszer M, Noszczyńska M, Kasperkiewicz K, Skurnik M. Human microbiome: When a friend becomes an enemy. Arch Immunol Ther Exp (Warsz). 2015;63:287–98.
24. Fry L, Baker BS, Powles AV, Engstrand L. Psoriasis is not an autoimmune disease? Exp Dermatol. 2015;24:241–4.
25. Castelino M, Eyre S, Upton M, Ho P, Barton A. The bacterial skin microbiome in psoriatic arthritis, an unexplored link in pathogenesis: Challenges and opportunities offered by recent technological advances. Rheumatology (Oxford). 2014;53:777–84.