ACTA SCIENTIFIC MICROBIOLOGY (ISSN: 2581-3226)

Volume 3 Issue 1 January 2020

Short Communication

IL-23/Th17 Cell Axis and Psoriasis

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Received: November 21, 2019; **Published:** December 09, 2019

DOI: 10.31080/ASMI.2020.03.0453

Psoriasis is an immune mediated inflammatory skin disease caused by a complex interplay between the immune system, Psoriasis-associated susceptibility loci, Psoriasis autoantigens and multiple environmental factors. Over the last two decades, researches has unequivocally shown that Psoriasis represents a T-cell mediated disease primarily driven by pathogenic T-cells that produce high levels of IL- 17 in response to IL- 23. The activation and up-regulation of IL- 17 in pre-psoriatic skin produces a feed forward inflammatory response in keratinocytes that is self-amplifying and drives the development of mature psoriatic plaques by inducing epidermal hyperplasia, epidermal cell proliferation and the recruitment of leukocyte subsets into the skin. The discovery of the central role for the IL- 23/Th17 cell axis in the development of Psoriasis has led to a major paradigm shift in the pathogenic model for this condition [1,2].

TNF-α is a potent pro-inflammatory cytokine and its upregulation in Psoriasis patients has been well characterized. One of the primary effects of TNF-α in Psoriasis is its regulation of IL-23. In response to some triggering event in the skin (e.g. trauma or infection), TNF released by plasmacytoid dendritic cells which results in the increased production of IL-23 from myeloid dendritic cells (mDCs). The increased production of IL- 23 by mDCs is the primary signal driving the activation of Th17 cells in Psoriasis plaques. Th17 producing cells in the skin produce substantial amounts of IL-17 (IL- 17A/IL- 17F) as well as TNF, IL- 26 and IL- 29 (IFN-λ1). Together, these cytokine signals create a feed forward inflammatory response in keratinocytes and induce epidermal hyperplasia, epidermal cell proliferation and recruiting leukocyte subsets into the skin. These define the master regulatory role of IL23 is pathogenesis of Psoriasis [3]. IL- 17 also acts synergistically with TNF to potentiate IL- 17 induced transcription of several pro-inflammatory genes (e.g. TNF, IL-1β, IL- 6 and IL- 8), which activate myeloid dendritic cells (mDCs) and promote the differentiation of Th17 cells in the skin and draining lymph nodes [4].

There is also an increased population of T-helper cells (Th1, Th17) in the skin lesions as well as in the peripheral circulation in Psoriasis. Emerging evidences suggest the interleukin IL-12B and IL-23R genes encoding the common p40 subunit of IL-12 and IL-23 are the key cytokines in Th1 and Th-17 differentiation and function. Certain allelic variants of these genes significantly influence the risk of Psoriasis. For this reason, current therapeutic strategies are now focused on the development of novel agents that disrupt the IL-23 or IL-17 cytokine signaling [5].

To date, three IL-17 pathway antagonists have been approved for the treatment of psoriatic disease: secukinumab, ixekizumab and brodalumab. Secukinumab, a fully human monoclonal antibody against IL-17A, was the first inhibitor of its kind approved for the treatment of psoriatic disease (approved in January 2016 for the treatment of moderate-to-severe Psoriasis). Ixekizumab, a humanized IgG4 monoclonal antibody directed against IL-17A was approved for the treatment of moderate-to-severe plaque Psoriasis in March, 2016. Brodalumab, a human monoclonal antibody that inhibits IL-17 receptor, was approved for the treatment of moderate-to-severe plaque Psoriasis in February 2017 [3].

In January 2011, ustekinumab, a human anti-interleukin-12/23p40 (IL-12/23p40) monoclonal antibody, was approved as for psoriasis. As a ''master regulator'' of Th17 cell development, IL-23 inhibition is currently in process using antibodies that target p19 subunit (eg: tildrakizumab, guselkumab, risankizumab). Some trial shows relatively long term treatment response with just one doses with these drugs. Phase III clinical trial is ongoing for treatment of mild to moderate Psoriasis [3].

The clinical efficacy of multiple TNF antagonists (e.g. adalimumab, etanercept and infliximab) underscore the importance of this cytokine in the promotion and maintenance of psoriatic skin lesions, though the percentage of patients experiencing dramatic improvement in their skin lesions is significantly lower than those seen with novel IL- 17 and IL- 23 antagonists [3].

The success of the IL- 17 and IL- 23 antagonists for the treatment of psoriatic disease has resulted in a modification of the primary clinical outcome. It not only bypasses the side effect of traditional drugs but also improves the quality of life by reducing disease severity and progression.

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Volume 3 Issue 1 January 2020