Beyond interleukin-17-targeted therapy: Complexity of environment-genetics-immunology needs to be addressed

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Ankylosing spondylitis (AS) is a prototype of spondyloarthritis (SpA) with long-term joint inflammation of the spine. SpA manifestations also include psoriasis, uveitis, and inflammatory bowel disease, which suggest these diseases may share some common genetic background.

In 2005, we identified a novel CD4$^+$ T cell subset, which produced interleukin-17 (IL-17) and developed independently of T helper type 1 (Th1) and Th2 cells. This T cell subset, named Th17, has a unique gene expressing profile and can drive tissue inflammation through the production of IL-17.[1] The first genome-wide association study (GWAS) of AS has found IL-23R, a Th17 regulator, as one of the most significantly associated genes with AS.[2] Then, a follow-up study by Xu et al further identified a strong association between AS and Stat3,[3] a transcription factor critical for Th17 cell development, acting downstream of IL-6 and IL-23.[4] Together, these genetic studies first hinted at a role for Th17 cells in AS. A clinical study further confirmed the phenotype of Th17 cells in AS.[5] Anti-IL-17 treatment for AS was then experimented in 2013[6] and has witnessed truly remarkable success. Anti-IL-17 agent was also approved for the treatment of plaque psoriasis and psoriatic arthritis. Although the IL-17 blocking biologics makes one of the most exciting advances in SpA therapeutics development, there are still patients resistant to this therapy. How do the environment–genetics–immunology interactions play in the pathogenic orchestra remains to be addressed.

Over the last decade, in addition to human leukocyte antigen B27 (HLA-B27), >100 associated/susceptible genes have been identified using technologies such as GWAS. Overall, such gene set only accounts for <30% of AS heritability.[7] Since genetic factors only partially explain AS pathogenesis, studies continue to search for other AS pathogenic factors. One such factor is the gut microbiome.[8] Experimental results showed that HLA-B27-positive rats under germ-free conditions did not develop AS, which relating the gut microbiota with AS pathogenesis.[9] Quantitative metagenomics observed growth in the composition of *Prevotella* (sp. C561, melaninogenica, copri) and *Bacteroides*-related depletion in AS patients.[10] Recently, gene–environment interaction has also been studied. An single nucleotide polymorphism in the gene *RUNX3* was found to affect the microbiome in AS patients, indicating the impact of a non-HLA-B27 host genetic variation on AS through the gut.[11] As a result, treatments based on gut microbiota and genetic features are promising in the future. Other environmental factors such as infection and environmental stress may also play a role.[12-15]

Overall, although diverse studies have been made in recent years, the exact mechanisms underlying the pathogenesis of AS remain to be fully elucidated. Interactions between multiple risk factors (genes, microbes, habits, and other environmental factors) may subject patients to AS pathogenesis. Identifying the pathways for gene–environment, intra- and inter-gene interactions can provide important clues into its pathogenesis,[16] which will ultimately contribute to precision diagnosis and more effective treatment.

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