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Editorial

Microdissecting Epigenetic Pathways in Oligoarticular Juvenile Idiopathic Arthritis: A New Avenue in Transforming Growth Factor β?

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In various autoimmune diseases, the host factors play a major role in the pathogenesis and continuation of the disease. Various epigenetic changes can influence gene expression and translation to effector proteins in autoimmune processes. These include histone modification and DNA methylation that is complemented by the regulation of microRNA (miRNA).[1] miRNA has potential translational properties. First, these are more stable than normal RNA and hence better candidates as diagnostic and therapeutic biomarkers. Second, most of them suppress protein expression and therefore have potential therapeutic applications. Third, they are highly specific, with an evolutionally conserved sequence of nucleic acid moieties and, thus, are theoretically less likely to elicit off-target effects as in the case of other epigenetic-targeted therapies such as histone deacetylase inhibitors. However, there are still many aspects of miRNA yet to be understood, including their roles in cell differentiation, proliferation, and death.[2]

In this issue of *The Journal of Rheumatology*, McAlpine and colleagues report the various miRNA associated with oligoarticular juvenile idiopathic arthritis (JIA).[3] Although there have been reports of various miRNA in JIA,[4-6] this report is unique in 2 aspects. First, it uses a droplet digital PCR array that targets 85 miRNAs known to be associated with various rheumatological disorders. Second, most previous studies had not looked exclusively at oligoarticular JIA. JIA is a heterogeneous group of disorders and it is incongruous to expect the pathogenesis of oligoarticular JIA to be similar to that of systemic JIA or enthesitis-related arthritis (ERA).

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The study by McAlpine et al[3] has looked at miRNA in cell-free serum and synovial fluid (SF), and also in extracellular vesicles and individual leukocyte samples. The JIA sera had higher levels of miR-15a-5p and miR-409-3p. miRNA produced by leukocytes were not different between patients and controls. However, a novel finding was that miR-409-3p and miR-451a were produced less by the SF leukocytes as compared to the serum leukocytes in patients with JIA. In between cell-free serum and SF, there was an overexpression of miR-21-5p and miR-146b-5p, and an underexpression of miR-451a.

After elucidation of the dysregulated miRNA, the authors proceeded with in silico pathway analysis using a standard DIANA-mirPath software (http://www.microrna.gr/miRPathv3) based on the KEGG (Kyoto Encyclopedia of Genes and Genomes) database. The maximum number of hits in this analysis was for the transforming growth factor β (TGF-β) pathway. Although the authors did not validate the in silico results in vivo, there is already evidence from previous transcriptomics studies that oligoarticular JIA fibroblast-like synoviocytes exhibit dysregulated TGF-β signaling.[7] The Figure summarizes how the different miRNA associated with oligoarticular JIA can influence both canonical and noncanonical pathways downstream of TGF-β.

Oligoarticular JIA is unique from other juvenile arthritis because it resolves spontaneously and rarely leaves residual damage in the joints. The involvement of the TGF-β pathway may have a role in this. Cartilage damage, osteophyte formation, and synovial fibrosis in osteoarthritis (OA) have been linked to high TGF-β.[8] The relationship between TGF-β and cartilage damage is itself complex: this cytokine appears to be protective for young healthy cartilage but harmful in the setting of damaged, aged cartilage.[9] How the miRNAs help to modulate TGF-β signaling in oligoarticular JIA may provide hints as to its function in maintaining healthy cartilage also. The aberration of TGF-β pathway activation is not specific to JIA-ERA, but further investigative

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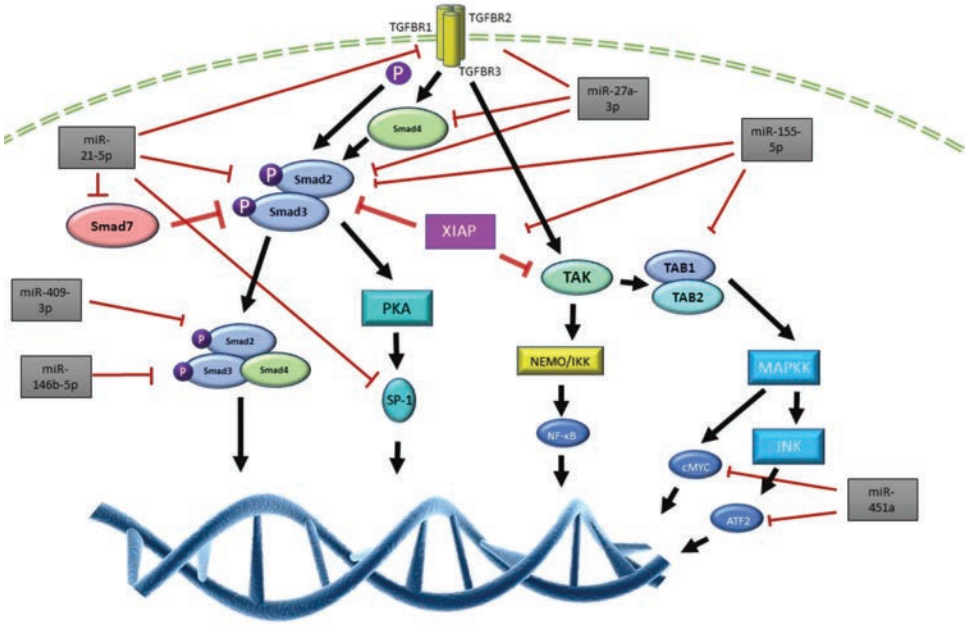

Figure. MicroRNAs associated with oligoarticular JIA and how they influence signaling downstream of TGF-β. JIA: juvenile idiopathic arthritis; TGF-β: transforming growth factor β.

work in this area is expected to lead to similar strategies in other arthritides. It may have implications for other diseases such as OA. All these need to be proven, but indeed, a newer avenue has opened up for exploration.

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