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Editorial

Entheses Ossification in Spondyloarthritis

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Editorial

Spondyloarthritis (SpA) is a group of diseases including Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), reactive arthritis, inflammatory bowel diseases, and undifferentiated arthritis, characterized by several common genetic, clinical and radiological features. Important common clinical features are spinal inflammation, sacroiliitis, peripheral arthritis and enthesitis.

Above all entheses, the attachment sites of tendons, ligaments, joint capsules, fasciae or muscles to bones, responsible for the dissipation of mechanical stress and for myofascial stabilization, play a key role in SpA pathogenesis. In fact, there are increasing evidences that entheses are the primary target tissue for inflammation in SpA, responsible for a lot of symptoms, and for the numerous locations of pain in SpA patients [1].

In past years, enthesis inflammation was believed to be involved in the destruction of the attachment of ligaments to bone, which in turn leads to reactive new bone formation [2]. Nevertheless, following evidences demonstrated that the sequence "inflammation-bone destruction-reactive osteoproliferation" was not acceptable. As demonstrated in murine studies both destruction and osteoproliferation occur simultaneously with inflammation and all process is driven by Tumor Necrosis Factor (TNF)-α [3-5]. Nevertheless, there are not studies that support this hypothesis in humans.

Even if cellular and molecular aspects of inflammation and bone destruction in SpA have been largely studied, very less is known concerning bone production. We know that it occurs by endochondral ossification; nevertheless factors involved in its induction and progression are not clear. Infact, human SpA ossification is not only a consequence of inflammation, but other processes are probably involved.

TNF-α is an inflammatory cytokine involved in the pathogenesis of these diseases as demonstrated by mononuclear infiltrates within the cartilage, and by TNF-α mRNA found in sacroiliac joints of patients affected by AS [6-8]. In consideration of the important role of TNF-α in the pathogenesis of these diseases, since the beginning of 2000, anti-TNF-α agents are increasingly used for the treatment of SpAs. Nevertheless, even if several studies reported the positive control of clinical and biological inflammation and joint destruction, persistent ossification has been often seen in SpA patients treated with anti-TNFα [9-12]. Taken together, these data suggest that TNF- α could contribute to inflammation and bone resportion, but other pathogenic pathways are also involved in inducing SpA bone formation.

Infact, IL-17/IL-23 axis is considered to play a key role in SpA pathogenesis and their serum levels have been associated with disease activity in active AS patients [13,14]. On one hand over expression of IL-17 has been associated with synovial inflammation and joint destruction *in vivo* and, on the other hand, IL-17 deficiency or inhibition has been seen to reduce joint inflammation and damage [15,16]. Moreover, IL-23 plays a role in entheses inflammation and promotes IL-17 and IL-22 expression by entheseal resident cells in mice with collagen-antibody–induced arthritis (CAIA) [17]. Thus, IL-17 plays a role in SpA enthesitis and bone erosion, whereas IL-22 is involved in the new bone formation. In fact, IL-22 induces genes involved in bone formation, such as genes encoding Wnt family members, bone morphogenic proteins and alkaline phosphatase. Moreover, IL-22 is responsible for the activation *in vivo* of the signal transducer and activator of transcription 3 (STAT3), a transcription factor involved in inducing bone formation [18]. Thus, IL-17 and Il-22 are involved in inflammation, bone erosion and bone formation, and are considered new therapeutic targets in the treatment of SpA, as demonstrated by trials in AS and PsA, using secukinumab, a fully human anti-IL-17A monoclonal antibody [19, 20]. The preliminary data show positive results on symptomatology and inflammation, while long-term studies are necessary to demonstrate an effect on excess bone formation [21].

It is conceivable that even other factors are probably involved in SpA entheseal ossification. In fact, a role in bone formation and in ligament ossification in AS has been described for transforming growth factor-β (TGF- β) and for chemokine (C-C motif) ligand 19 (CCL19) and 21 (CCL21) [22,23].

Other agents involved in bone formation are leptin and adiponectin [24,25]. These two molecules are adipokines produced by adipose tissue, responsible for controlling various physiological systems via an extensive network of communication both within adipose tissue and with other organs. If we consider that 45.8% of AS patients are at risk of occurrence of Metabolic Syndrome (MetS) versus 10.5% of healthy controls [26], and that adipokines play a regulatory role in MetS [27], it is hypothesizable that these molecules may be probably involved in SpA bone formation.

Another factor which probably plays a role in the pathogenesis of SpA is mechanical stress, as demonstrated by recent observations in murine studies [28].

Taken together, these observations underline the complexity of the mechanisms involved in SpA pathogenesis. Thus, TNF-α, IL-17 and IL-23 may be considered as components of a great molecular

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cauldron, where they certainly play a key role, but where even other mechanisms, only in part known, influence important clinical aspects of SpA, such as entheseal ossification. Therefore, further research and clinical trials are needed to better determine these mechanisms and to identify the most appropriate therapeutic strategies.

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