# SPONDYLOARTHRITIS: FROM INFLAMMATION TO OSTEOPROLIFERATION

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The identification of specific proinflammatory cytokines (e.g. TNF ) and immune cells in chronic arthritis has lead to the development of new targeted therapies. These drugs, in particular antibodies and soluble receptors directed against TNF, have an unprecedented effect on signs and symptoms of the disease. Activation of TNF and related cytokines also contributes to the process of joint destruction. Therefore in chronic joint diseases such as rheumatoid arthritis, inhibition of TNF does not only improve signs and symptoms but also positively affects the long-term outcome of the disease by preventing joint destruction. Ankylosing spondylitis is another chronic skeletal disorder that preferentially affects the spine and sacroiliac joints[1]. Its prevalence and burden are similar to that of rheumatoid arthritis[2]. The outcome of this disease is not determined by joint destruction but by progressive spine and joint ankylosis which together with ongoing inflammation lead to disability[3]. TNF blocking drugs are highly successful as symptomatic treatment in these patients but current clinical and experimental evidence does not support the concept that these drugs will also prevent further damage and hence long-term disability[4-6].

Progression of ankylosis has been linked to activation of developmental signaling pathways such as bone morphogenetic proteins (BMPs) and Wnts. Our group has demonstrated that inhibition of BMPs prevents and stabilizes ankylosis in a specific mouse model[7]. In contrast, inhibition of DKK1, a Wnt antagonist, shifts the phenotype of destructive arthritis in human TNF transgenic mice towards remodeling with new bone formation and also triggers ankylosis of the sacroiliac joints[8,9].

Links and coupling between inflammation and activation of these pathways are a rapidly evolving research area which could lead to the identification of new therapeutic targets to prevent ankylosis. Emerging data indicate that biomechanical factors and microdamage could play an important role in this type of rheumatic disease and that these may provide an explanation for the unusual association of inflammation with new tissue formation. The preferred anatomic site for disease development is probably found in the enthesis, an anatomical zone in which tendons and ligaments insert into the underlying bone and therefore a site of mechanical strain[10]. We have put forward the entheseal stress hypothesis to explain the sequence of events in ankylosing spondylitis and to understand the differences between control of inflammation and disease progression[11]. In this hypothesis, we suggest that microdamage in the enthesis may act as trigger of disease with subsequent activation of two different processes: acute inflammation and progenitor cell activation. Under normal circumstances these activations would be short-lived and lead to restoration of tissue homeostasis. However, factors such as genetic susceptibility may sustain these processes leading to chronic disease in AS patients. New genetic data obtained in mouse models also appear to support this concept.

These clinical and experimental observations appear to be rapidly changing our understanding of AS and related disorders further separating this disease from rheumatoid arthritis and its associated concepts. The differences between these common forms of arthritis thereby trigger new questions and will hopefully lead to more specific targeted therapies adapted to the individual patient's needs.

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