

Mechanobiology likely contributes to immunobiology pathways in the pathogenesis of ankylosing spondylitis

Sirs,

The interactions of the innate and adaptive arms of the immune system in the pathogenesis of spondyloarthritis (SpA) and ankylosing spondylitis (AS) were recently reviewed by Stoll (1). The innate immune system is generally believed to be activated at entheses sites and to express as an autoinflammatory reaction (1, 2). The adaptive immune system is also believed to participate in SpA pathogenesis and contribute to joint inflammation (1, 3).

The first issue raised by Stoll (1) was the stimulus for chronic interactions of the immune systems in SpA and AS. Trauma was proposed as one possibility as well as repeated biomechanical stress at entheses sites (1, 3), which are the natural loci for force concentrations in the body (2, 4). Regarding AS, one implication is that patients experience exaggerated innate and adaptive immunological reactivity to normal degrees of biomechanical stress. Alternatively, AS patients may have increased biomechanical stresses, due to innate or extrinsic factors, which could initiate and chronically activate their immunological responses (5-7).

Tissue injury could locally activate the innate immune system by release of damage-associated molecules, cytokines, or other mediators (1-3). In normal subjects, pro-inflammatory cytokine release is increased in skeletal muscle following eccentric exercise (8). However, a circulating systemic pro-inflammatory response is not seen, possibly due to activation of anti-inflammatory cytokines (8). Sustained, local pro-inflammatory cytokines are also believed to contribute to the clinical presentation of chronic tendon pain in tendinopathy (9).

We agree with Stoll (1) and others (2, 3, 10) that micro-trauma and biomechanical stress

may be important initiating triggers and chronic perpetuating stimuli in AS. In addition, we propose that AS patients may have a contributory innate axial (spinal) myofascial hypertonicity, which was previously reviewed (5-7). Normally-relaxed muscles act to absorb and dissipate stress. Conversely, stiffer muscles transmit greater stresses to tendons/ligaments and to bony entheses sites (4, 6). An increased axial stiffness in AS could predispose to exaggerated stress transmissions through entheses, leading to greater microdamage and abnormal tissue repair responses (4-6).

Notably, entheses are the characteristic sites of pathology in AS, which is consistent with a biomechanical contribution (2, 4-6, 11). Entheses normally function to efficiently transmit forces and dissipate stress, and are the critical link in connected tissues of muscle, tendon/ligament, and bone (2, 4, 11). They provide efficient force transmission and help maintain biomechanical integrity (4, 6). In normal persons, microtrauma and over-use injuries also occur at entheses sites (11). Although such episodes of mechanical stress may cause an injury reaction, they usually resolve over a period of days.

Assuming a structural axial myofascial hypertonicity does occur in AS patients, it could chronically exaggerate enthesal stresses and amplify the innate and adaptive arms of the immune system. Furthermore, a constitutional biomechanical diathesis, in combination with a pro-inflammatory predisposition, and other genetic factors, could initiate and perpetuate inflammation as well as osteoproliferation (syndesmo-phyte formation) in the AS patient (5, 10, 12) (Fig. 1).

Mechanotransduction translates intrinsic and extrinsic forces into cellular and molecular responses. Accordingly, cells modify their responses to varied stress by mechanobiology pathways (13). Increased structural and enthesal stresses on extracellular matrix (ECM), tendon, and bone (5, 13) in AS patients could be expected to result in altered

and pathological tissue responses (2, 5, 6, 11, 13).

In a rodent *in vivo* tendon model, mechanical stress can alter the expression of IL-1 in a load dependent fashion (14). In bone, osteoblasts are also load-sensitive cells and can produce bone morphogenetic proteins (13), found to be increased in a murine model of ankylosing enthesitis (9, 15). Moreover, microtrauma can release cartilaginous molecules that activate inflammation by pattern recognition receptors (1, 16). Those released ECM fragments can be incorporated intracellularly and initiate a pro-inflammatory cascade (16).

Thus, a proposed structural biomechanical perspective in AS (5-7) can complement the immunobiology pathways summarised by Stoll (1) (Fig. 1). Further critical investigation is needed to test the hypothesised axial myofascial hypertonicity in AS (5-7, 17) and its relation to the proposed immunological pathways (1).

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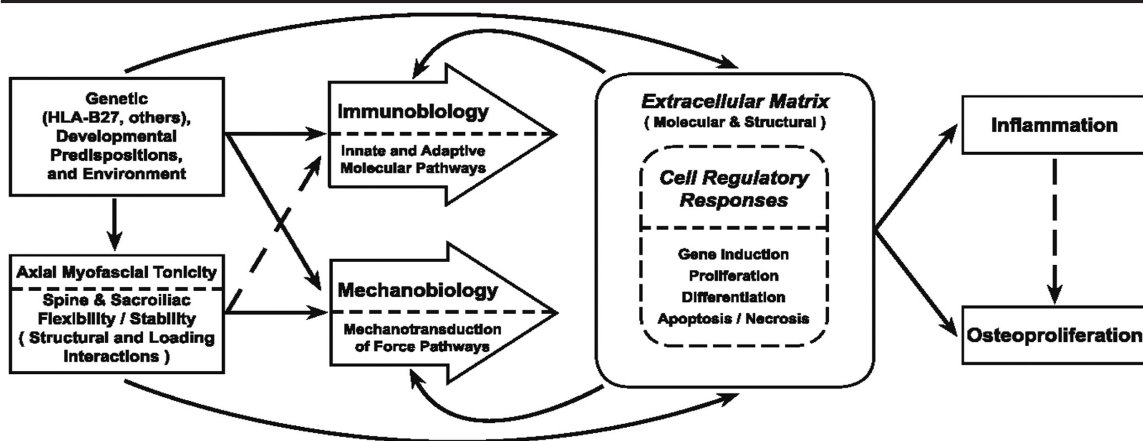


Fig. 1. A modified theoretical outline of immunobiology and mechanobiology processes interacting in initiation and perpetuation of pathways in ankylosing spondylitis. [Modified from (7), with permission for reprinting from *J Rheumatol* 2011; 38: 2092-4.

Letters to the Editors

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