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The role of mechanical stress in the pathogenesis of spondyloarthritis and how to combat it☆

Peggy Jacques [a], Dennis McGonagle [b, *]

[a] University Hospital Ghent, De Pintelaan 185, 9000 Ghent, Belgium
[b] The Leeds Institute of Rheumatic and Musculoskeletal Medicine, 2nd Floor, Chapel Allerton Hospital, Chapeltown Road, Leeds LS7 4SA, UK

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A B S T R A C T

Given that entheses are sites of high mechanical stress that concentrate the forces of large contracting muscles down onto a small footprint of bone contact, it was recognized nearly 60 decades ago that stress and injury at such sites may play a role in the pathogenesis of mechanically related enthesopathy. In recent years, the role of mechanical stress and its related consequences on inflammatory enthesitis have also been recognized. Clinical imaging studies and experimental animal models of spondyloarthropathy including tumor necrosis factor (TNF) transgenic models and interleukin (IL)-23 overexpression systems are associated with a primary enthesitis with disease subsequently spreading to adjacent joint structures including the synovium and bone. Joint mechanical stress, without discernible microdamage or injury, leads to spondyloarthritis (SpA) in a TNF transgenic model. Normal-aged human entheses often demonstrate microdamage, but it is unclear whether an abnormal response to mechanical stress alone or the need for stress-induced microdamage is involved in human disease initiation. Clinically, the contribution of mechanical stress to SpA including psoriatic arthritis (PsA) helps conceptualize the disease in a new way and provides obvious mechanistic links to skin and nail Koebner responses. It also offers novel epidemiological explanations for why PsA develops in subjects with high body mass indices most typically in the fourth and fifth decades. Molecularly, the monogenic forms of SpA including caspase recruitment domain-containing protein 14 (CARD14) and

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* Corresponding author.
E-mail address: D.G.McGonagle@leeds.ac.uk (D. McGonagle).

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IL36RN mutations have site-specific expression of mutated proteins in the skin, thus offering a direct molecular link between local inflammation-related pathway dysregulation and local stress or injury in disease causation. Given that many of the pathways that govern both immunity and mechanical stress including extracellular-signal-regulated kinase (ERK) and mitogen-activated protein kinase (MAPK) are shared, it may be difficult to develop strategies that selectively target mechanical stress-related pathways. However, occupational- and obesity-related factors may be potentially modifiable in susceptible individuals to prevent or ameliorate disease.

Introduction

The target organ distribution in spondylarthropathies (SpA) has historically been hard to explain in terms of a specific autoantigen or autoantibody that could account for the diverse patterns of organ involvement [1]. Inflammatory arthritis in SpA typically shows a propensity for lower limb over upper limb involvement and large joint over small joint involvement. The human leukocyte antigen (HLA)-B27-associated juvenile form of SpA typically starts in the ankle and foot and migrates to the sacroiliac joint (SIJ) and spine during teenagehood or early adulthood. The extra-articular features of uveitis and aortic root inflammation in particular spurred the eminent osteoarticular pathologist Bywaters to suggest that tension at the aortic root provided a unifying biomechanical theory for SpA [2].

With the complex pattern of skeletal pathology evident in tissues from subjects with later stages of SpA, the pre-eminence of entheseal disease in SpA was not fully comprehended with pathologists including Bywaters and Ball not attempting to link enthesitis to synovitis and osteitis, the other two cardinal features of SpA [3]. In the 1990s, magnetic resonance imaging (MRI) studies showed that clinically unrecognized enthesitis was not uncommon in synovitic joints and that enthesitis was associated with adjacent osteitis [4,5]. This led to the realization that other joint structures including fibrocartilaginous joints such as the SIJ and regions where tendons change direction or wrap around bone, dubbed “functional enthesis,” share similar histological and identical patterns of mechanical stress and thus a theoretical enthesis-based biomechanical model for all SpA features was proposed [6]. The idea that mechanical stress and microdamage may be instrumental in inflammatory enthesitis as a primary driver in SpA resonated with the ideas from the 1950s where La Cava pointed out that sports injury-related enthesopathy might be linked to an inflammatory reaction characterized by fibrosis and calcification occurring at the enthesis in response to continuously recurring microtrauma [7].

Enthesis microanatomical configuration

It is not clear whether every arthritic joint in SpA is characterized by the co-occurrence of enthesitis and synovitis [8], which could reflect the limitations of the currently used imaging techniques such as ultrasonography and MRI. This is particularly the case in small joints due to the close proximity of the synovium, enthesis, and other joint structures. The prototypical enthesis of the Achilles tendon should be considered not only as a focal attachment site to bone but rather as a complex organ, including the periosteal and sesamoid fibrocartilages, the retrocalcaneal bursa, and the tip of Kager's fat pad covered by synovium, which together form an enthesis organ [9]. The concept of a synovio–entheseal complex illustrates the complex integration of entheses with the joint's synovium indicating a complex anatomical link between the enthesis and synovium [10]. The close anatomical relationship between the enthesis, prone to mechanical stress, and the vascularized synovium, in contact with a diversity of immune mediators, may provide the pathogenic basis for joint inflammation in SpA [11].

Entheses are, unlike the synovium, avascular structures and are composed of dense regular connective tissue that serves to minimize the chances of damage during locomotion. This is, in particular,