

# Basic Concepts of Enthesis Biology and Immunology

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**ABSTRACT.** The article highlights key features of entheses relevant to understanding psoriatic arthritis (PsA). It is emphasized that entheses are regions of stress concentration and that stress levels are reduced by anatomical adaptations at the insertion site and its adjoining tissues. These adaptations for stress dissipation include fascial expansions, the flaring out of soft tissue as it approaches the enthesis, the reduction of insertional angle changes by pulleys or retinacula, and fibrocartilage buffers near the bony interface. Despite such adaptations, however, microdamage is common at entheses and can be associated with the presence of microscopic cellular infiltrates, including macrophages and lymphocytes that can be seen as a normal age-related finding. Observations pertaining to the close functional interdependence between the enthesis and adjacent synovium have led to the concept of a synovio-enthesal complex, which is important for understanding joint physiology and pathophysiologic mechanisms of synovitis in PsA. (*J Rheumatol* 2009;36 Suppl 83:12-13; doi:10.3899/jrheum.090211)

*Key Indexing Terms:*

ENTHESES  
ENTHESIS ORGAN

PSORIATIC DISEASE  
SYNOVIO-ENTHESEAL COMPLEX

An enthesis is the attachment of a tendon, ligament, or joint capsule – usually to bone, but also to cartilage in the growing child. As entheses are regions where hard and soft tissues meet, they are sites of stress concentration, particularly under load. Not surprisingly, therefore, they are regions of wear and tear. Such considerations have led us to propose that mechanical factors at entheses are important in the pathogenesis of the seronegative spondyloarthropathies (SpA)<sup>1</sup>. In our view, factors intrinsic to the anatomy of entheses are pivotal in understanding these diseases. Here, we explain basic principles of enthesis biology that underpin such thinking in a way that is relevant to readers interested in psoriatic disease. Much of the information is covered more extensively elsewhere<sup>1-4</sup>.

The basic function of entheses is providing firm anchorage with minimal stress levels. Perhaps surprisingly, many entheses have little compact bone, and thus the attachment may seem tenuous<sup>5</sup>. This is not age related bone loss, for it is seen in younger individuals as well. Bywaters' illustrations of the Achilles tendon enthesis in young subjects<sup>6</sup> shows a thin subchondral plate similar to that seen in older individuals. The relative absence of compact bone means that the adjacent cancellous bone must be involved in the attachment by dissipating the

load to adjacent parts of the skeleton. This is reflected by a difference in the density and orientation of spicules near entheses<sup>3</sup>. We have emphasized the anchorage role of such spicules by comparing them to the roots of a tree<sup>5</sup>. We have also suggested that the mechanical loading of spicules around an attachment site helps to explain why osteitis and enthesitis can be linked in SpA. Attachment is also ensured by the complexity of the interface between the calcified fibrocartilage in the terminal part of the tendon and the adjacent bone<sup>7</sup>. The 2 tissues knit into each other to form microscopic dove-tail joints. The stability of the anchorage site can also be increased by a marked flaring of the tendon or ligament at its enthesis and by many fascial interconnections between attachments. It is helpful to recognize that the deep fascia of the limbs acts as an "ectoskeleton" that provides an alternative pathway of force transmission for muscles, tendons, and ligaments<sup>8</sup>. In relation to psoriatic arthritis, the reader should note that finger extensor tendons can have fascial expansions embracing the nail root – perhaps explaining why nail disease is linked to extensor tendon enthesitis<sup>9</sup>.

Stress concentration at many attachments is reduced by fibrocartilage on the soft tissue side of the junction<sup>1</sup>. The stiffness of this tissue (promoted by aggrecan) ensures that collagen fibers bend gradually as the insertional angle changes with joint movement, rather than abruptly at the hard soft tissue boundary<sup>1</sup>. Most insertional angle changes in long tendons, however, may already have been reduced away from the enthesis itself, by pulleys and retinacula that prevent tendons from bowstringing. It should also be remembered that the attachment site may form part of an enthesis organ complex, where contact between tendon/ligament and bone adjacent to the insertion leads to the development of ancillary fibrocartilages and bursae<sup>10</sup>. Such anatomical specializations ensure that

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some stress is dissipated immediately adjacent to the attachment site as well as at the enthesis itself, which helps explain why enthesopathies may not present as focal insertional disorders, but can also affect the adjacent area<sup>11</sup>. The archetypal enthesis organ is that of the Achilles tendon, but there are others as well<sup>11,10</sup>.

The presence of an Achilles enthesis organ hinges on the prominence of the superior calcaneal tuberosity. This acts as a tendon pulley in a dorsiflexed foot – thus accounting for its fibrocartilaginous periosteum and the sesamoid fibrocartilage in the tendon. These fibrocartilages ensure that the forces exerted during Achilles tendon function are dissipated over the entire posterior surface of the calcaneum, and this explains why enthesitis at this site may be associated with diffuse osteitis<sup>11</sup>. In a similar way, the head of the proximal or intermediate phalanx acts as an extensor tendon pulley when the finger joints are flexed. Consequently, there is a sesamoid fibrocartilage in the deep surface of the tendon at the attachment site.

A concept arising directly from the idea of an enthesis organ, also relevant to psoriatic disease, is that of a synovio-enthesal complex (SEC)<sup>2</sup>. This concept highlights the association between a proinflammatory and vascular tissue (synovium) and an avascular structure (enthesis). It provides a rational basis for understanding the importance of autoinflammatory rather than autoimmune factors in the onset and development of SpA. It embraces the notion that a synovial membrane at an enthesis is not necessarily that of a synovial joint<sup>4</sup>. The most obvious example is the Achilles tendon insertion, where the synovium of the retrocalcaneal bursa is independent of that of the ankle joint. Of particular relevance to the SEC concept is the evidence for microdamage and repair at numerous entheses that is seen in dissecting room cadavers<sup>3,4</sup>. This probably reflects a lifetime of mechanical loading. The damage and repair is on both the hard and the soft tissue sides of the interface, but frequently presents as fissuring and cell clustering in the uncalcified fibrocartilage zone<sup>4</sup>. Of course normal fibrocartilage, like articular cartilage, lacks resident macrophages or neutrophils, so inflammation in association with this is likely to manifest in the adjacent synovial tissues.

The hypothesis associated with the SEC concept relating to SpA is that the damage and repair at entheses trigger an inflammatory reaction in the synovium. Hence, it is proposed that tissue-specific, biomechanical factors at entheses may regulate immune activation at these sites in patients with SpA. Certainly the presence of immune cells in association with tissue necrosis at entheses is more common than is widely believed, and lymphocytes and macrophages are present at subclinical levels at many attachments<sup>4</sup>. Perhaps their presence becomes significant when microdamage occurs in individuals of the right genotype.

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