The Synovio-entheseal Complex and Its Role in Tendon and Capsular Associated Inflammation

DENNIS McGONAGLE, SIBEL ZEHRA AYDIN, and AI LYN TAN

ABSTRACT. Tendon, ligament, and capsular insertions are parts of "enthesis organs" whereby the enthesis itself has an elaborate functional integration with the adjacent soft tissues and the synovium in particular. The purpose of this article is to review the sophisticated degree of integration between insertions and adjacent synovium in what has been dubbed "synovio-entheseal complexes" (SEC). SEC arise at multiple sites in the immediate vicinity of insertions and may also arise within the joint capsule at sites well away from enthesis insertions. Not only does this relationship between the enthesis and synovium hold in synovial joints, but it is also crucial for understanding the microanatomical basis for joint disease localization to tendons in the seronegative spondyloarthropathies as well as in other conditions including osteoarthritis. The fibrocartilages at insertions are prone to microdamage whereas this tissue is completely devoid of immune cells. In healthy conditions, the synovium lubricates and nourishes the entheseal associated fibrocartilages, but damage or aberrant tissue repair responses at the insertion may manifest as an immediately adjacent synovitis or tenosynovitis, given that the synovium has resident immune cell populations and the ability to undergo substantial hyperplasia. Therefore SEC are likely to represent key orchestrators that contribute to joint inflammation by mechanisms that have been hitherto poorly appreciated. (J Rheumatol 2012;39 Suppl 89:11–14; doi:3899/jrheum.120233)

Key Indexing Terms:
ENTHESIS TENDONS LIGAMENTS SPONDYLOARTHRITIS SYNOVIUM

The microanatomical basis for the understanding of inflammation in the spondyloarthropathies (SpA) has greatly improved in the last decade. It is now recognized that enthesitis-related inflammation is much more prevalent than was historically appreciated by clinical evaluation, where Achilles enthesitis, plantar fasciitis, and other peripheral enthesopathies were discernible in the clinic or at the bedside in a subgroup of cases. The widespread application of modern imaging techniques including magnetic resonance imaging (MRI) and ultrasound (US) have shown that clinically hidden enthesitis is common in diseased synovial joints and throughout the axial skeleton at the time of clinical presentation or even before clinically evident joint swelling[1,2].

A combination of imaging studies with detailed histological evaluation of normal entheseal tissue led to the realization that insertions comprised more than just a focal insertion and that the entire region of the insertion was actually an "enthesis organ"[3]. How the enthesis comprises a group of related tissues at the insertion and adjacent fibrocartilages lining the bone and immediately adjacent tendons/ligaments has been reviewed in detail elsewhere[4], as well as how the enthesis organ is functionally integrated into the trabecular bone network[5].

After the original development of the enthesitis theory as the unifying basis for SpA, it remained difficult to conceptualize how focal insertional inflammation could be associated with such widespread synovitis. To better address this, in 2007 we described an anatomical unit termed the synovio-entheseal complex (SEC), whereby the normal enthesis-related fibrocartilages were critically dependent on immediately adjacent synovium (Figure 1)[6]. SEC are common immediately adjacent to insertion sites of ligaments, capsules, and tendons but are also common in other sites away from the actual points of insertion (Figure 2). The purpose of this review is to describe SEC and to briefly cover the improved understanding that is emerging on how these structures may contribute to inflammation.

SYNOVIO-ENTHESEAL COMPLEXES AND MECHANISMS OF SYNOVITIS AND JOINT DAMAGE

Synovio-entheseal complexes are associated with the presence of age-related microdamage in healthy subjects. We have recently shown that enthesis-related fibrocartilage

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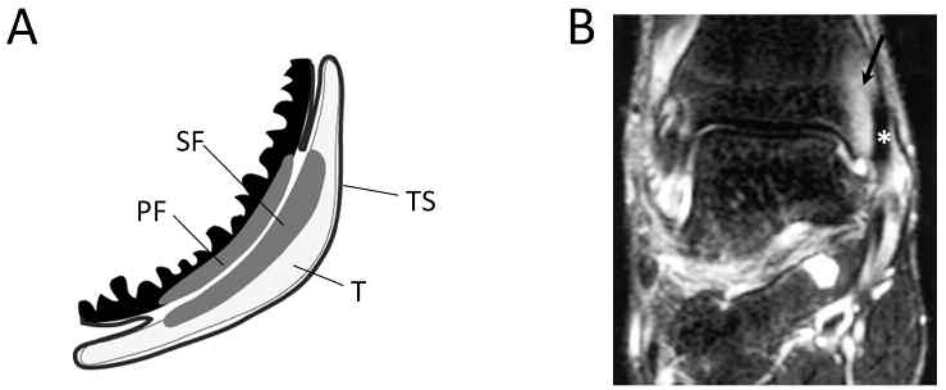

Figure 1. Synovio-entheseal complexes (SEC) are ubiquitous structures. A. Cartoon depicting the change in direction of a tendon (T) over a bony tuberosity. The tenosynovial sheath (TS) disappears at sites of high compressive forces at bony point of contact. At this point fibrocartilage is present and thus forms an SEC, which is likely to underlie the mechanism of tenosynovitis at such sites in spondyloarthropathies (SpA) and contribute to the pain and dysfunction associated with degenerative tendinopathies in older subjects. B. Magnetic resonance imaging scan that shows a patient with early ankle arthropathy related to SpA; in this case there is florid underlying bone edema (arrow) in addition to tenosynovitis (asterisk). PF: periosteal fibrocartilage; SF: sesamoid fibrocartilage. From McGonagle, et al. Arthritis Rheum 2003;48:896-905[6] and Arthritis Rheum 2007;56:2482-91[6]; adapted with permission.

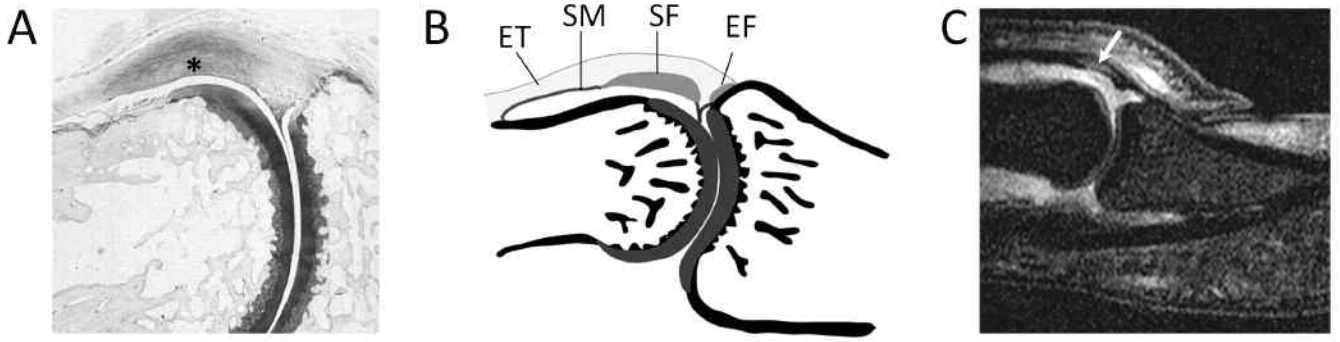

Figure 2. Synovio-entheseal complexes (SEC) are confined not only to the region immediately adjacent to insertions such as the retrocalcaneal bursa in the heel or at numerous insertion points in synovial joints. This example shows the complex nature of an SEC, in this case in the extensor tendon apparatus in the human hand. A. Histology image showing some cartilage within the capsule at the point of capsule compression during joint flexion (asterisk). B. Depiction of SEC-related cartilage in this region. C. Illustration of how this is relevant to the pathological changes that occur in disease. In this case the patient has clinically presented with distal interphalangeal joint swelling, appearing on magnetic resonance imaging as both joint synovitis and capsular edema. The high signal within the tendon (arrow) corresponded to SEC structure inflammation. The epicenter of disease at this SEC therefore offers an explanation for both intra- and extraarticular soft tissue inflammation. ET: extensor tendon; SM: synovial membrane; SF: sesamoid fibrocartilage; EF: enthesis fibrocartilage. From McGonagle, et al. Arthritis Rheum 2007;56:2482-9[6]; adapted with permission.

damage can also be delineated in some young healthy subjects using novel US-based imaging whereby the fibrocartilage can be visualized[7]. As part of the normal tissue repair response, microdamage begets microscopic inflammation as part of the process leading to tissue homeostasis restoration. Not surprisingly, we found that tissue from ostensibly normal joints had evidence for asymptomatic microscopic synovitis in the SEC region joint lining[8]. Occasionally pannus tissue or an invasive stromal component that contributes to cartilage damage could be seen[8].

The elaborate nature of SEC in small joints including the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints offered a novel concept for understanding periarticular erosion in these structures. We and others have reported on the proclivity for erosions in rheumatoid arthritis (RA) adjacent to the lateral collateral ligament especially on the radial side of the second and third MCP joints[9]. Likewise we and others have shown that microscopic erosions occur in an identical territory in healthy subjects[9,10]. It transpired that the region of the PIP and MCP joints previously designated as "bare areas" on the basis that the synovial intima was in direct contact with bone were not so bare after all[11]. In fact these structures are often covered by SEC-related fibrocartilages with microscopic erosion occurring at these sites of high mechanical stressing. In the joint environment associated with the primary synovitis of RA

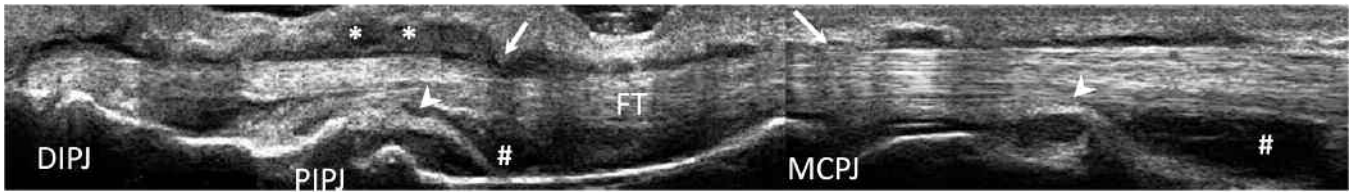

Figure 3. Longitudinal US scan of the volar aspect of the hand. Panoramic image of the second finger flexor tendon (FT) demonstrates tenosynovitis with synovial effusion (#) and proliferation (*) inside the tendon sheath. A1 and A3 pulleys are thickened (arrows), and joint capsule is widened at the proximal interphalangeal joint (PIPJ) and metacarpophalangeal joint (MCPJ) level (arrow head). The insertion of the flexor digitorum profundus tendon onto the base of the terminal phalanx is thickened. DIPJ: distal interphalangeal joint.

this leads to an accrual of joint damage due to the acceleration of tissue destruction and the impairment of tissue repair mechanism. This is not specific for RA but also helps explain the distribution of erosions in small joints in SpA and in inflammatory osteoarthritis[8]. In the latter a disease process that commences with ligament thickening appears to favor joint damage at sites of increased bony compression[12].

TENDON DISEASE — ANIMAL MODELS

Some tumor necrosis factor (TNF) transgenic models of inflammatory arthritis have been likened to RA but also exhibit sacroiliitis and excellent anti-TNF therapy responses, with the absence of autoantibodies, and are therefore much more akin to SpA. In human TNF transgenic mice, serial sacrifice of animals to ascertain where disease initially commences shows inflammatory infiltration in the peritendinous regions that equated with a tenosynovitis[13]. Crucially, this was accompanied by osteoclast activation in the immediately adjacent bone. It is critical to point out that there is no actual tendon insertion at this location, but rather a site where tendons exert pressure against the bone. Regions where tendons change direction as they traverse bony prominences have been designated as functional entheses, where there is no actual insertion but where fibrocartilage is present on the bony surface and adjacent tendon point of contact[3]. These regions share an identical pattern of mechanical stressing and identical patterns of entheseal type pathology on MRI.

Other animal model studies have demonstrated the pivotal role of non-synovial membrane tissue as the initiator of joint inflammation in animal model settings. The earliest events in the evolution of arthritis in a different TNF-mediated murine SpA model take place at the Achilles tendon enthesis with the inflammation appearing to spread to the adjacent synovium thereafter. Of even greater importance was the observation that inflammation in this model was dependent on aberrant TNF production by stromal cells at the enthesis rather than by cells of either the innate or adaptive immune system[14]. It is worth pointing out that animal model studies in the DBA-1 mouse model also showed that disease commencing at the enthesis appeared to spread to the adjacent joint and nail[13].

These models provide proof of the principle that subtle abnormalities of nonimmune cells at the enthesis could subsequently manifest as joint synovitis, underlining the delicate balance between insertions and the adjacent synovium. The SEC model for inflammation underscores how inflammation against self that was historically considered autoimmune may in fact be related to tissue-specific dysregulation at insertion points. That therapy with noggin, a bone morphogenetic protein antagonist, could prevent the DBA-1-related disease attests powerfully to the fact that targeting molecular pathways viewed to be major players in joint homeostasis and remodeling, rather than inflammation or immunity, offers a new way of thinking about site specific or SEC-related tissue-specific factors in disease expression.

CLINICAL CORRELATES WITH TENDON SEC DISEASE

As set out in Figure 1, imaging studies have shown that the recognition of SEC helps explain tenosynovial disease in tendons in humans with SpA. At the point where tendons traverse bony prominences, the tenosynovial sheath is replaced by fibrocartilage at sites of high mechanical stress. This is likely to be a key mechanism that underlies tenosynovitis development in SpA. This may also contribute to pain and dysfunction associated with degenerative tendinopathies in older subjects.

A related example is the role of the SEC in synovitis in man. Recent studies employing power Doppler (PD) US have demonstrated synovitis. Gutierrez, *et al* showed that increased PD signal in extracapsular tissues adjacent to tendon was commoner in SpA compared to RA[15]. An epicenter of disease located within capsular SEC, thus accounting for synovitis and extracapsular pathology, offers a unifying explanation for such observations (Figure 3).

SEC FUTURE DIRECTIONS

Disease within SEC structures also explains why subjects with SpA may not have focal insertional inflammation on MRI or US imaging as the lesion may be located intraarticularly adjacent to the synovium and manifests as synovitis. This makes the use of imaging enthesitis to diagnose SpA somewhat problematic now that the more extensive nature of the enthesis organ can be delineated.

The role of SEC as possible sites of initiation of joint inflammation in autoantibody-positive RA also merits consideration. In that regard we have shown that the volume of inflamed synovial tissue in RA and SpA in the knee is greater at the quadriceps SEC region and that this is not well suppressed following conventional disease-modifying antirheumatic drug therapy in comparison to synovitis in the more distant suprapatellar pouch[16].

With respect to the underlying immunopathogenesis of enthesitis, the genetic basis for inflammation at SEC in SpA awaits elucidation. The key will be to define specific genes and then to demonstrate their expression at SEC, especially before the development of clinically detectable synovitis.

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