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Enthesitis in psoriatic arthritis (Part 1): pathophysiology

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Abstract

Enthesitis is a key manifestation of PsA and current knowledge supports the concept that it may be among the primary events in the development of this disease, as well as other forms of SpA. Patients with PsA seem to have a different threshold to mechanical stress, which may be genetically determined. Hence patients with psoriatic disease respond pathologically with inflammation after being exposed to physiological mechanical stress. Activation of pro-inflammatory mediators such as IL-17 and TNF-α as well as the influx of innate immune cells are key events in the development of enthesitis in PsA. Chronic entheseal inflammation is accompanied by new bone formation, leading to bony spurs in peripheral (entheseophytes) and axial (syndesmophytes) structures. This article reviews the current knowledge on the mechanisms involved in the development of enthesitis in patients with PsA.

Key words: psoriatic arthritis, enthesitis, interleukin 23, interleukin 17, entheseophyte

Rheumatology key messages

- Exaggerated inflammatory responses to mechanical stress in patients with PsA lead to initiation of enthesitis.
- Enthesitis is associated with the generation of pro-inflammatory cytokines such as IL-17 and TNF-α.
- Chronic entheseal inflammation is accompanied by new bone formation in peripheral and axial structures.

REVIEW

Introduction

Reviewed in this article are the current concepts of cellular and molecular pathways that lead to enthesitis in light of a better understanding of the clinical features of PsA and the response to targeted anti-inflammatory treatment. The article will discuss the nature and function of tendon and ligament insertion sites ('entheses') and the pathways that lead to inflammation of entheses ('enthesitis'). Thus it will highlight the role of mechanical factors as initiators of enthesitis, the key non-immune and immune cells involved in the process and the currently identified clinically relevant mediators of enthesitis, including IL-17, IL23, TNF-α and prostaglandin E2 (PGE2). The article will also address the structural consequences of enthesitis, focussing on local new bone formation and the mechanisms translating inflammation into structural responses.

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Nature of entheses

Entheses are essential for locomotion, as these structures connect tendons and ligaments to the bone. They have two main functions: to transduce mechanical forces to the skeletal system and to confer stability [1]. Inflammation of these tendon and ligament insertion sites (enthesitis) is a hallmark manifestation of PsA and other forms of SpA, including axial SpA (axSpA). The importance of enthesitis in PsA is acknowledged by the incorporation of this clinical manifestation in the core requirements of the Classification Criteria for Psoriatic Arthritis (CASPAR) [2]. Also, current knowledge supports the idea that enthesitis may be the primary event in PsA [3] and axSpA [4]. Biomechanics, PGE2-mediated vasodilatation, innate immune responses and several cytokines are implicated in the development of enthesitis [1]. A better understanding of its pathophysiology in recent years has allowed for a more targeted approach when treating patients suffering from PsA.

Entheses are typically located outside the joint, which means that the insertion is outside the joint capsule, tackling the periosteal surface. However, there are some specific joints, such as the sacroiliac, sternoclavicular and distal interphalangeal joints, in which fibrocartilaginous tissue—a typical feature of entheses—is a dominant

feature of the joint itself. Such structures are often involved in PsA and other forms of SpA. A fibre-rich portion, with scattered fibroblasts, as well as areas with chondrocytes and cartilaginous matrix, composes the entheses [5, 6]. This unique structure allows for the smooth transduction of mechanical forces to the bone as well as stable anchorage of tendons and muscles to the bone. Entheses are sometimes referred to be an 'organ', as they possess a unique microenvironment [7]. Hence resident mesenchymal cells with the potential to differentiate into chondrocytes or osteoblasts are part of entheseal structures [8, 9] in the same way as 'resident' immune cells, such as γδ T cells and type 3 innate lymphoid cells can be found enriched in entheseal structures [10, 11]. In disease, these cells have been implicated in triggering inflammation.

Mechanical stress as a trigger for enthesitis

Mechanical stress is often the triggering event in the development of enthesitis [12]. In healthy individuals, enthesitis may develop after repetitive trauma, such as in the case of work or sports activities. A typical example is lateral epicondylitis, the so-called tennis elbow. This condition usually resolves spontaneously after avoidance of the repetitive movement. For reasons not completely understood and potentially involving genetic factors, patients with PsA and other forms of SpA have a lower threshold for the development of enthesitis. In such patients, long-standing inflammation may be triggered by mechanical stress or trauma [13]. Seminal studies from Cambre *et al.* [14], for instance, showed that mechanical stress can trigger the local expression of chemokines such as CXCL1 and CCL2, which allow the influx of innate immune cells to the sites of stress. Hence anatomical localization of the disease in patients with PsA and other forms of SpA could be determined, at least in part, by entheseal sites in conjunction with individual mechanical stress to such sites. Innate immune activation upon the recognition danger signals (disease-associated molecular patterns) by the immune system appears to be a central feature for understanding the rapidity of onset of enthesitis as well as its chronicity when such danger signals are not adequately controlled or removed [15]. Disease-associated molecular patterns may be built by mechanical, infectious or other triggers in the context of PsA and SpA and are likely to represent the early events that lead to the activation of a cascade of inflammatory mediators that ultimately results in the full-blown picture of enthesitis.

Key mediators of inflammation in enthesitis

PGE2 is an early mediator of enthesitis. The main proof that PGE2 plays a crucial role in enthesitis is the fact that NSAIDs are effective in treating this condition. Paulissen *et al.* [16] showed a critical role for the cyclooxygenase-2/PGE2 pathway in stimulating production of IL-17 by T cells, which may occur independently from IL-23. PGE2 appears to be important for mounting inflammation in the entheses, as it promotes vasodilation, which helps recruit neutrophils and other innate immune cells from the bone marrow to the entheseal sites, most likely through using the highly abundant transcortical blood vessels as shortcuts [17, 18].

IL-23, which is produced by macrophages and dendritic cells, has been implicated in the pathogenesis of PsA. Its role in enthesitis was elucidated in an elegant study published by Sherlock *et al.* [19]. In their study, the authors identified entheseal resident cells, which are $CD4^{-}CD8^{-}$ T cells that express the IL-23 receptor. In the presence of IL-23, these activated cells promote the development of entheseal inflammation and local bone remodelling in a mouse model through the production of several effector mediators, including IL-22, IL-17 and TNF [20]. Interestingly, in these animals, inflammation can also be detected at other exposed mechanical spots in the body, such as the aortic root as well as the ciliary body in eye sites, which are sometimes involved in patients with SpA [19]. While this study showed that IL-23 can lead to the development of enthesitis, the role of T cells in this process remains to be defined, as enthesitis can also develop in models devoid of T cells [14]. Hence IL-23-responsive cells other than T cells may also play a role in the development of enthesitis. Group 3 innate lymphoid cells (ILC3s) play a central role in barrier tissues such as the skin and gut, which are often involved in PsA and other forms of SpA. These cells also produce IL-17A and were found in interspinous ligament of healthy donors [11]. Furthermore, ILC3 may be important in linking skin and joint disease, as a higher number of circulating ILC3s have been found in patients with active PsA and are linked to a higher burden of joint disease in patients with PsA [21].

A distinct group of inflammatory cytokines is considered to enhance inflammation in the entheses. Notably, mesenchymal cells express receptors for IL-17, TNF-α and IL-22 [22–24]. IL-17 is considered to represent a key amplifier of the inflammatory response in the entheses, as it initiates the synthesis of several other inflammatory mediators such as granulocyte-macrophage colony stimulating factor, PGE2 and IL-8, which enhance the recruitment of, for example, neutrophils to the site of inflammation, which in turn increase the inflammatory cascade through the release of proteases and reactive oxygen species [25, 26]. As several immune cell lineages described to be a major source of IL-17, such as γδ T cells [10, 27] and ILC3 [11, 28], reside in entheseal structures, it is conceivable that IL-17 is locally produced in the entheses and allows site-specific attraction of effector cells of inflammation. While most studies to date have focussed on IL-17A as the main mediator triggering enthesitis within the IL-17 family of cytokines, it may well be that other forms, in particular IL-17F, exert similar actions and augment inflammation as well.

Furthermore, clinical observations suggest that TNF-α represents an important effector cytokine in enthesitis. Apart from that, mechanistic studies with transgenic mice overexpressing TNF-α showed that TNF-α can induce an SpA-like phenotype in mice, which showed features of enthesitis and did depend on TNF receptor 1 in mesenchymal cells [29]. These data suggest that TNF-α, like IL-17, may stimulate local mesenchymal cells to produce inflammatory mediators, which are required for initiating and maintaining enthesitis.

Structural consequences of enthesitis

Next to pain and impaired function, new bone formation is the key feature of chronic enthesitis [30]. Depending on which structures are involved, local bony overgrowth can lead to peripheral entheseophytes (e.g. calcaneal spur) or the formation of syndesmophytes in the spine. New bone formation in the context of enthesitis is thought to be initiated by resident mesenchymal cells, which proliferate and then differentiate into chondroblasts and osteoblasts, leading to periosteal bone apposition [8, 9, 31]. Several factors involved in the process of enthesitis have been shown to mediate bone remodelling in the context of response to stress. Hence PGE2 is a strong inducer for osteoblast differentiation [32], but IL-17 has also been shown to augment mesenchymal responses associated with bone repair [33, 34]. Finally, IL-22, which is a cytokine produced in conjunction with IL-23 activation, has been shown to play a role in new bone formation [24]. Bone responses in the context of enthesitis are specific local processes that are different from overall bone remodelling. In this context, it needs to be mentioned that cytokines like IL-17 and IL-23 also have profound osteoclastogenic properties [35, 36], which explains systemic bone loss in the context of PsA and SpA [37, 38]. As such, they also appear to revisit molecular expression programs that are initiated during the process of fracture repair, in which new bone has to be formed rather rapidly [39]. For instance, robust activation of Wnt and BMPs has been shown to occur during bony spur formation, factors that are essentially required to form new bone during fracture repair [40, 41]. While such repair processes can be considered as the body's response to entheseal inflammation and a potential attempt to stabilize such structures during inflammation, the formation of new bone can also represent a pathology in itself, as it can lead to loss of function of 'flexible' interosseous connections such as joints or intervertebral discs, which are then fixed by bony ankylosis.

Future directions

While some initial interesting concepts about the pathophysiology of enthesitis have been established in recent years, there is still a substantial lack of knowledge about this important disease process. For instance, it is still unclear why entheses are highly prone to inflammation in patients with PsA and in patients with other forms of SpA. As enthesitis often develops in subjects without systemic diseases, additional potential genetically based enhancers must exist to explain the high disease burden of enthesitis in this patient group. Also, it is unclear whether the link between inflammation and structural responses requires a specific molecular pattern of inflammation or is mostly dependent on the degree and duration of enthesitis, independent of its molecular features. Notably, little is known about the molecular and cellular process going on in human enthesitis, as tissue access is limited and therefore most of the knowledge to date stems from either cadaveric material or from animal models of enthesitis. Hence more in-depth molecular studies on this interesting feature of PsA are needed.

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