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REVIEW ARTICLE

The roles of inflammatory mediators and immunocytes in tendinopathy

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Abstract Tendinopathy is a common disease of the musculoskeletal system, particularly in athletes and sports amateurs. In this review, we will present evidence for the critical role of inflammatory mediators and immunocytes in the pathogenesis of tendinopathy and the efficacy of current antiinflammatory therapy and regenerative medicine in the clinic. We hereby propose a hypothesis that in addition to pulling force there may be compressive forces being exerted on the tendon during physical activities, which may initiate the onset of tendinopathy.

The translational potential of this article: Understanding the mechanisms of inflammation and existing antiinflammatory and regenerative therapies is key to the development of therapeutic strategies in tendinopathy.

We performed literature searches on MEDLINE from the inception of this review to February 2018. No language restrictions were imposed. The search terms were as follows: ("Tendinopathy"[Mesh] OR "Tendon Injuries"[Mesh] OR "Tendinitis"[Mesh] OR "Tendon"[Mesh]) AND (Inflammation OR "Inflammatory mediator*" OR Immunocyte*) OR ("anti inflammatory*" OR "regenerative medicine"). Inclusion criteria included articles that were original and reliable, with the main contents being highly relevant to our review. Exclusion criteria included articles

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that were not available online or have not been published. We scanned the abstract of these articles first. This was then followed by a careful screening of the articles which might be suitable for our review. Finally, 84 articles were selected as references. This review article is written in the narrative form.

Q4 A brief introduction to tendon

Tendon is a type of dense connective tissue that connects skeletal muscles to bone. From muscle to bone, tendon can be divided into three parts, including muscle tendon junction, tendon and enthesis. Tendons are rich in collagen fibres, mainly type 1 collagen fibrils. The tendon contains a small number of cells, such as tenocytes. Studies have found the presence of a variety of immunocytes, which play important roles in the pathogenesis of tendinopathy [1]. Tendinopathy is a common disease of the musculoskeletal system, characterised by pain, swelling and limited function. Various factors can cause tendon disease, which can be subdivided into two major categories: extrinsic and intrinsic factors. Amongst the extrinsic factors, overuse is considered one of the most important factors, which is associated with sports activities and physical training injuries [2]. Intrinsic factors including age, gender, anatomical abnormalities, systemic diseases (e.g., hyperlipaemia) and genetic diseases (e.g., Marfan syndrome) should also be considered.

Pathology—degeneration or inflammation

In the 1970s, Puddu et al found that acute inflammatory cells do not play a role in chronic tendinopathy [3]. At the beginning of the 21st century, the theory of degeneration has become the mainstream concept of tendinopathy [4]. Researchers have proposed a continuous process in tendinopathy [5]. Initially, the onset of tendinopathy is caused by many factors, particularly physical overuse [6]. Therefore, in response to the damage caused by overuse, noninflammatory reactions arise in tendon, including tendon thickening and increasing hardness in response to physical stress [6]. If physical overuse persists, this will ultimately lead to tendon self-repair failure, and tendon tissue will become disordered, eventually leading to degenerative tendinopathy [5] (Figure 1). Tendon specimens from symptomatic patients exhibit degenerative changes such as being hypoxic, mucoid, hyaline, myxoid, and showing fatty degeneration [7]. Changes to the paratendon are also very common [8].

Inflammation is a series of responses to harmful stimuli, which is considered as an essential physiological process within the human body [9]. Acute and controlled inflammation exerts a protective effect on tissues, but chronic and unregulated inflammation is harmful [9]. There is much opinion that inflammation has no role in tendinopathy, but considering tendinopathy to be purely a degenerative disease may oversimplify the pathogenesis of tendon disease and we may thus overlook the appropriate therapeutic targets [4]. Recently, some experimental models have found evidence of early inflammatory responses in tendinopathy [10]. Human biopsy studies of tendons with smaller tears found significant infiltration of inflammatory mast cells and macrophages [11]. Furthermore, with the advancement of immunohistochemistry and molecular biology techniques, the concept of degenerative tendon disease has become less convincing [4].

It is assumed that there is a continuous transition from physiological to pathological processes in tendon. Factors such as overuse can cause injury to the tendon, as described previously. Under these circumstances, microdamages to tendon fibres occur, and the body will consequently secrete a number of substances to promote healing, which includes inflammatory factors [2]. In the pathogenesis of tendinopathy, inflammation and degeneration may not be two separate processes, as these usually interact with each other. Degenerative process may be triggered by inflammation, and inflammation will also play some roles in later degenerative processes [9] (Figure 1).

Inflammatory mediators and immunocytes in tendinopathy

Inflammatory mediators

Soluble factors such as cytokines and complements that are involved in inflammatory responses are known as inflammatory mediators. Cytokines are signalling molecules that are produced by different cell types. Many different cellular functions can be controlled by cytokines, including cell proliferation, differentiation and apoptosis [12]. Cytokines possess immunomodulatory properties and are also known to play key roles in cell signalling and communication [12].

Interleukin-1β

Interleukin-1β (IL-1β), which may be produced under various pathological conditions such as infection and injury, is an important mediator in the inflammatory response and is implicated in diverse cellular functions [13]. Previously, IL-1β was thought to be produced exclusively by monocytes and macrophages, but it is now known to be produced by some cells in the connective tissue [12]. IL-1β can induce Q5 human tenocytes to produce inflammatory mediators such as COX2, PGE2 and MMP-1, and these mediators can

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