Musculoskeletal conditions are the most common disorders in the worldwide population, with an estimated prevalence of approximately 20%. Tendinopathies represent the most frequent type of musculoskeletal disorder, with the prevalence in the athletic population estimated to be 40–50%. Such injuries are typically recurrent, with symptoms of pain and functional disability. The most extensively studied tendinopathies involve the Achilles tendon, patellar tendon, and rotator cuff tendons.

Tendon injury processes are not well understood, but two major contributing factors have been identified. One is the relatively avascular nature of tendon tissue, and the other is continuous exposure to tensile stress. Tendon tension can create focal hypoxia-ischemia within the tissue. Repetitive periods of hypoxia-ischemia can stimulate angiogenesis (i.e., the process of forming new blood vessels), which degrades the extracellular matrix of the tendon structure and reduces its mechanical loading capacity. Pain, inflammation, and micro-structural lesions can develop, which are collectively designated as tendinopathy.

The purpose of this report is to review information pertaining to biological factors involved in the pathophysiology of tendon degeneration, thereby facilitating the delivery of effective treatments for patients with tendinopathies.

**Tendon Histology**

The relatively avascular nature of tendon tissue limits its capacity for healing. The tendon is primarily composed of Type I collagen fibers that are aligned with the tensile load generated by the associated muscle fibers. The adult tendon contains very few cells, which include (a) mature tenocytes that are arranged in columns parallel to the orientation of the collagen fibers (the predominant cell type) and (b) undifferentiated fibroblasts.

The function of a tendon is to transmit tensile forces generated by the associated muscle fibers to bone attachments, which produce movement of one or more segments or stabilize a joint. Two tendon types are based on functional characteristics: (a) “traction” tendons that directly transmit muscle force without a change in the line of action and (b) “gliding” tendons that are adjacent to bony prominences that change the line of action of the muscle force. The tendon of
the coracobrachialis muscle is an example of traction tendon, whereas the tendon of the peroneus longus represents a gliding tendon. Gliding tendons normally have fibrocartilage in the region that makes contact with a bony prominence, which is the portion of the tendon that has poorest regeneration potential.

**Hypoxia–Ischemia Processes**

Hypoxia specifically refers to low oxygen saturation of tissue, whereas ischemia specifically refers to inadequate delivery of oxygen and nutrients to cells as a result of diminished blood flow to the tissue. A cellular attempt to minimize tissue damage from hypoxia–ischemia initiates processes that ultimately contribute to changes associated with tendinopathies.3

The tensile load imposed on a tendon may produce hypoxia–ischemia, mainly in gliding zones around bony prominences. The transient hypoxia–ischemia activates a vasodilation response and an increase in local blood flow. If the hypoxic-ischemic state is prolonged, angiogenesis can be triggered. The combination of hypoxia–ischemia and mechanical load can create areas of tissue weakness, loss of cell viability, and eventual disruption of the tendon’s macro-structure (i.e., tendon rupture). Poor tissue perfusion may be the primary cause of tendon injuries.

**HIF–1 Regulation of the Tissue Response to Hypoxia–Ischemia**

Activation of the response to oxygen deficiency within the tendon depends on a transcription factor called hypoxia-inducible factor 1 (HIF-1), which is quickly degraded when a normal oxygen level has been reestablished. HIF-1 has been reported to increase in fibroblasts that are subjected to mechanical stress at a normal level of oxygen saturation. Thus, HIF-1 expression may be induced by both hypoxia–ischemia and mechanical loading.4 HIF-1 modifies the expression of mediators that control processes associated with improvement of tissue perfusion (e.g., vasodilation and angiogenesis), including vascular endothelial growth factor (VEGF), transforming growth factor beta 1 (TGF-β1), and inducible nitric oxide synthase (iNOS).

**Angiogenesis**

Angiogenesis is a crucial component of the normal healing process, but it may also play a role in development of tendinopathy. Alfredson et al.5 proposed hypervascularization as the cause of tendon pathologies, but other researchers6 have demonstrated an elevated level of angiogenesis within damaged tendon areas. New blood vessels develop in the tendon as part of the inflammatory and repair responses to tissue damage, but the exact role of angiogenesis in tendon degeneration has not been clearly established.

The extent to which new blood vessels develop depends on the balance between pro-angiogenic and anti-angiogenic factors. One of the most important anti-angiogenic factors is endostatin, which originates from the proteolytic digestion of Type XVIII collagen. Endostatin inhibits the formation of new vessels, which is largely responsible for the relatively avascular nature of tendon tissue. Mechanical loading can excessively activate this anti-angiogenic factor. The primary pro-angiogenic factor is vascular endothelial growth factor (VEGF), which also increases vascular permeability. VEGF is normally over-expressed in pathologic adult tendon.7 Tendon overloading can produce hypoxia–ischemia, which can activate transcription factor HIF-1, thereby inducing expression of VEGF. The presence of VEGF has been closely linked to tissue hypoxia.8

Angiogenesis involves the development of a tunnel network within the extracellular matrix (ECM) of the tendon tissue, which includes enzymes called matrix metalloproteases (MMPs). MMPs 1, 2, 8, 13, and 14 are responsible for ECM degradation and remodelling, and they can disrupt the structure of collagen fibers. ECM degradation is a normal physiologic process, but it can result in loss of structural integrity when it is excessive. Under normal conditions, this degradation process is balanced with simultaneous synthesis of ECM and collagen fibers. An imbalance between the synthesis and degradation of ECM and collagen could lead to development of a tendinopathy.9 Injection of VEGF has been demonstrated to produce over-expression of tissue MMPs, which weakens the tendon structure and renders it susceptible to overload damage. MMP-3 may also induce apoptosis (i.e., programmed cell death) of endothelial cells. The action of MMPs is influenced by tissue inhibitor matrix metalloproteases (TIMPs), which could be a key factor in promoting optimal tendon healing through their inhibition of MMPs.

Transforming growth factor beta 1 (TGF-β1), which is activated by HIF-1, can regulate the expression of both VEGF and MMPs. TGF-β1 has been related to cell migration within the nervous system and during cardiac development, but its role in the tendon healing is not clear.10 It appears to play a key role in the