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An Emerging Role for Angiogenesis in Tendinopathy

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Viennese philosopher Karl Popper, the father of scientific reasoning, wrote that "science must begin with the criticism of myth". It is with this in mind that Khan et al. have re-examined the histology underlying chronic tendinopathies, concluding that the pathology formerly known as 'tendinitis' is better characterised as 'tendinosis' – a condition characterised by the proliferation of vascular tissue and the disruption of normal tendon architecture.[1] If tendinitis is a myth to be abandoned, after Khan et al., tendinosis provides the basis for new theories regarding the cause of chronic tendon pain.

So, what is tendinosis? It is a degenerative state of tendon tissue, characterised primarily by an increased presence of fibrovascular (reparative) tissue.[2] This tissue is hypercellular, rich in glycosaminoglycan and characterised by thin, disorganised (mostly type III) collagen.[3,4] Commonly, there is phenotypic change within the tendon as well: usually chondroid change and, occasionally, bony change.[5] Inflammatory cells are scarce or absent. Tenocytes display evidence of ongoing proliferation as well as cell death, indicating an abnormal increase in the rate of cellular turnover.[6,7] In summary, tendinosis is the evidence of a 'failed healing response' – the body's unsuccessful attempt to repair the tendon following an accumulation of overuse injuries.

Tendinosis should not be confused with age-related tendon degeneration.[8,9] Age-related degeneration is primarily characterized by a loss of tenocyte numbers, not by the expansion of vascularity. Age-related degeneration is typically asymptomatic and occurs in the absence of extensive neovascularisiation. It is not yet known which features of tendinosis lead to chronic tendon pain. However, the increased presence of vessels – and their accompanying nerves – is the leading candidate.[10]

A promising new therapy that specifically targets nerves and vessels as they enter the tendon is the use of sclerosing injections. This approach has been successfully used to treat both Achilles and patellar tendinopathies.[11,12] The same rationale underlies the use of minimally invasive surgical procedures that disrupt the neurovascular structures as they enter the tendon. In both approaches, treatments are performed with the aid of colour Doppler

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ultrasound to visualise the vessels before and immediately after treatment. The disruption of flow within the tendon is associated with successful treatment.[11,12]

These findings raise many interesting questions and may allow us to understand how chronic tendon pain develops in the first place. Do the increased blood vessels on colour Doppler ultrasound correspond to the number of vessels in the tissue? If so, could this process also lead to an increased number of nerves in the tendon and, therefore, a state of pain and irritability?

Collaborative research recently undertaken in Sweden, Canada and Norway has examined the vascular and neural tissue that is excessively present in the patellar and Achilles tendons of patients with long-standing tendinopathy.[6,13–23] In addition to confirming prior reports regarding the prevalence of tendinosis and the absence of tendinitis, the studies generated some new insights about the nerves and vessels in the painful area that suggest there may be an association between pain and neurovascular changes resulting from overuse.

First, the vessels that were present in tendinopathic tissue were accompanied by both sensory and autonomic nerve fibres. Nerves stained positively for substance P and calcitonin-gene-related peptide (CGRP) (sensory nerves), acetylcholine esterase (parasympathetic) and tyrosine hydroxylase (sympathetic).[13–17] This provides the anatomical basis to understand that pain may originate from the injured tissue, vessels may be used as a visual clue to the location of the nerves and interfering with the nerves/vessels may influence both the transmission of pain and the local regulation of blood flow.

A second insight was that the vessels displayed evidence of active proliferation in tendinopathy samples. Two proliferation markers – Ki67 and proliferating cell nuclear antigen (PCNA) –labeled tendinopathy vessels to a greater degree than normal vessels.[23,24] This suggested the presence of an ongoing angiogenesis. An important angiogenic peptide, vascular endothelial growth factor (VEGF), was also increased.[22] Although the findings are still preliminary, it appears that VEGF is expressed specifically in the endothelial cells (rather than in tenocytes or other cell types), and only in association with tendinosis.[22] Perhaps not surprisingly, the density of vessels was also found to be increased in tendinosis tissue.[23] This shows us that some condition is present in tendinosis that leads to the proliferation of vessels, and VEGF appears to play a role in the process.

VEGF is the body’s main cytokine used to respond to hypoxia, via upregulation of the oxygen-sensitive transcriptional factor hypoxia inducible factor-1 alpha.[25] VEGF is upregulated in a variety of pathologies characterised by angiogenesis, such as diabetic neuropathy, invasive tumours and scar tissue.[26] In normal tissue healing, hypoxia resulting from disrupted blood supply and increased tissue metabolism leads to local VEGF expression and angiogenesis. As the local blood supply expands and healing resolves, VEGF expression declines and the vessels withdraw.[27] Could it be that there is some condition present in tendons that leads to the persistence of VEGF and vessels in tendons? Nerves respond to many of the same growth factors, including VEGF, as vessels, which may explain why the two travel together in tendinopathic tendons. Perhaps ongoing hypoxia or the

imposition of ongoing mechanical loading influences the healing process in a way that leads to the pathological persistence of vessels and nerves in the tissue.

The data at present do not let us definitively propose a model whereby tendinosis and tendon pain develop, in part due to the difficulty of modeling tendon overuse pathology in the laboratory setting. It appears that the early stages of tendon overuse are characterised by an adaptive response: tenocytes experience the stress in the collagen matrix and attempt to proliferate and reinforce the tendon by increasing production of insulin-like growth factor 1 (IGF-I) and extracellular matrix.[27] If this mechanical loading continues with inadequate rest bouts, injury may result. Following injury, an angiogenic response develops, leading to tendinosis, as described above.

Another layer of complexity is suggested by the fact that tenocytes themselves both produce and respond to neural substances that could influence both pain and angiogenesis processes. These substances include glutamate, acetylcholine, noradrenaline, adrenaline and substance P;[16,17] therefore, tenocytes may be driving some aspects of the pathology via a direct influence on tendon nerves and vessels. Importantly, it must not be forgotten that, as in any connective tissue, mast cells are present in tendon. They are increased in tendinosis tissue proportionally to the increase in vessel density.[28] They are usually present in a perivascular distribution, ideally situated to influence physiological blood flow, angiogenesis or neurogenic inflammation by releasing substance P.[28] Thus, there is sufficient evidence to warrant investigations of mast-cell stabilisers or inhibitors as a treatment for tendinopathy.

A further implication of the angiogenesis model of tendinosis is the use of imaging technologies to predict the development of symptoms in at-risk groups. Alfredson reported that increased prominence of vessels on colour Doppler ultrasound usually occurs in areas of change detectable on greyscale ultrasound (areas of hypoechogenicity or collagen discontinuity).[10] Is there a sequence of changes that can be observed by imaging and that corresponds to vascular remodeling? Unfortunately, colour Doppler is not without problems (e.g. user dependency, amount of blood flow and state of dilatation of vessels, etc.), and the current consensus is that this imaging modality is not accurate enough to make clinical predictions. The application of more specific angiogenesis imaging assays could be able to detect early tissue pathology and thus improve our ability to prevent this pathology in at-risk populations, or to monitor response to treatment.

Despite the gaps in our understanding of how tendinosis develops, the current state of knowledge does provide some new avenues for nerve- or vessel-targeted treatments and prevention trategies. Given the recent re-examination of the tendinitis myth, the opportunity now exists for more targeted pharmacological approaches that may lead to more effective treatments.

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