Angiogenesis in spondyloarthritis: target for new diagnostic approaches

"A dysregulation in angiogenesis is well recognized as one of the critical mechanisms involved in the progression of inflammatory arthritis."

KEYWORDS: angiogenesis ■ psoriatic arthritis ■ spondyloarthritis ■ VEGF

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Dysregulation in angiogenesis is well recognized as one of the critical mechanisms involved in the progression of inflammatory arthritis. Ultrasound (US) and power Doppler ultrasound (PDUS) have been proposed as useful techniques to clearly demonstrate inflammation and blood flow in spondyloarthritis (SpA). Given the efficacy of PDUS in visualizing vascularization, and the relevance of proangiogenic mediators in the development of neoangiogenesis, combining both tools could improve the monitoring of clinical activity and the efficacy of therapy.

Angiogenesis

Angiogenesis is the growth of new blood vessels from pre-existing ones. This is the predominant mechanism of blood vessel formation in the later stages of embryonic development and, in postnatal life, in wound repair and cyclically in the female reproductive system. Under physiologic conditions, angiogenesis depends on the balance of positive and negative angiogenic mediators within the vascular microenvironment and requires the functional activities of a number of molecules, including angiogenic factors, extracellular matrix proteins, adhesion receptors and proteolytic enzymes [1]. Angiogenesis is also associated with pathologic conditions in direct response to tissue demands, such as chronic inflammation, fibrosis and tumor growth [2].

Numerous inducers of angiogenesis have been identified, including vascular permeability factor/VEGF, members of the FGF family, angiogenin, TGF-α and TGF-β, PDGF, TNF-α, HGF, GM-CSF, interleukins, chemokines and angiopoietin (Ang)-1 and -2. Among them, VEGF is the most potent direct-acting regulator of angiogenesis and inducer of vasodilatation. It is often overexpressed in chronic inflammation, fibrosis and cancer. VEGF induces proliferation, migration and tube formation of endothelial cells, and promotes the secretion of interstitial collagenases and expression of chemokines, as well as leukocyte adhesion molecules [3]. VEGF acts principally on endothelial cells through its functional receptor VEGFR-2, although it can influence other cell types, including hematopoietic stem cells, monocytes, osteoblasts and neurons. The proangiogenic activity of VEGF, as well of other promoters of neovascularization, is tightly regulated by endogenous inhibitors, including endostatin, thrombospondin-1, IFN-α, angiostatin and TIMPs [4]. Some of them, such as endostatin, can downregulate the migration and proliferation of microvascular endothelial cells in the tumor bed and in chronic inflammation, helping in the suppression of pathological angiogenesis [5].

Angiogenesis in SpA

There is considerable evidence to suggest that angiogenesis and chronic inflammation are codependent [6]. In chronic inflammatory diseases, such as rheumatoid arthritis (RA), SpA and some systemic autoimmune diseases, the proliferating synovial tissue contains an abundance of inflammatory cells and angiogenic blood vessels. When the environment in the joint becomes hypoxic or inflammatory, many resident cells, such as fibroblasts, synoviocytes, mast cells and/or infiltrating cells, such as monocytes-macrophages, neutrophils and lymphocytes, synthesize and secrete VEGF, promoting *in situ* neovascularization. This seems to take place in the early stages of inflammatory processes, and to actively contribute to the progressive structural changes [6]. A dysregulation in angiogenesis is well recognized as one of the critical mechanisms involved in the progression of inflammatory arthritis [7], leading to synovial hypertrophy, cartilage damage and erosion. Increased levels of proangiogenic factors such as VEGF, FGF-1,

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FGF-2, Ang-1, Ang-2 and PDGF, HGF have been widely described in RA since 1980 [8]. Among them, VEGF seems to be the main proangiogenic mediator overexpressed in RA synovial fluids and tissue [9,10] and seems to play a prominent role in regulating angiogenesis in this disease [8]. Significant abnormalities of vascular morphology and upregulation of angiogenic growth factors have been recently described in SpA [11], particularly in psoriatic arthritis (PsA) [3,12]. Increased levels of VEGF have been detected in the synovium and in the serum of patients with PsA and this correlates with disease activity and inflammatory parameters [11]. Differential expression of pro-angiogenic mediators such as Ang-2 and VEGF in the synovium of patients with PsA, relative to RA parallels distinct synovial vascular morphology. Specifically, Fearon *et al.* have shown that blood vessels in PsA appear highly tortuous with respect to those in RA, which were predominantly straight and branching [13]. It has been hypothesized that these morphological differences might be due to differences in the levels of proangiogenic mediators [13] and expression of MMP-9 [12] in the synovium.

Role of ultrasound technique for studying angiogenesis in SpA

Since the demonstration that high-frequency linear probes used in grayscale ultrasonography can visualize synovial membrane thickening, joint effusions and bone erosions [14], US has been used more widely by rheumatologists; at the same time, the application of Doppler techniques (color, power and, recently, spectral Doppler) have determined a new era in the definition of disease activity and remission. Several studies have described US features of pathological synovial vascularization in SpA, revealing the high frequency of clinically asymptomatic findings and the added value of PDUS for the diagnosis of SpA. Recent evidence suggests that increased PDUS signals might be indirect markers of synovial vascularity in SpA as was previously demonstrated in RA [15]. Taking into account that US and PDUS are able to clearly demonstrate inflammation and blood flow, these approaches have been proposed to be more sensitive than clinical examination and synovial histopathology in detecting active joint inflammation (particularly, relating to enthesitis), and in the evaluation of response to treatment [16]. When the data of US signals were related to the levels of proangiogenic mediators in the synovial fluids of SpA patients, Ang-1 was found to be positively correlated with effusion, cumulative grayscale and cumulative activity, and FGF-2 to all US findings [17]. This suggests that PDUS is a more sophisticated diagnostic tool for assessing synovial vascularization and may be considered as a reference imaging modality in the assessment of synovitis.

Conclusion

Angiogenesis appears to play an important role in the development and progression of SpA. Given the efficacy of PDUS in visualizing vascularization, and the relevance of proangiogenic mediators in the development of neoangiogenesis, combining both tools could improve the monitoring of clinical activity and the efficacy of therapy.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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