Angiogenesis markers in rheumatoid arthritis

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Angiogenesis markers consist chiefly of proangiogenic cytokines, most notably VEGF and the angiopoietins, and angiostatic factors, such as angiostatin and thrombospondin. Markers for disease activity and outcomes in rheumatoid arthritis (RA) are crucial for tailoring the treatment to the needs of each individual. Serum angiogenesis markers are associated with disease activity and severity in RA, although they are not specific to the disease. Doppler ultrasonography of the synovial vessels is highly sensitive, allowing early detection of the active disease. In the future, the development of treatments that target angiogenesis, with tailoring based on angiogenesis markers, can be expected to improve the management of RA.

Keywords: angiogenesis, biologics, experimental models, inflammation, monoclonal antibodies, rheumatoid arthritis, ultrasonography, vaccination

future medicine part of fsg

Angiogenesis, or the development of new blood vessels from pre-existing vessels, is not only crucial to embryogenesis and wound healing, but also contributes to the pathogenesis of many diseases, including malignancies, proliferative retinopathy and chronic inflammatory conditions. The sequence of events that leads to new vessel formation starts with endothelial cell activation by an angiogenic stimulus, which leads to breakdown of the basement membrane and extracellular matrix; then, the endothelial cells migrate and divide, forming new vessels, whose maturation with reconstruction of the basement membrane constitutes the last step in the sequence [1].

Antiangiogenic therapy: lessons from cancer

Angiogenesis occurs when proangiogenic and antiangiogenic factors fall out of balance [2]. VEGF and the members of the angiopoietin family are the main proangiogenic factors. Several VEGF isoforms, produced by alternative splicing, exist. The effects of VEGF include the proliferation and migration of endothelial cells and an increase in blood vessel permeability. VEGF binds to two tyrosine kinase receptors, VEGFR-1 and VEGFR-2, which are chiefly expressed by endothelial cells [3]. Angiopoietins and their receptor, Tie-2, were identified recently [4]. Angiopoietin-1 acts synergistically with VEGF to promote maturation and stabilization of newly formed vessels [5]. Angiopoietin-2 is generally believed to be a natural angiopoietin-1 antagonist that sensitizes endothelial cells to the effects of VEGF [6].

Since the 1970s, when Jonah Folkman established the dependency of malignancies on angiogenesis, an increasingly detailed picture of the factors involved in tumor growth and metastasis development has emerged. Angiogenesis, and more specifically VEGF, is now a key target for new treatment strategies [7,8]. Bevacizumab (Avastin®, Genentech, Inc., CA, USA), a monoclonal antibody against VEGF, was proven to be effective in combination with standard chemotherapy in the treatment of metastatic colon cancer. Subsequently, efficacy has been established in several other cancer types. Other means of inhibiting VEGF and angiogenesis have been investigated more recently. Examples include vatalanib, sunitinib malate (Sutent®, Pharmacia & Upjohn [part of Pfizer, NY, USA]), and sorafenib (Nexavar®, Bayer AG, Leverkusen, Germany), which are tyrosine kinase receptor inhibitors. Vatalanib is undergoing development, whereas sunitinib malate and sorafenib have been approved for the treatment of advanced renal carcinoma. A VEGF kinoid vaccine that directly inhibits VEGF was effective in several animal tumor models [9]. Antiangiogenic agents prolong the survival of cancer patients, although without cure and at the expense of side effects. Placental growth factor (PlGF) binds VEGFR-1 and displaces VEGF from it. As with VEGFR-1, PlGF has a restricted angiogenic role in pathological conditions [10]. PlGF inhibitors might reduce pathological angiogenesis but, unlike VEGF inhibitors, without affecting healthy blood vessels, and thus provide an attractive drug with a better safety profile [11]. Fischer *et al.* offer compelling evidence that a monoclonal antibody against PlGF inhibits growth and metastasis in different tumor models in monotherapy and amplifies the antitumoral effect of chemotherapy without any effect on healthy blood vessels [11].

Inflammatory mediators have a significant effect on angiogenesis. The reverse is also true, as proangiogenic factors, such as VEGF or angiopoietins, upregulate several proinflammatory pathways, leading to leukocyte recruitment, infiltration and secretion of inflammatory mediators [12]. VEGF production can push T cells towards a T helper 1 phenotype by increasing the production of IFN-γ and decreasing the production of IL-10, showing the interdependence of inflammation and angiogenesis [13].

Angiogenic factors in rheumatoid arthritis

Rheumatoid arthritis (RA) is not only one of the most common chronic inflammatory joint diseases, but is also one of the most severe. Early initiation of effective treatment, including drugs that prevent joint destruction, is clearly beneficial. However, given the considerable heterogeneity of patients with early RA, disease activity markers and outcome predictors are needed to select the treatment strategy that will provide the best risk:benefit ratio in each individual patient. The advent of biologics, whose efficacy comes at the price of side effects and high financial cost, together with continuing uncertainty regarding the best order for switching between treatment targets, further supports the need for markers that reflect disease activity and predict outcomes. To identify markers that are useful in the individual patient, candidate markers must be investigated in cohorts of patients with RA or early inflammatory polyarthritis that mirror the diversity of patients seen in everyday practice. Presence of rheumatoid factor or antibodies to cyclic citrullinated peptides has consistently been found to indicate severe disease, whereas results for the shared epitope have been somewhat conflicting. The factors most commonly associated with disease activity are laboratory evidence of inflammation (elevations in the erythrocyte sedimentation rate and C-reactive protein level) and the Disease Activity Score, which is a composite index based on clinical and laboratory data. Finally, although treatment efficacy has improved greatly in recent years, some patients fail multiple treatments, either from the outset or after experiencing escape phenomenon. To date, no factors are available for predicting whether an individual patient will respond to a specific medication.

Cell proliferation and invasiveness are features shared by the rheumatoid pannus and by malignant tumors. In common with cancer, RA is characterized by uncontrolled cell division, an inflammatory environment and new vessel formation. Histology shows an inflammatory infiltrate within the synovial membrane and tendons, as well as synovial-membrane hyperplasia. Destruction of the cartilage and subchondral bone leads to loss of function. Blood vessel growth is a key factor in progression to chronic disease. The expanded vascular network supplies the large amounts of nutrients and oxygen required by the synovial mass and also provides inflammatory cells and proinflammatory cytokines with easy access to the synovium. In addition to the increase in blood vessels, there is a change in blood vessel distribution within the synovium, which creates hypoxic foci. Hypoxia promoted by synovial proliferation, together with the release of proinflammatory factors, acts as a powerful proangiogenic stimulus. Hypoxia-inducible factor (HIF) is highly inducible by hypoxia and inflammatory mediators, promoting angiogenesis and contributing to the pathogenesis of RA [14]. HIF induces the expression of proangiogenic factors and stabilizes *VEGF* gene transcription [15–17] . Finally, angiogenesis is not only a mandatory step in the progression to chronic disease, but is also an extremely early event, as demonstrated by our laboratory in mice with collagen-induced arthritis [18]. This study confirmed an earlier report that angiogenesis antedated the development of inflammatory infiltrates in the rheumatoid synovium [19].

Numerous proangiogenic factors are expressed by the rheumatoid synovium [20,21]. Some of these factors are not specific to angiogenesis, such as FGF, PDGF, HGF and EGF. However, inflammatory joint diseases, including RA, are characterized by upregulated expression of angiogenesis factors, most notably VEGF, angiopoietins -1 and -2, and the angiopoietin receptor, tie-2 [22–27]. In addition, overexpression of adhesion molecules occurs in the rheumatoid synovium [28] and resolves with treatment, most notably TNF-α antagonist therapy [29].

VEGF as a major marker in rheumatoid arthritis

Studies of animal models have provided additional evidence that angiogenesis plays a crucial role in RA [30,31]. In mice with collagen-induced arthritis, manifestations of inflammation develop in close correlation with expansion of the synovial vasculature [18]. Furthermore, the administration of proangiogenic cytokines such as VEGF or FGF [32] increases the severity of experimental arthritis. Many studies in various models investigated antiangiogenic interventions, such as specific inhibition of proangiogenic mediators [33–35] or

administration of cytokines that normally inhibit angiogenesis, for instance angiostatin [36] and thrombospondin [37].

Serum angiogenesis markers, including VEGF and angiopoietin-1, are elevated in patients with RA [38–42]. Although these increases are not specific to RA, they are larger in patients with inflammatory joint disease compared with patients with osteoarthritis or healthy individuals. Angiogenesis markers increase very early in the course of the disease and their levels are usually higher in patients with early RA than in those with long-standing RA. This difference over time may be ascribed to the correlation of VEGF with disease activity and to the influence of treatments. Disease severity correlates closely with serum VEGF levels. Vascular changes occur at the earliest stages of the disease course; thus, Hirohata and Sakakibara reported that the growth of synovial vessels antedated the development of clinical joint inflammation [19]. In addition to being associated with the degree of inflammation, angiogenesis markers predict disease severity and bone destruction. In a recent study [39], we showed that serum VEGF levels in 314 patients with early polyarthritis were associated with radiological progression 1 year later. In keeping with earlier studies, angiogenesis marker levels showed no significant differences across diagnostic groups. Thus, elevation of angiogenesis markers may indicate progressive inflammatory joint disease rather than the presence of a specific diagnosis. In a study of 64 patients with established RA, serum levels of VEGF and endothelin-1 correlated with indices of inflammation (DAS28, ESR and CRP); interestingly, levels of both markers were associated with systemic involvement [42].

Conventional DMARDs, as well as NSAIDs and glucocorticoids, have been shown to exert antiangiogenic effects *in vivo* and *in vitro* [43]. More recently, a very early drop in serum VEGF levels was reported after TNF-α antagonist initiation in patients with RA [44,45]. This decrease was associated with the treatment response. Similar findings were obtained in patients with other inflammatory joint diseases, most notably psoriatic arthritis [46]. Immunohistochemical studies show that infliximab infusion is followed by both a drop in serum VEGF levels and inhibition of synovial angiogenesis, leading to a decrease in synovial vessel density. Serum endostatin levels, although not elevated at baseline in patients with RA, increased after infliximab administration [43,47,48]. The decrease in angiogenesis markers in patients who respond well to treatment highlights the key role of angiogenesis in perpetuation of the disease. Overall, these data confirm the usefulness of angiogenesis markers, most notably VEGF, for assessing disease activity and severity in patients with inflammatory joint disease [49,50].

VEGF polymorphisms in patients with RA were evaluated in several studies, with conflicting results. In a study of 140 RA patients and 149 controls conducted in the Republic of Korea, several haplotypes were associated with RA [51]. These findings were not replicated in a study conducted in Spain [52]. Finally, the 936 T allele may protect against psoriatic arthritis [53].

Although VEGF seems to be a good target for RA, some of the side effects observed with anti-VEGF treatments have led to suggestion that other angiogenic factors might be better candidates. Among them, PlGF has a restricted angiogenic activity in pathological conditions [10]. Monoclonal antibody against PlGF inhibited tumoral angiogenesis without the side effects of VEGF inhibitors.

Angiogenesis & cardiovascular diseases in rheumatoid arthritis

Rheumatoid arthritis is associated with excess mortality that is ascribable, in part, to an increase in the risk of cardiovascular disease. The severity of inflammation is not only associated with the degree of subsequent joint damage, but also with an increased cardiovascular risk. It has been proposed that, in RA, increased levels of circulating inflammatory mediators may cause activation and damage of endothelial cells, contributing to endothelial dysfunction. Endothelial dysfunction is central to the development of early-stage atheroma lesions. Abnormalities in arterial endothelial function are strongly associated with atheroma progression. RA is associated not only with changes in the number and distribution of blood vessels, but also with alterations in endothelial cell morphology and function [28]. Endothelial dysfunction has been documented in early-stage RA, even in young patients who had no cardiovascular risk factors [54]. Endothelial function improves with treatment, most notably with TNF-α antagonists [55–57]. Endothelial progenitor cells (EPCs) contribute to new vessel formation in adults and their reduction has been shown to be predictive of cardiovascular outcomes; they are also a biological marker for vascular function and increased cardiovascular risk. In RA, EPC levels are decreased in the peripheral blood of patients with active RA. EPC levels are in the normal range in patients with inactive disease or in patients receiving TNF blockers or glucocorticoid therapy [58].

Systemic sclerosis is another disease in which angiogenesis has been extensively studied. Whereas RA is characterized by blood vessel expansion, in systemic sclerosis blood vessel density is decreased. The loss of blood vessels is evident in the skin, where it can be easily documented by capillaroscopy. Ischemic digital ulcers may develop. Despite the vessel loss, proangiogenic factors are overexpressed, suggesting a role for other pathogenic factors [2].

Imaging vascularization

Synovial vessels can be assessed *in vivo* to investigate angiogenesis in patients with polyarthritis. The introduction of high-frequency ultrasound probes used in conjunction with power Doppler has enabled *in vivo* studies of the synovial blood supply in patients with RA. Ultrasonography is far more sensitive than physical examination for detecting rheumatoid synovitis [59–61]. Decreases in synovial-membrane thickness and power Doppler signals are extremely sensitive means of evaluating treatment responses, as shown after local glucocorticoid injection or systemic administration of methotrexate or TNF-α antagonists [62–64]. A single study looked for associations between serum VEGF levels and power Doppler scores at the wrist [45]; none were found, probably because serum VEGF seems to reflect systemic inflammation and may therefore fail to correlate with inflammation at one specific site. Microbubble contrast agents will probably improve the sensitivity of power Doppler for detecting synovial inflammation. However, the improvement in sensitivity may well be counterbalanced by a decrease in specificity; in addition, microbubble contrast-agent use increases the duration and cost of ultrasonography and transforms this imaging technique into an invasive procedure.

Conclusion

Angiogenesis plays a central role in RA. Serum angiogenesis-marker levels are associated with RA severity and progression. Although their lack of specificity makes them unsuitable for diagnostic purposes, their close correlation with disease severity is consistent with a role in patient follow-up. Ultrasonography with power Doppler, which directly visualizes the synovial-membrane vessels, provides very early information on changes in synovitis activity during the course of inflammatory joint disease. This technique has similar sensitivity to MRI but is both far easier to use and considerably less expensive.

Finally, the development of effective antiangiogenic medications, most notably in oncology, can be expected to impact future research on treatments for chronic inflammatory diseases. Such medications may not only control the synovial inflammation at a very early stage, but also correct the endothelial dysfunction seen in patients with chronic inflammatory diseases. In this context, it is important to minimize the adverse effects of blocking VEGF signaling, especially thrombosis and hypertension. New targets, such as PlGF, may constitute an alternative. Furthermore, various angiogenesis markers may enable the identification of a subset of patients with highly aggressive disease who may be most likely to benefit from medications, most notably biologics and, in the near future, antiangiogenic agents.

Future perspective

The identification of markers for disease activity and outcomes in patients with RA is difficult, yet crucial. Angiogenesis markers, most notably VEGF, reflect the degree of inflammation in patients with RA and other inflammatory joint diseases. Furthermore, they predict disease outcomes. Use of angiogenesis markers in everyday practice should help to identify the subset of patients who require aggressive treatment. Vascular imaging, most notably using power Doppler ultrasonography, not only helps to monitor patients but also, and more importantly, provides an early assessment of the response to a specific treatment. In the near future, the development and validation of standard criteria will enable the widespread use of this method in individual patients seen in everyday clinical practice.

Medications that specifically target angiogenesis have produced promising results in other fields. Their use in the treatment of RA will probably be considered in the near future, although adjustments for the specific features of RA will be needed. Angiogenesis markers can be expected to help identify those patients most likely to benefit from antiangiogenesis treatment strategies.

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Executive summary

- Angiogenesis results from imbalance between proangiogenic and angiostatic factors. In rheumatoid arthritis (RA), angiogenesis is a crucial step in the development of synovitis.
- Serum angiogenic markers, most notably VEGF and its receptor, are associated with RA activity and with disease outcomes, both in terms of severity and bone destruction. They may prove useful for evaluating the individual patient and for assessing treatment responses.
- Power Doppler ultrasonography is effective in visualizing the synovial vasculature. Although no quantitative criteria have been validated, this imaging method is highly sensitive for monitoring patients and assessing treatment responses.
- Endothelial dysfunction is the first step in the sequence of events that leads to atheroma. Morphological and functional alterations in endothelial cells explain the increased cardiovascular risk seen in patients with RA. Interestingly, disease-modifying drugs used to treat RA, most notably TNF-α antagonists, restore normal endothelial function and decrease the risk of cardiovascular disease.

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