

EDITORIAL

Linking Angiogenesis to Bone Destruction in Arthritis

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Among disease mechanisms contributing to the pathogenesis of rheumatoid arthritis (RA), angiogenesis has increasingly gained interest as a focus of investigation into new therapy (1–3). This interest reflects the recognition that new blood vessel formation constitutes a very early event of synovial hyperplasia that, in the course of RA, promotes the destruction of cartilage and bone (4). In RA, the role of angiogenesis is likely complex and varied. In addition to supplying nutrients for hyperplastic synovium, angiogenesis promotes persistence of synovial inflammation through the influx of inflammatory cells to create the disease-specific micro-environment in RA. More than just lining blood conduits, endothelial cells, when activated in the RA synovium, may themselves produce inflammatory mediators to intensify synovitis.

Although angiogenesis occurs physiologically in adults in very distinct situations such as the reproductive cycle, it can be induced dramatically in disease. Settings involving pathologic angiogenesis include malignancy, diabetic retinopathy, and chronic inflammatory conditions such as psoriasis and RA. As a consequence, angiogenesis has been considered an essential step in the development of chronic arthritis. It has been further suggested that inhibition of angiogenic factors could reduce the progression of synovial hyperplasia and joint destruction in RA (5).

Angiogenesis is a multistep process that is under the delicate control of a variety of agonistic and antagonistic effector molecules. Among the proangiogenic molecules, vascular endothelial growth factor (VEGF) and angiopoietin 1 (Ang-1) have been identified as key players in the development of new blood vessels. VEGF regulates multiple steps of angiogenesis including the

initial vasodilatation, endothelial cell permeability, remodeling of the perivascular matrix by the induction of matrix metalloproteinase 1 and plasminogen activators, and the induction of proliferation and migration of endothelial cells (3).

The importance of VEGF for vessel development is highlighted by studies in knockout mice showing that disruption of a single VEGF allele leads to early embryonic death due to severe vascular defects. Consequently, VEGF has been the most frequently targeted molecule in therapeutic approaches designed to inhibit angiogenesis. For instance, treatment of colorectal cancer with the humanized monoclonal anti-VEGF antibody bevacizumab, in addition to standard chemotherapy, increases response rates and patient survival (6). Bevacizumab is now approved by the US Food and Drug Administration for the treatment of metastatic colorectal cancer, but to date, clinical trials with anti-VEGF in RA are not yet in progress.

Another proangiogenic factor, Ang-1, exhibits functions distinct from those of VEGF and, therefore, could represent an additional target for therapeutic antiangiogenic approaches. Ang-1 is the ligand of the tyrosine kinase receptor Tie2 and is preferentially secreted by periendothelial cells such as vascular smooth muscle cells. In contrast to VEGF, Ang-1 by itself is not capable of inducing proliferation or tube formation in endothelial cells in vitro. Mice lacking Ang-1 or Tie2, however, experience severe defects in the development of primitive vessels, indicating that Tie2 signaling is essential for maturation and stabilization of the vasculature as well as for normal remodeling (3).

In this context, an article by Chen et al in this issue of *Arthritis & Rheumatism* sheds new light on the potential of Tie2 signaling in mediating angiogenesis and bone destruction in inflammatory arthritis (7). These investigators determined the effects of gene transfer of a soluble Tie2 receptor on collagen-induced arthritis (CIA) in mice. In an important extension of their studies on the role of Tie2 in mediating tumor necrosis factor α (TNF α)-induced angiogenesis in ar-

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Submitted for publication December 21, 2004; accepted in revised form January 25, 2005.

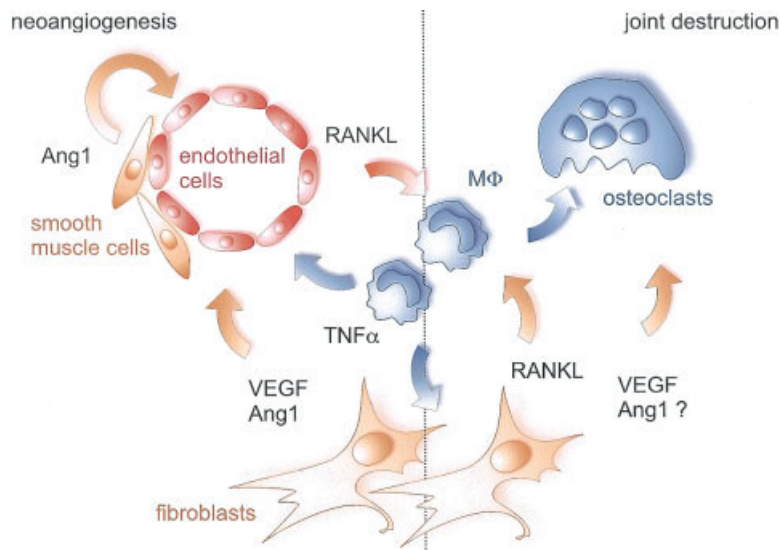


Figure 1. Cellular interactions linking neoangiogenesis to bone destruction in rheumatoid arthritis. Ang1 = angiopoietin 1; MΦ = macrophage; TNF α = tumor necrosis factor α ; VEGF = vascular endothelial growth factor.

thritis (8), they demonstrated a reduced onset of arthritis as well as less severe disease following the systemic administration of an adenoviral construct expressing the soluble Tie2 receptor. Interestingly, treatment with soluble Tie2 receptor also inhibited CIA progression after disease onset, which is consistent with data indicating a major role of Ang-1/Tie2 in vessel maturation and remodeling.

Taken together, these data confirm and amplify previous descriptions of Ang-1 and Tie2 expression in the rheumatoid synovium (9–11) as well as animal studies showing that inhibition of angiogenesis may reduce the severity of arthritis and synovial hyperplasia (12–16). Of note, in these studies, it has been observed that inhibition of angiogenesis not only reduces the inflammatory response but also affects the destruction of articular cartilage and bone (13,15,16). These findings are of interest, because angiogenic factors such as VEGF may contribute to joint destruction directly by stimulating osteoclasts and osteoclast precursors, as well as indirectly by supporting synovial hyperplasia (see Figure 1).

Following the observations that osteoclasts express both VEGF receptors and that VEGF stimulates osteoclastic bone resorption *in vitro* (17), Matsumoto et al showed that in Raw 264.7 osteoclastlike cells, VEGF treatment stimulated chemotaxis, cell proliferation, and association of the VEGF receptor Flt-1 with focal adhesion kinase (18). In addition, it has been shown that

angiostatin, an angiostatic factor that reduces synovial hyperplasia and cartilage destruction in CIA (19), can inhibit the formation of bone metastases and bone resorption through direct antiosteoclast activity (20). In light of these data, reduction of bone erosions is a notable feature of the findings by Chen and colleagues. As demonstrated in high-resolution paw radiographs, gene transfer of the soluble Tie2 receptor protected against bone damage, and inhibition of bone erosions was observed even in paws with similar degrees of clinical signs. This finding may indicate a specific effect on osteoclast function. Interestingly, Chen et al did not observe significant differences in the number of osteoclasts between animals that were treated with soluble Tie2 receptor and those that were untreated; at the same time, significantly lower levels of RANKL in the Tie2 receptor-treated group were observed.

Based on their previous data (8), the authors suggest that TNF α regulates the production of RANKL in endothelial cells via Tie2. Although there is evidence that endothelial cells express RANKL in response to TNF α (21) and that angiogenic factors such as VEGF contribute to the production of RANKL in endothelium (22), these links will need further investigation. In this context, it is interesting that VEGF not only up-regulates RANKL, but that both factors induce osteoclast chemotaxis through an ERK-1/2 MAP kinase-dependent mechanism (23). It will be important, therefore, to identify the source of increased RANKL in

the soluble Tie2 receptor-treated animals and to determine the effects of Ang-1 on osteoclastlike cells. The definition of these issues may increase understanding of the role of angiogenesis in RA and determine whether the blood vessel can enter the list of new targets of therapy in RA.

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