The role of angiogenesis in rheumatoid arthritis: recent developments

Alisa Erika Koch

Northwestern
University Medical
School and Veteran's
Administration
Chicago Healthcare
System, Lakeside
Division, Ward
Building 3-315, 303 E
Chicago Avenue,
Chicago, IL 60611,
USA

Correspondence to:
Dr Koch
(ac-koch@northwestern.edu)

Rheumatoid arthritis (RA) is characterised by synovial tissue leucocyte ingress and angiogenesis, or new blood vessel growth.¹⁻⁸ The disease is thought to occur as an immunological response to an as yet unidentified antigen. Even in early RA, some of the earliest histological observations are blood vessels.⁹ A mononuclear infiltrate characterises the synovial tissue along with a luxuriant vasculature. Angiogenesis is integral to formation of the inflammatory pannus and without angiogenesis, leucocyte ingress could not occur.

Angiogenesis is regulated by a complex set of inducers and inhibitors. In this paper we will present representative examples of both angiogenesis inducers and inhibitors that may regulate RA neovascularisation (fig 1). In inflammatory states like RA, angiogenesis inducers outweigh angiogenesis inhibitors.

Angiogenesis inducers

ENDOGLIN AS AN ANGIOGENIC MEDIATOR

There are a number of angiogenesis inducers that may play a part in RA. Among these are endoglin, an endothelial glycoprotein, which

contains an arginine-glycine-aspartic acid (RGD) motif, and also acts as an adhesion molecule.^{10 11} Endoglin is a receptor for transforming growth factor β . Mice lacking the endoglin gene die from defective vascular development.¹² We have shown that endoglin is upregulated in RA synovial endothelial cells compared with normal synovial tissue endothelial cells.¹³

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

An angiogenic mediator that has attracted much attention recently is VEGF, which is an endothelial selective growth factor.¹⁴ VEGF induces vascular permeability as well.¹⁵ In human RA, several groups have described VEGF in the joints and serum of RA patients.¹⁶⁻²³ VEGF is inducible by hypoxia, which may occur in the inflamed joint.^{17 24} Hypoxia inducible factor-1 (HIF-1), which is made of HIF-1 α , and hydroxycarbon nuclear translocator (ARNT), controls many transcriptional responses to hypoxia by binding to hypoxia response elements of target genes like the VEGF gene.²⁵ In RA patients treated with anti-tumour necrosis factor α (TNF α), vascular deactivation occurs so that serum levels of VEGF fall along with clinical improvement.²⁶ A number of groups presented at the 1999 National American College of Rheumatology (ACR) meeting on the regulation of VEGF production by synovial fibroblasts, mainly from patients with RA (fig 2).²⁷⁻³⁰ Not only do cytokines like interleukin 1 (IL1) and TNF α induce fibroblast expression of VEGF, but so does engagement of CD 40 ligand. Bone morphogenetic proteins (or BMPs), which induce formation of cartilage and bone, and seem to downregulate IL1 induced VEGF production. VEGF induces endothelial decay accelerating factor (DAF), which is cytoprotective against activated complement and may regulate endothelial proliferation and angiogenesis.

Similarly, the role of VEGF has been examined in animal arthritis models. In collagen induced in rats, a reduction in arthritis disease severity by angiogenesis inhibitors results in reduced serum levels of VEGF.³¹ Administration of the fungal derivative TNP-470 in rodent arthritis leads to attenuated arthritis and serum VEGF production.³² Administration of the VEGF receptor soluble flt-1 in mouse collagen induced arthritis results in attenuated arthritis.³³ These results indicate that modulation of angiogenesis may alter arthritis, at least in animal models. Hence, VEGF is probably an important mediator of angiogenesis in the RA joint.

Figure 1 Balance of angiogenesis inducers and inhibitors in inflammatory states such as rheumatoid arthritis.

Figure 2 Proposed mechanism of action of cytokines inducing angiogenesis via integrin usage. Abbreviations are: decay accelerating factor (DAF), protein kinase C (PKC), tumour necrosis factor α (TNF α), transforming growth factor β (TGF β), and bone morphogenetic protein (BMP).

Figure 3 Proposed regulation of vascular endothelial growth factor (VEGF) in the RA joint. Abbreviations are protein kinase C (PKC) and matrix metalloproteinase-2 (MMP-2).

THE MECHANISM OF ACTION OF SOME ANGIOGENIC CYTOKINES: VIA ADHESION MOLECULES LIKE INTEGRINS

The invasion, migration, and proliferation of endothelial cells is regulated at least in part by the integrin family of cell adhesion molecules. Mice made deficient in αv integrins predominantly die in utero.³⁴ However, 20% of animals survive until term and die hours after birth of extensive brain and intestinal vascular abnormalities and haemorrhaging. It is very interesting that $\alpha v\beta 3$ is minimally, if at all expressed on resting or normal blood vessels but is highly expressed in RA synovial blood vessels.³⁵ Some angiogenic factors like basic fibroblast growth factor (bFGF) and TNF α may act via integrins.³⁶ TNF α seems to act to mediate angiogenesis via $\alpha v\beta 3$ integrin (fig 3). Angiogenesis can be inhibited by using $\alpha v\beta 3$ antagonists that promote unscheduled programmed cell death (apoptosis) of newly sprouting blood vessels.³⁷ VEGF or transforming growth factor α appear to act via an alpha v beta 5 integrin mechanism using protein kinase C (PKC). This may turn out not to be a main mode of VEGF's action in RA as alpha v beta 5 integrin has been reported to be expressed in normal and osteoarthritis (OA) synovial tissue, but not RA synovial tissue.³⁸ None the less, the mechanisms by which some of these cytokines act to promote angiogenesis are rapidly becoming identified.

$\alpha v\beta 3$ has been targeted using animal arthritis models. Administration of an $\alpha v\beta 3$ antagonist ameliorates angiogenesis and decreases arthritis in a synovitis model in rabbits.³⁹ At the ACR meeting, there were several groups who have studied the role of this molecule in angiogenesis. An oral non-peptide $\alpha v\beta 3$ antagonist

Figure 4 Structure of fractalkine, a CX₃C chemokine. (Adapted from Rollins BJ. *Blood* 1997;90:909.)

ameliorates rat adjuvant induced arthritis, both prophylactically and therapeutically.⁴⁰ A proapoptotic $\alpha v\beta 3$ antagonist composed of an RGD peptide linked to a heptapeptide dimer is therapeutic in mouse collagen induced arthritis.⁴¹ However, this antagonist selectively homes to mouse arthritic versus normal joint endothelium and versus control organs. In this study, targeted apoptosis of synovial neovascularity resulted in improvement of arthritis. These studies indicate that this integrin can be modulated in vivo with resultant improvement in arthritis, possibly via effects on angiogenesis.

CHEMOKINES AS ANGIOGENIC MEDIATORS

Among other important mediators of angiogenesis are chemokines. Most chemokines are low molecular weight (8 kDa to 10 kDa) proteins that are predominantly known for their ability to recruit leucocytes.⁴² Chemokines are divided into the C-X-C, CC, and C-X₃-C families based on the presence or absence of an amino acid, X, between a pair of cysteine residues near the amino terminus of the protein. In collaboration with Dr Robert Strieter, Peter Polverini, and Steve Kunkel, our group found that monocyte/macrophage derived interleukin 8 (IL8), a prototype of the C-X-C chemokine subfamily, was angiogenic.⁴³ This factor seemed important in that synovial tissue macrophage derived chemotactic activity for endothelial cells in vitro and angiogenesis in vivo was significantly decreased if IL8 was immunodepleted. In general, chemokines like IL8, of the C-X-C class containing the amino acid E-L-R motif are angiogenic, while those lacking this motif are angiostatic.⁴⁴ Exceptions to this generalisation exist in that the C-X-C chemokine stem cell derived factor-1, which lacks the E-L-R motif is angiogenic.⁴⁵

We have recently shown that fractalkine is the first chemokine described of the CX₃C class to mediate angiogenesis.^{46,47} Fractalkine is termed for its fractal geometry and is the sole member of the CX₃C class of chemokines.⁴⁸ It contains a chemokine motif atop a mucin-like stick, the so called chemokine on a stick (fig 4). Fractalkine is a unique chemokine in that it can also act as an adhesion molecule when cell bound. Fractalkine induces endothelial tube formation on the matrix Matrigel in vitro. Similarly fractalkine induces angiogenesis in Matrigel plugs implanted in mice in vivo. When fractalkine is immunodepleted from RA synovial fluids, the ability of these synovial fluids to chemoattract endothelial cells, a facet of the angiogenic response in vitro, is decreased. Hence, chemokines are probable contributors to RA angiogenic activity.

SOLUBLE ADHESION MOLECULES AS ANGIOGENIC MEDIATORS

Endothelial cells express soluble adhesion molecules, particularly upon cytokine stimulation. Cellular adhesion molecules can be shed from the cell surface and secreted. The function of these soluble adhesion molecules is unclear. A prevailing paradigm was that these molecules might serve an anti-inflammatory role by binding leucocytes, thus preventing

them from adhering to endothelium and entering inflamed tissues. We proposed the converse paradigm that these molecules may be proinflammatory in some cases. Our laboratory found that the cellular adhesion molecules sE-selectin and soluble vascular cell adhesion molecule-1 (sVCAM-1) are angiogenic.^{49 50} It is probable that activated cells in the synovial milieu, such as endothelial cells, bear E-selectin and VCAM-1, which they then shed into the synovial fluid. These soluble adhesion molecules then interact with vascular endothelial cells via sialyl Le^x in the case of sE-selectin, and VLA-4, in the case of sVCAM-1 to mediate angiogenesis.^{49 50} Additionally, the soluble adhesion molecules may bind other, as yet unidentified, receptors on endothelial cells that mediate angiogenesis. Interestingly, RA patients treated with monoclonal anti-TNF α have an element of endothelial deactivation in which treatment results in reduced levels of soluble E-selectin. Hence, these findings may be important clinically in RA.

GLYCOCONJUGATES AS ANGIOGENIC MEDIATORS

We have described another novel related angiogenic mediator in our laboratory. This antigen, termed 4A11, is an endothelial selective, cytokine inducible, endothelial angiogenic antigen.^{51 52} We first raised monoclonal antibody (mAb) 4A11 by immunising mice with adherent cells from human rheumatoid synovial tissue. The mAb we produced recognised endothelium in the synovium, thymus, skin, and lymph node selectively, perhaps suggesting a role in cell homing to these regions. Moreover, the mAb was endothelial selective, recognising endothelium and keratinocytes only. This antigen is upregulated in RA compared with normal synovial tissue and is rapidly cytokine inducible in vitro, being stored in cytoplasmic vesicles and upregulated on the cell surface within 5 to 20 minutes of contact with cytokines. We have obtained a partial structure of the antigen recognised by mAb 4A11. The mAb detects Lewis^x-6 and H-5-2 antigens (Le^x/H). These structures are mainly recognised for their function as blood group

antigens. Interestingly, these antigens are structurally related to the E-selectin ligand sialyl Lewis^x. Because of the angiogenic properties of soluble E-selectin, we hypothesised these endothelial antigens were released by activated endothelium and induced angiogenesis. Glucose analogues of these molecules or the glycolipids themselves induced a potent endothelial chemotactic response. Moreover, the glucose analogues are angiogenic in vivo in the corneal bioassays. mAb 4A11 abrogated the angiogenic responses. We reasoned that if these molecules mediated angiogenesis, they could be detected in clinical samples from RA patients. We found that soluble 4A11 antigen is increased in RA compared with OA serum and synovial fluid. These results describe a novel endothelium selective antigen that functions as an angiogenic mediator. As with the E-selectin and VCAM-1, it is probable that endothelial cells exposed to cytokines bear the 4A11 antigen, which is shed in the inflamed joint and mediates angiogenesis (fig 5).

Glycoconjugates (glycoproteins/glycolipids) have been known for some time to constitute the chemical basis for several blood group systems in humans and to act as adhesion molecules for microbial ligands, though no physiological role has been shown for them until recently.⁵³ A mAb MIA-15-15, detecting Le^y/Le^x/H, inhibited the motility of tumour cells in vitro.⁵⁴ As the potential of tumour cells for invasion is closely associated with motility, which seems to depend on specific glycosylation, it followed that patients bearing lung carcinomas identified by mAb MIA-15-15 had a strikingly worse prognosis than those whose tumours were MIA-15-15 negative.⁵⁴ The importance of glycoconjugates in the induction of autoimmunity was recently underscored by the finding that *Helicobacter pylori*, the microorganism involved in gastritis, ulcers, adenocarcinoma, and lymphoma of the stomach, expresses Le^y/Le^x/H, which is also found in gastric mucin.^{55 56} Mice bearing hybridomas making *H. pylori* induced anti-Le antibodies developed gastritis, pointing to a mechanism by which *H. pylori* participates in "molecular mimicry". Hence, antibodies directed against *H. pylori* Le^y result in gastritis via an autoimmune reaction directed against gastric mucin Le^y. In diseases such as RA, the inciting agent is unknown. Thus, it is possible that Le^y/H may also trigger a "molecular mimicry" immune reaction in inflammatory angiogenic sites such as RA.

There exists a hypothesis that while endothelium is quiescent for weeks or longer, endothelial cells must also require a mechanism of storage of "preformed" regulators of angiogenesis that are capable of inducing new capillary growth within hours in response to angiogenic stimuli, such as those found in a wound or an inflamed synovial tissue.⁵⁷ Despite this hypothesis, with the possible exception of bFGF, examples have not been described for angiogenesis inducers. The rapid cell surface expression of Le^y/H may fit this paradigm. However, an alternative scenario concerning the regulation of angiogenesis by inducers and inhibitors may be that "structural" mimicry plays a part.

Figure 5 Proposed induction of angiogenesis in RA by soluble 4A11 antigen (Le^x/H).

Hence, for instance, a search based on crystal structure revealed that the angiogenic inhibitor endostatin was most homologous to the angiogenic mediator E-selectin (Bjorn Olsen, data presented at the Angiogenesis in Cancer Meeting, Orlando, FL 24–28 January 1998). It is probable that in an RA joint Le^v/H may be stored for expedient use during times of active inflammation and subsequent angiogenesis.

Angiopoietins and ephrins control vascular growth and development

Though as yet not examined in RA, the angiopoietins are increasingly being recognised as modulators of vascular development that may eventually play a part in vascular targeting. Angiopoietin-1 participates in the maturation of blood vessels while angiopoietin-2 is a natural antagonist of angiopoietin-1.^{58–60} Interestingly, both angiopoietin-1 and -2 bind the tyrosine kinase receptor Tie2. In vascular development, membrane bound ephrin-B2 marks future arterial cells and its Eph-B4 receptor marks future venous cells.^{61 62} If either the angiopoietin-1 gene or the ephrin-B2 gene are deleted in mice, angiogenic remodelling is perturbed.^{58 61} A new aspect of angiogenesis has recently been explored. Angiopoietin-1 overexpressing mice form blood vessels that are not leaky.^{58 59 63} This is in sharp contrast with VEGF overexpressing mice, who form leaky vessels. Moreover, overexpression of angiopoietin-1 results in resistance to leakage caused by inflammatory agents in mice. As we learn more about the process of vessel growth and development, it is tempting to speculate that in the future certain types of angiogenic factors may be used to “harden” vessels against the effects of inflammatory mediators.

Angiogenesis inhibitors

PARADIGM OF INHIBITORS RESIDING WITHIN LARGER PROTEINS

The regulation of angiogenesis is likely to result from a delicate balance of angiogenesis inducers and inhibitors (fig 1).⁶⁴ Currently, a number of angiogenesis inhibitors have been identified, some of which fit neatly into emerging paradigms. One paradigm mentioned above is that angiostatic activity often resides in portions of larger common proteins that may or may not themselves be angiostatic.⁵⁷ Examples of this include many molecules thought to play a part in RA pathogenesis, like thrombospondin, fibronectin and propeptides of type II collagen, platelet factor IV, and fragments of epidermal growth factor. Other mediators fitting this paradigm are: the 29 kDa fragment of fibronectin, the 16 kDa fragment of prolactin, and angiostatin (a fragment of plasminogen), among others.^{65–68}

THROMBOSPONDIN AS AN ANGIOGENESIS INHIBITOR

The idea that endothelium is quiescent for long periods of time and yet can be induced to sprout new capillaries in a matter of hours in response to an angiogenic stimulus, suggested that angiogenesis regulators might be stored for expedient use. The first indication of this paradigm was described by Dr Noel Bouck and coworkers, who found that a non-tumorigenic hamster cell line became tumorigenic with a

mutation that inactivated a tumour suppressor gene.⁶⁹ The inhibitory activity was found to be a fragment of the adhesive glycoprotein thrombospondin-1 whose expression was linked to the presence of a tumour suppressor gene. Thrombospondin seems to act via inducing endothelial cell apoptosis.⁷⁰ Recently metallopondins have been found using molecular techniques, and are even more potent angiogenic inhibitors than thrombospondin.⁷¹ We were unable to show an effect of inhibiting arthritis or angiogenesis in a rat model of adjuvant induced arthritis.^{71 72}

ANGIOSTATIN AS AN ANGIOGENESIS INHIBITOR

Another inhibitor of angiogenesis termed “angiostatin” has been identified in some very elegant studies by Dr Judah Folkman’s group.^{66 73–77} This factor is a potent inhibitor of tumour growth. Angiostatin is a fragment of the clotting factor plasminogen. Plasminogen itself is not angiostatic. This factor acts by depleting energy required for blood vessel growth by binding ATP-synthase and induces endothelial cell apoptosis by activating focal adhesion kinase.^{76–78} The role of angiostatin in RA has not yet been defined.

ENDOSTATIN AS AN ANGIOGENESIS INHIBITOR

Likewise, endostatin, an angiogenesis inhibitor produced by mouse haemangioendothelioma cells, is a fragment of collagen type XVIII.⁷⁹ Thus, the fact that abundant components of the circulatory system such as fibrinogen and plasminogen can be converted to potent angiostatic factors suggests a new form of regulation by proteases, such as serine proteases to specifically release these molecules from their parent molecules. One might envision that in the case of RA, these inhibitors might be present, but downregulated.

Can angiogenesis regulation help us in the treatment of patients with RA?

ANGIOGENESIS INHIBITORS RELEVANT TO THE RHEUMATIC DISEASES

Some of the endogenous and exogenous inhibitors of angiogenesis that have been identified to date include: a cartilage derived factor, troponin, angiostatic corticosteroids, minocycline, fumigillin, thalidomide, chloroquine, sulfapyridine, methotrexate, penicillamine, thiol containing compounds such as gold compounds, taxol, thalidomide, 2-methoxyestradiol, and cyclooxygenase-2 (COX-2) inhibitors.

Interestingly, cartilage is avascular as well as relatively tumour resistant. So, it is reasonable that among the earliest described inhibitors of neovascularisation were cartilage derived inhibitors. Inhibitors of angiogenesis have been purified from various types of cartilage.^{80–84} Shark cartilage contains a potent inhibitor of angiogenesis, accounting for its popularity in some circles as an unorthodox treatment for cancer.⁸⁵ A cartilage derived inhibitor from bovine scapula has been described that is also an inhibitor of collagenase. Recently, a human cartilage derived angiogenesis inhibitor has been shown to be troponin I, a protein responsible for regulation of muscle contractions.^{80 81 86} Like angiostatin, troponin I acts by binding ATPase,

thus depleting energy needed for blood vessel growth. Regardless of the source, it is intriguing that cartilage, which lies in juxtaposition to the inflamed RA synovium, may hold a key to the understanding of how one might inhibit the angiogenic process in the joint.

Fumagillin is an angiostatic compound discovered as a fungal contaminant on an endothelial culture dish that inhibited endothelial growth.⁸⁷⁻⁹⁰ Derivatives of this compound termed AGM-1470 or TNP-470 inhibit both angiogenesis and arthritis in rodent models.⁹⁰⁻⁹¹ Interestingly, angiogenesis may also play a part in bone formation. TNP-470 inhibited ectopic bone formation induced by bone morphogenetic protein in mice.⁹² Fumagillin may be a potential therapeutic agent inhibiting arthritis and angiogenesis in RA.

Several angiogenesis modulating agents have recently been tried in rodent models of arthritis. These include taxol, thalidomide, and 2-methoxyestradiol. Thalidomide is an inhibitor of both angiogenesis, which may account for its teratogenic effects on limb bud formation, and TNF α .⁷⁸⁻⁹³ Thalidomide suppressed rat collagen induced arthritis but not via inhibition of the angiogenic cytokines TNF α or VEGF.⁹⁴ Taxol, a chemotherapeutic agent, inhibited collagen induced arthritis in rats and inhibited synovial angiogenesis.⁹⁵ 2-methoxyestradiol treatment of collagen induced arthritis in mice resulted in a decrease in arthritis. In vitro, this compound inhibited proliferation of endothelial cells.⁹⁶

Prostaglandins, such as prostaglandin E₂ are potent mediators of angiogenesis.⁹⁷ COX-2 inhibitors have recently been released and used for the treatment of RA. Not surprisingly, they have been shown to inhibit angiogenesis mainly in tumour models.²²⁻⁹⁸⁻¹⁰¹ It is quite possible that these modulators are also effective in reducing RA angiogenesis.

Sulfasalazine is commonly used in the treatment of a variety of diseases including RA. The active metabolite of sulfasalazine may be sulfapyridine. In one study, while sulfapyridine inhibited endothelial proliferation, sulfasalazine and 5 aminosalicylic acid metabolites did not.¹⁰² We have recently shown that sulfasalazine and sulfapyridine reduce endothelial proliferation as well as chemotaxis.¹⁰³ Sulfapyridine can also inhibit phorbol myristate acetate (PMA) induced endothelial tube formation in vitro. We have also shown that sulfapyridine may mediate this effect by reducing endothelial IL8 production.

Therapeutic considerations

CAN ANGIOGENIC MARKERS HELP GUIDE

TREATMENT IN RA?

Recently soluble CD 146, an endothelial cell adhesion molecule involved in leucocyte-endothelial interactions, was found to be upregulated in synovial fluids from patients with RA compared with traumatic injury.¹⁰⁴ Patients with early RA had the highest values of this marker in their synovial fluid. Soluble CD 146 correlated significantly with the degree of morning stiffness, the number of tender joints, and the number of swollen joints.

In papers presented at the ACR meeting VEGF and bFGF were shown to be increased in RA compared with normal serum, especially in early erosive RA and in patients who had antibodies to Sa, an endothelial antigen, as well as to collagen.¹⁰⁵ Serum VEGF is increased in early RA.¹⁰⁶ Early RA synovial fluid VEGF and matrix metalloproteinase (MMP)-9 correlate with each other and with arthroscopic synovitis and vascularity scores.¹⁰⁷ Evidence is mounting that markers of angiogenesis may help us assess early RA.

CAN ANGIOGENIC MARKERS PREDICT RA DISEASE OUTCOME?

Also at the ACR, meeting preliminary data using the Euridiss cohort study indicated that sVCAM-1 and CD 31 can predict disability and radiological changes in RA.¹⁰⁸ Serum VEGF was associated with greater disease activity and soluble selectins were associated with increased disability. Hence, it is tempting to speculate that angiogenic markers may help guide us in RA treatment in the future.

WHAT DOES THE FUTURE HOLD IN ANGIOGENESIS MODULATION?

One might envision vascular targeting strategies. For targeting to be effective, it will be necessary to develop markers to assess the synovial vasculature. In addition to clinical markers of disease activity described above, various imaging techniques are being assessed for evaluating synovial vascularity. One such technique used in rat adjuvant induced arthritis is the use of a radiolabelled E-selectin binding peptide.¹⁰⁹ Some imaging techniques already tried in humans include gadolinium-DTPA enhanced magnetic resonance imaging of RA joints, which correlates with blood vessel density as determined by synovial tissue histology.¹¹⁰ High resolution ultrasound is also new technique that has been tried for RA joint imaging.¹¹¹ Using this technique, the investigators found that inactive versus active RA patients had increased vascularity.

Once strategies are developed for monitoring vascular therapies, and if vascularity is shown to be reflective of disease activity, it is probable that vascular targeting may become a reality. Possible strategies include viral vector targeted antiangiogenic gene treatment, as has been tried in animal models of tumour growth with angiostatin, the VEGF receptor flt-1, and the Tie2 angiopoietin-1 and 2 endothelial receptor.⁷⁸⁻¹¹²⁻¹¹⁴ One may envision strategies like gene treatment with dominant negative VEGFR-1 mutants that prevent VEGF mediated effects on the vasculature. Another therapeutic avenue might be gene treatment with modulation of hypoxia response elements that become selectively activated under hypoxic conditions. Methods aimed at inducing vascular proliferation, perhaps by induction of apoptosis may be another potential strategy to disease modification.

Funding: support for this work was provided by NIH grants AI40987 and HL58695, the Veteran's Administration Research Service, and the Gallagher Professorship for Arthritis Research.

1 Szekanecz Z, Szegedi G, Koch AE. Angiogenesis in rheumatoid arthritis: pathogenic and clinical significance. *J Invest Med* 1998;46:27-41.

- 2 Koch AE. Review: angiogenesis: implications for rheumatoid arthritis. *Arthritis Rheum* 1998;41:951-62.
- 3 Fitzgerald O, Bresnahan B. Synovial membrane cellularity and vascularity. *Ann Rheum Dis* 1995;54:511-15.
- 4 Kimball ES, Gross JL. Angiogenesis in pannus formation. *Agents Actions* 1991;34:329-31.
- 5 Kaul A, Blake DR, Pearson JD. Vascular endothelium, cytokines, and the pathogenesis of inflammatory synovitis. *Ann Rheum Dis* 1991;50:828-32.
- 6 Paleolog EM, Miotla JM. Angiogenesis in arthritis: role in disease pathogenesis and as a potential therapeutic target. *Angiogenesis* 1998;2:295-307.
- 7 Winkler JD, Seed MP. Angiogenesis in inflammatory disease. *Inflam Res* 1997;46:157-8.
- 8 Walsh DA. Angiogenesis and arthritis. *Rheumatology* 1999;38:103-12.
- 9 Hayes AJ. Angiogenesis in rheumatoid arthritis. *Lancet* 1999;354:423-4.
- 10 Gougos A, St Jacques S, Greaves A, O'Connell PJ, d'Apice AJ, Buhning HJ, *et al.* Identification of distinct epitopes of endoglin, an RGD-containing glycoprotein of endothelial cells, leukemic cells, and syncytiotrophoblasts. *Int Immunol* 1992;4:83-92.
- 11 Gougos A, Letarte M. Primary structure of endoglin, an RGD-containing glycoprotein of human endothelial cells. *J Biol Chem* 1990;265:8361-4.
- 12 Li DY, Sorensen LK, Brooke BS, Urness LD, Davis EC, Taylor DG, *et al.* Defective angiogenesis in mice lacking Endoglin. *Science* 1999;284:1534-7.
- 13 Szekanecz Z, Haines GK, Harlow LA, Shah MR, Fong TW, Fu R, *et al.* Increased synovial expression of TGF- β receptor endoglin and TGF- β 1 in rheumatoid arthritis. *Clin Immunol Immunopathol* 1995;76:187-94.
- 14 Ferrara N. Molecular and biological properties of vascular endothelial growth factor. *J Mol Med* 1999;77:527-43.
- 15 Ferrara N. The role of vascular endothelial growth factor in pathological angiogenesis. *Breast Cancer Res Treat* 1995;36:127-37.
- 16 Koch AE, Harlow LA, Haines GK, Amento EP, Unemori EN, Wong WL, *et al.* Vascular endothelial growth factor. A cytokine modulating endothelial function in rheumatoid arthritis. *J Immunol* 1994;152:4149-56.
- 17 Jackson JR, Minton JA, Ho ML, Wei N, Winkler JD. Expression of vascular endothelial growth factor in synovial fibroblasts is induced by hypoxia and interleukin 1 β . *J Rheumatol* 1997;24:1253-9.
- 18 Harada M, Mitsuyama K, Yoshida H, Sakisaka S, Taniguchi E, Kawaguchi T, *et al.* Vascular endothelial growth factor in patients with rheumatoid arthritis. *Scand J Rheumatol* 1998;27:377-80.
- 19 Fava RA, Olsen NJ, Spencer-Green G, Yeo KT, Yeo TK, Berse B, *et al.* Vascular permeability factor/endothelial growth factor (VPF/VEGF): accumulation and expression in human synovial fluids and rheumatoid synovial tissue. *J Exp Med* 1994;180:341-6.
- 20 Kikuchi K, Kubo M, Kadono T, Yazawa N, Ihn H, Tamaki K. Serum concentrations of vascular endothelial growth factor in collagen diseases. *Br J Dermatol* 1998;139:1049-51.
- 21 Bottomley MJ, Webb NJ, Watson CJ, Holt PJ, Freemont AJ, Brenchley PE. Peripheral blood mononuclear cells from patients with rheumatoid arthritis spontaneously secrete vascular endothelial growth factor (VEGF): specific up-regulation by tumour necrosis factor- α (TNF- α) in synovial fluid. *Clin Exp Immunol* 1999;117:171-6.
- 22 Ben-Av P, Crofford LJ, Wilder RL, Hla T. Induction of vascular endothelial growth factor expression in synovial fibroblasts by prostaglandin E and interleukin-1: a potential mechanism for inflammatory angiogenesis. *FEBS Lett* 1995;372:83-7.
- 23 Nagashima M, Yoshino S, Ishiwata T, Asano G. Role of vascular endothelial growth factor in angiogenesis of rheumatoid arthritis. *J Rheumatol* 1995;22:1624-30.
- 24 Berse B, Hunt JA, Diegel RJ, Morganelli P, Yeo K, Brown F, *et al.* Hypoxia augments cytokine (transforming growth factor- β and IL-1)-induced vascular endothelial growth factor secretion by human synovial fibroblasts. *Clin Exp Immunol* 1999;115:176-82.
- 25 Jones A, Harris AL. New developments in angiogenesis: a major mechanism for tumor growth and target for therapy. *Cancer J Sci Am* 1998;4:209-17.
- 26 Paleolog EM, Young S, Stark AC, McCloskey RV, Feldmann M, Maini RN. Modulation of angiogenic vascular endothelial growth factor by tumor necrosis factor α and interleukin-1 in rheumatoid arthritis. *Arthritis Rheum* 1998;41:1258-65.
- 27 Frazer A, Fearon UM, Smith J, Reece R, Emery P, Veale DJ. Angiogenesis, apoptosis and vascularity in early arthritis. *Arthritis Rheum* 1999;42:S85.
- 28 Cho CS, Cho ML, Min SY, Yoon J, Lee SS, Min DJ, *et al.* CD 40 engagement on synovial fibroblast upregulates expression of vascular endothelial growth factor. *Arthritis Rheum* 1999;42:S397.
- 29 Edwards CJ, Paleolog EM, Brennan FM, Feldman M, Maini RN. Contrasting effects of TGF β 1 and BMP-2/4; regulators of vascular endothelial growth factor in rheumatoid arthritis. *Arthritis Rheum* 1999;42:S91.
- 30 Mason JC, Lidington EA, Yarwood H, Lublin DM, Haskard DO. Endothelial cell decay-accelerating factor (DAF) is induced by vascular endothelial growth factor (VEGF), is cytoprotective against activated complement and may be involved in regulating endothelial cell proliferation in chronic synovitis. *Arthritis Rheum* 1999;42:S397.
- 31 Oliver SJ, Cheng TP, Banquerigo ML, Brahn E. Suppression of collagen-induced arthritis by an angiogenesis inhibitor, AGM-1470, in combination with cyclosporin: reduction of vascular endothelial growth factor (VEGF). *Cell Immunol* 1995;166:196-206.
- 32 deBandt M, Grossin M, Weber AJ, Pla M, Chopin M, Picodalo MA, *et al.* Angiogenesis inhibitor suppresses arthritis and preserves from bone destruction in a new transgenic mouse model of RA. *Arthritis Rheum* 1999;42:S118.
- 33 Miotla JM, Paleolog E, Maciewicz R, Kendrew J, Feldmann M, Maini R. Blockade of vascular endothelial growth factor activity attenuates murine collagen-induced arthritis. *Arthritis Rheum* 1999;42:S121.
- 34 Bader BL, Rayburn H, Crowley D, Hynes RO. Extensive vasculogenesis, angiogenesis, and organogenesis precede lethality in mice lacking all α v integrins. *Cell* 1998;95:507-19.
- 35 Johnson BA, Haines GK, Harlow LA, Koch AE. Adhesion molecule expression in human synovial tissue. *Arthritis Rheum* 1993;36:137-46.
- 36 Brooks PC, Clark RA, Cheresh DA. Requirement of vascular integrin α v β 3 for angiogenesis. *Science* 1994;264:569-71.
- 37 Brooks PC, Montgomery AM, Rosenfeld M, Reisfeld RA, Hu T, Klier G, *et al.* Integrin α v β 3 antagonists promote tumor regression by inducing apoptosis of angiogenic blood vessels. *Cell* 1994;79:1157-64.
- 38 Pirila L, Heino J. Altered integrin expression in rheumatoid synovial lining type B cells: in vitro cytokine regulation of α 1 β 1, α 6 β 1, and α v β 5 integrins. *J Rheumatol* 1996;23:1691-8.
- 39 Storgard CM, Stupack DG, Jonczyk A, Goodman SL, Fox RI, Cheresh DA. Decreased angiogenesis and arthritic disease in rabbits treated with an α v β 3 antagonist. *J Clin Invest* 1999;103:47-54.
- 40 Badger A, Swift B, Rieman D, Stroup G, Hoffman S, Blake S, *et al.* The effect of SB 2730005, an orally active, non-peptide α v β 3 vitronectin receptor antagonist in the adjuvant arthritic rat. *Arthritis Rheum* 1999;42:S118.
- 41 Gerlag DM, Borges E, Ellerby HM, Pasqualini R, Bredesen DE, Tak PP, *et al.* Targeted apoptosis of synovial neovasculation in murine collagen-induced arthritis. *Arthritis Rheum* 1999;42:S120.
- 42 Mantovani A. The chemokine system: redundancy for robust outputs. *Immunol Today* 1999;20:254-7.
- 43 Koch AE, Polverini PJ, Kunkel SL, Harlow LA, DiPietro LA, Elner VM, *et al.* Interleukin-8 as a macrophage-derived mediator of angiogenesis. *Science* 1992;258:1798-801.
- 44 Strieter RM, Polverini PJ, Kunkel SL, Arenberg DA, Burdick MD, Kasper J, *et al.* The functional role of the ELR motif in CXC chemokine-mediated angiogenesis. *J Biol Chem* 1995;270:27348-57.
- 45 Salcedo R, Wasserman K, Young HA, Grimm MC, Howard OM, Anver MR, *et al.* Vascular endothelial growth factor and basic fibroblast growth factor induce expression of CXCR4 on human endothelial cells: In vivo neovascularization induced by stromal-derived factor-1 α . *Am J Pathol* 1999;154:1125-35.
- 46 Volin MV, Woods JM, Amin AM, Connors MA, Harlow LA, Koch AE. Fractalkine, a novel angiogenic chemokine in rheumatoid arthritis. *Arthritis Rheum* 1999;42:S250.
- 47 Ruth JH, Volin MV, Haines GK III, Katschke KJ, Woodruff D, Rottman JB, *et al.* Fractalkine, a novel chemokine in rheumatoid arthritis and rat adjuvant induced arthritis. *Arthritis Rheum* 1999;42:S197.
- 48 Bazan JF, Bacon KB, Hardiman G, Wang W, Soo K, Rossi D, *et al.* A new class of membrane-bound chemokine with a CX3C motif. *Nature* 1997;385:640-4.
- 49 Koch AE, Halloran MM, Haskell CJ, Shah MR, Polverini PJ. Angiogenesis mediated by soluble forms of E-selectin and vascular cell adhesion molecule-1. *Nature* 1995;376:517-19.
- 50 Ferrara N. Missing link in angiogenesis. *Nature* 1995;376:467.
- 51 Halloran MM, Carley WW, Polverini PJ, Haskell CJ, Phan S, Anderson BJ, *et al.* Le^x/H^x and endothelial-selective, cytokine inducible angiogenic mediator. *J Immunol* 2000;164:4868-77.
- 52 Koch AE, Nickoloff BJ, Holgersson J, Seed B, Haines GK, Burrows JC, *et al.* 4A11, a monoclonal antibody recognizing a novel antigen expressed on aberrant vascular endothelium. Upregulation in an in vivo model of contact dermatitis. *Am J Pathol* 1994;144:244-59.
- 53 Holgersson J, Breimer ME, Samuelsson BE. Basic biochemistry of cell surface carbohydrates and aspects of the tissue distribution of histo-blood group ABH and related glycosphingolipids. *APMIS Suppl* 1992;27:18-27.
- 54 Miyake M, Taki T, Hitomi S, Hakomori S. Correlation of expression of H/Lc(y)/Lc(b) antigens with survival in patients with carcinoma of the lung. *N Engl J Med* 1992;327:14-18.
- 55 Appelmelk BJ, Simoons-Smit I, Negrini R, Moran AP, Aspinall GO, Forte JG, *et al.* Potential role of molecular mimicry between *Helicobacter pylori* lipopolysaccharide and host Lewis blood group antigens in autoimmunity. *Infect Immun* 1996;64:2031-40.
- 56 Aspinall GO, Monteiro MA. Lipopolysaccharides of *Helicobacter pylori* strains P466 and MO19: structures of the O antigen and core oligosaccharide regions. *Biochemistry* 1996;35:2498-504.
- 57 Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell* 1996;86:353-64.
- 58 Suri C, Jones PF, Patan S, Bartunkova S, Maisonpierre PC, Davis S, *et al.* Requisite role of Angiopoietin-1, a ligand for

- the TIE2 receptor, during embryonic angiogenesis. *Cell* 1996;87:1171–80.
- 59 Suri C, McClain J, Thurston G, McDonald DM, Zhou H, Oldmixon EH, *et al.* Increased vascularization in mice overexpressing angiopoietin-1. *Science* 1998;282:468–71.
 - 60 Davis S, Aldrich TH, Jones PF, Acheson A, Compton DL, Jain V, *et al.* Isolation of Angiopoietin-1, a ligand for the TIE2 receptor, by Secretion-Trap Expression Cloning. *Cell* 1996;87:1161–9.
 - 61 Wang HU, Chen ZF, Anderson DJ. Molecular distinction and angiogenic interaction between embryonic arteries and veins revealed by ephrin-B2 and its receptor Eph-B4. *Cell* 1998;93:741–53.
 - 62 Yancopoulos GD, Klagsbrun M, Folkman J. Vasculogenesis, angiogenesis, and growth factors: ephrins enter the fray at the border. *Cell* 1998;93:661–4.
 - 63 Thurston G, Suri C, Smith K, McClain J, Sato TN, Yancopoulos GD, *et al.* Leakage-resistant blood vessels in mice transgenically overexpressing angiopoietin-1. *Science* 1999;286:2511–14.
 - 64 Brower V. Tumor angiogenesis—new drugs on the block. *Nat Biotechnol* 1999;17:963–8.
 - 65 Homandberg GA, Williams JE, Grant D, Schumacher B, Eisenstein R. Heparin-binding fragments of fibronectin are potent inhibitors of endothelial cell growth. *Am J Pathol* 1985;120:327–32.
 - 66 O'Reilly MS, Holmgren L, Shing Y, Chen C, Rosenthal RA, Moses M, *et al.* Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a lewis lung carcinoma. *Cell* 1994;79:315–28.
 - 67 Clapp C, Martial JA, Guzman RC, Rentier-Delure F, Weiner RI. The 16-kilodalton N-terminal fragment of human prolactin is a potent inhibitor of angiogenesis. *Endocrinology* 1993;133:1292–9.
 - 68 Ferrara N, Clapp C, Weiner R. The 16K fragment of prolactin specifically inhibits basal or fibroblast growth factor stimulated growth of capillary endothelial cells. *Endocrinology* 1991;129:896–900.
 - 69 Good DJ, Polverini PJ, Rastinejad F, Le Beau MM, Lemons RS, Frazier WA, *et al.* A tumor suppressor-dependent inhibitor of angiogenesis is immunologically and functionally indistinguishable from a fragment of thrombospondin. *Proc Natl Acad Sci USA* 1990;87:6624–8.
 - 70 Jimenez B, Volpert OV, Crawford SE, Febbraio M, Silverstein RL, Bouck N. Signals leading to apoptosis-dependent inhibition of neovascularization by thrombospondin-1. *Nat Med* 2000;6:41–8.
 - 71 Vazquez F, Hastings G, Ortega MA, Lane TF, Oikemus S, Lombardo M, *et al.* METH-1, a human ortholog of ADAMTS-1, and METH-2 are members of a new family of proteins with angio-inhibitory activity. *J Biol Chem* 1999;274:23349–57.
 - 72 Koch AE, Szekanecz Z, Friedman J, Haines GK, Langman CB, Bouck NP. Effects of thrombospondin-1 on disease course and angiogenesis in rat adjuvant-induced arthritis. *Clin Immunol Immunopathol* 1998;86:199–208.
 - 73 Gately S, Twardowski P, Stack MS, Patrick M, Boggio L, Cundiff DL, *et al.* Human prostate carcinoma cells express enzymatic activity that converts human plasminogen to the angiogenesis inhibitor, angiostatin. *Cancer Res* 1996;56:4887–90.
 - 74 Cao Y, Ji RW, Davidson D, Schaller J, Marti D, Sohndel S, *et al.* Kringle domains of human angiostatin. Characterization of the anti-proliferative activity on endothelial cells. *J Biol Chem* 1996;271:29461–7.
 - 75 O'Reilly MS, Holmgren L, Chen C, Folkman J. Angiostatin induces and sustains dormancy of human primary tumors in mice. *Nat Med* 1996;2:689–92.
 - 76 Holmgren L, O'Reilly MS, Folkman J. Dormancy of micrometastases: balanced proliferation and apoptosis in the presence of angiogenesis suppression. *Nat Med* 1995;1:149–53.
 - 77 Moser TL, Stack MS, Asplin I, Enghild JJ, Hojrup P, Everitt L, *et al.* Angiostatin binds ATP synthase on the surface of human endothelial cells. *Proc Natl Acad Sci USA* 1999;96:2811–16.
 - 78 Claesson-Welsh L, Welsh M, Ito N, Anand-Apte B, Soker S, Zetter B, *et al.* Angiostatin induces endothelial cell apoptosis and activation of focal adhesion kinase independently of the integrin-binding motif RGD. *Proc Natl Acad Sci USA* 1998;95:5579–83.
 - 79 O'Reilly MS, Boehm T, Shing Y, Fukai N, Vasios G, Lane WS, *et al.* Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. *Cell* 1997;88:277–85.
 - 80 Moses MA, Sudhalter J, Langer R. Identification of an inhibitor of neovascularization from cartilage. *Science* 1990;248:1408–10.
 - 81 Moses MA. A cartilage-derived inhibitor of neovascularization and metalloproteinases. *Clin Exp Rheumatol* 1993;11: S67–9.
 - 82 Kuettner KE, Pauli BU. Inhibition of neovascularization by a cartilage factor. *Ciba Found Symp* 1983;100:163–73.
 - 83 Brem H, Folkman J. Inhibition of tumor angiogenesis mediated by cartilage. *J Exp Med* 1975;141:427–39.
 - 84 Langer R, Brem H, Faltermann K, Klein M, Folkman J. Isolation of a cartilage factor that inhibits tumor neovascularization. *Science* 1976;193:70–2.
 - 85 Lee A, Langer R. Shark cartilage contains inhibitors of tumor angiogenesis. *Science* 1983;221:1185–7.
 - 86 Moses MA, Wiederschain D, Wu I, Fernandez CA, Ghazizadeh V, Lane WS, *et al.* Troponin I is present in human cartilage and inhibits angiogenesis. *Proc Natl Acad Sci USA* 1999;96:2645–50.
 - 87 Kusaka M, Sudo K, Fujita T, Marui S, Itoh F, Ingber D, *et al.* Potent anti-angiogenic action of AGM-1470: comparison to the fumagillin parent. *Biochem Biophys Res Commun* 1991;174:1070–6.
 - 88 Antoine N, Greimers R, De Roanne C, Kusaka M, Heinen E, Simar LJ, *et al.* AGM-1470, a potent angiogenesis inhibitor, prevents the entry of normal but not transformed endothelial cells into the G1 phase of the cell cycle. *Cancer Res* 1994;54:2073–6.
 - 89 Kusaka M, Sudo K, Matsutani E, Kozai Y, Marui S, Fujita T, *et al.* Cytostatic inhibition of endothelial cell growth by the angiogenesis inhibitor TNP-470 (AGM-1470). *Br J Cancer* 1994;69:212–16.
 - 90 Peacock DJ, Banquerigo ML, Brahn E. Angiogenesis inhibition suppresses collagen arthritis. *J Exp Med* 1992;175:1135–8.
 - 91 Peacock DJ, Banquerigo ML, Brahn E. A novel angiogenesis inhibitor suppresses rat adjuvant arthritis. *Cell Immunol* 1995;160:178–84.
 - 92 Mori S, Yoshikawa H, Hashimoto J, Ueda T, Funai H, Kato M, *et al.* Antiangiogenic agent (TNP-470) inhibition of ectopic bone formation induced by bone morphogenetic protein-2. *Bone* 1998;22:99–105.
 - 93 Corral LG, Kaplan G. Immunomodulation by thalidomide and thalidomide analogues. *Ann Rheum Dis* 1999;58 (suppl 1):1107–13.
 - 94 Oliver SJ, Cheng TP, Banquerigo ML, Brahn E. The effect of thalidomide and 2 analogs on collagen induced arthritis. *J Rheumatol* 1998;25:964–9.
 - 95 Arsenaault AL, Lhotak S, Hunter WL, Banquerigo ML, Brahn E. Taxol involution of collagen-induced arthritis: ultrastructural correlation with the inhibition of synovitis and neovascularization. *Clin Immunol Immunopathol* 1998;86:280–9.
 - 96 Josefsson E, Tarkowski A. Suppression of type II collagen-induced arthritis by the endogenous estrogen metabolite 2-methoxyestradiol. *Arthritis Rheum* 1997;40:154–63.
 - 97 Ziche M, Jones J, Gullino PM. Role of prostaglandin E1 and copper in angiogenesis. *J Natl Cancer Inst* 1982;69:475–82.
 - 98 Hla T, Ristimaki A, Appleby S, Barriocanal JG. Cyclooxygenase gene expression in inflammation and angiogenesis. *Ann NY Acad Sci* 1993;696:197–204.
 - 99 Majima M, Isono M, Ikeda Y, Hayashi I, Hatanaka K, Harada Y, *et al.* Significant roles of inducible cyclooxygenase (COX)-2 in angiogenesis in rat sponge implants. *Jpn J Pharmacol* 1997;75:105–14.
 - 100 Tsujii M, Kawano S, Tsuji S, Sawaoka H, Hori M, DuBois RN. Cyclooxygenase regulates angiogenesis induced by colon cancer cells. *Cell* 1998;93:705–16.
 - 101 Daniel TO, Liu H, Morrow JD, Crews BC, Marnett LJ. Thromboxane A2 is a mediator of cyclooxygenase-2-dependent endothelial migration and angiogenesis. *Cancer Res* 1999;59:4574–7.
 - 102 Madhok R, Wijelath E, Smith J, Watson J, Sturrock RD, Capell HA. Is the beneficial effect of sulfasalazine due to inhibition of synovial neovascularization? *J Rheumatol* 1991;18:199–202.
 - 103 Volin MV, Harlow LA, Woods JM, Campbell PL, Amin MA, Tokuhira M, *et al.* Treatment with sulfasalazine or sulapyridine, but not 5-aminosalicylic acid, inhibits basic fibroblast growth factor-induced endothelial cell chemotaxis. *Arthritis Rheum* 1999;42:1927–35.
 - 104 Neidhart M, Wehrli R, Bruhlmann P, Michel BA, Gay RE, Gay S. Synovial fluid CD146 (MUC18), a marker for synovial membrane angiogenesis in rheumatoid arthritis. *Arthritis Rheum* 1999;42:622–30.
 - 105 Lee J, Hoxworth J, Goldbach-Mansky R, Deville C, Yarburo C, Smolen J, *et al.* Serum levels of angiogenic growth factors in patients with early synovitis. *Arthritis Rheum* 1999;42:S87.
 - 106 Ballara SC, Paleolog EM, Taylor PC, Feldmann M, Maini RN. Elevated serum vascular endothelial growth factor in early arthritis. *Arthritis Rheum* 1999;42:S244.
 - 107 Frazer A, Fearon UM, Smith J, Reece R, Emery P, Veale DJ. Angiogenesis, apoptosis and vascularity in early arthritis. *Arthritis Rheum* 1999;42:S85.
 - 108 Chary-Valckenaere I, Guillemin F, Kollop-Sarda MN, Bene MC, Faure G, Poullet J. Angiogenesis markers for predicting outcomes in rheumatoid arthritis. *Arthritis Rheum* 1999;42:S173.
 - 109 Zinn KR, Chaudhuri TR, Smyth CA, Wu Q, Liu HG, Fleck M, *et al.* Specific targeting of activated endothelium in rat adjuvant arthritis with a 99mTc-radiolabeled E-selectin-binding peptide. *Arthritis Rheum* 1999;42:641–9.
 - 110 Gaffney K, Cookson J, Blades S, Coumbe A, Blake D. Quantitative assessment of the rheumatoid synovial microvascular bed by gadolinium-DTPA enhanced magnetic resonance imaging. *Ann Rheum Dis* 1998;57:152–7.
 - 111 Hau M, Schultz H, Tony HP, Keberle M, Jahns R, Haerten R, *et al.* Evaluation of pannus and vascularization of the metacarpophalangeal and proximal interphalangeal joints in rheumatoid arthritis by high-resolution ultrasound (multidimensional linear array). *Arthritis Rheum* 1999;42:2303–8.
 - 112 Tanaka T, Cao Y, Folkman J, Fine HA. Viral vector-targeted antiangiogenic gene therapy utilizing an angiostatin complementary DNA. *Cancer Res* 1998;58:3362–9.
 - 113 Folkman J. Antiangiogenic gene therapy. *Proc Natl Acad Sci USA* 1998;95:9064–6.
 - 114 Goldman CK, Kendall RL, Cabrera G, Sorocanu L, Heike Y, Gillespie GY, *et al.* Paracrine expression of a native soluble vascular endothelial growth factor receptor inhibits tumor growth, metastasis, and mortality rate. *Proc Natl Acad Sci USA* 1998;95:8795–800.