Best Practice & Research Clinical Rheumatology 28 (2014) 637–649

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

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Inhibitors of angiogenesis: Ready for prime time?

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Keywords:
Angiogenesis
Inhibition
Inflammation
Rheumatoid arthritis
VEGF
Integrins
Cytokines
Chemokines
Nuclear factor-κB

A B S T R A C T

Angiogenesis plays a crucial role in the pathogenesis of inflammatory diseases, including rheumatoid arthritis (RA). Therefore, targeting neovascularization in RA may hold great therapeutic potential. Several mediating factors are involved in synovial angiogenesis, including growth factors, cytokines, chemokines, adhesion molecules, and matrix-remodeling enzymes. This review aims to summarize the current understanding of these contributing factors in RA, as well as to describe both the preclinical and clinical studies in which these factors are targeted in an attempt to ameliorate the symptoms associated with RA. In addition, we highlight methods to monitor synovial angiogenesis in patients and discuss possible future therapeutic approaches in RA, including the combination of existing immunosuppressive anti-rheumatic therapies and anti-angiogenic treatments to potentially maximize efficacy with limited toxicity.

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http://dx.doi.org/10.1016/j.berh.2014.10.012
1521-6942/

Angiogenesis

Angiogenesis is a vital biological process, forming new capillaries from preexisting blood vessels and infusing tissue with supplies of oxygen and nutrients. It plays an important role in physiological conditions such as reproduction, development, wound healing, and tissue repair. Accumulating evidence also demonstrates that aberrant angiogenesis is a crucial mediator in a growing list of diseases such as cancer, chronic inflammatory diseases, atherosclerosis, and diabetic retinopathy, making substantial contributions to disease pathogenesis. Thus, studying the mechanisms that regulate angiogenesis holds vast therapeutic potential in alleviating or halting disease progression in such diseases [1–3].

The process of angiogenesis is complex, consisting of tightly regulated steps and the involvement of several cell types interacting with each other as well as with the surrounding microenvironment. Angiogenesis is generally induced by hypoxia, leading to the upregulation of pro-angiogenic factors, most notably vascular endothelial growth factor (VEGF), that activate the endothelial cells (ECs) of the preexisting vasculature to sprout and increase vascularization of the tissue. Vessel sprouting relies on a migrating endothelial "tip" cell that guides the vessel and endothelial "stalk" cells that elongate the sprouting vessel via proliferation. VEGF is a tip cell signal, whereas delta-like 4 (DLL4)/Notch signaling is a stalk cell signal. Subsequently, these cells start to migrate in the direction of the hypoxic tissue, following a gradient of VEGF, while simultaneously proliferating and attracting endothelial progenitor cells (EPCs) to make up the inner layer of the newly formed vasculature. In order to construct vessels within the preexisting tissue architecture, degradation of the extracellular matrix (ECM) must also occur and this is done mainly through the actions of matrix-remodeling enzymes such as matrix metalloproteinases (MMPs). Once the vasculature has extended into the hypoxic region, maturation begins with pericytes localizing to the nascent blood vessels and forming an outer layer around the ECs. Next, ECs form tighter junctions through adhesion molecules, followed by deposition of a basement membrane. Finally, the vessel is mature and ready for perfusion of the hypoxic tissue [4,5].

Several mediators are involved in this highly orchestrated process, creating a fine balance between angiogenic and angiostatic signals that support the ultimate goal of mature vessel formation and perfusion. Besides VEGF, other growth factors such as placental growth factor (PlGF), fibroblast growth factor-2 (FGF-2), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), and transforming growth factor-beta (TGFβ) contribute to this process. Cytokines and chemokines have a dual role in this process. The cytokines tumor necrosis factor alpha (TNFα), interleukin (IL)-1, IL-6, IL-8, IL-15, IL-17, IL-18, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), and oncostatin M, and the chemokines C–C motif ligand (CCL)-2, C–X–C motif ligand (CXCL)-5, CXCL1, CXCL6, CXCL12, and macrophage migratory inhibitory factor (MIF) are known stimulators of angiogenesis [6], whereas interferon gamma (IFNγ), interferon alpha (IFNα), IL-4, IL-12, IL-13, CXCL4, CXCL9, CXCL10, and CCL21 may have inhibitory functions 7. Importantly, adhesion molecules ($\alpha_v\beta_3$, E-selectin, vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 2 (ICAM-2), and platelet/endothelial cell adhesion molecule 1 (PECAM-1)) and MMPs (MMP1, MMP2, MMP3, and MMP9) also contribute to effective angiogenic responses. The key signaling molecules that are involved in angiogenesis include angiopoietins (Ang-1 and Ang-2), intermediates of Notch signaling, [6] and members of the nuclear factor (NF)-κB family of transcription factors, including upstream activating kinases [7]. Under normal physiological circumstances, the balance between angiogenic and angiostatic signals is maintained. However, under pathological conditions such as tumor growth or chronic inflammation, the balance is tipped towards a pro-angiogenic phenotype and angiogenesis occurs continuously with a lack of resolution. This is, for a large part, due to immune cells and the factors that they produce.

Angiogenesis in rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by the infiltration of immune cells into the synovial joint, in conjunction with an increase of the synovial lining layer leading