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Review

Targeting synovial neoangiogenesis in rheumatoid arthritis☆

Agathe Leblond [a], Yannick Allanore [a,b], Jérôme Avouac [a,b,*]

[a] Université Paris Descartes, Sorbonne Paris Cité, INSERM U1016 and CNRS UMR8104, Institut Cochin, Paris, France
[b] Université Paris Descartes, Sorbonne Paris Cité, Service de Rhumatologie A, Hôpital Cochin, Paris, France

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ABSTRACT

In Rheumatoid arthritis (RA), neoangiogenesis is an early and crucial event to promote the development of the hyperplasic proliferative pathologic synovium. Endothelial cells are critical for the formation of new blood vessels since they highly contribute to angiogenesis and vasculogenesis. Current therapies in RA target the inflammatory consequences of autoimmune activation and despite major improvements these last years still refractory patients or incomplete responders may be seen raising the point of the need to identify complementary additive and innovative therapies. This review resumes the mechanisms of synovial neoangiogenesis in RA, including recent insights on the implication of vasculogenesis, and the regulation of synovial neoangiogenesis by angiogenic and inflammatory mediators. In line with the recent development of vascular-targeted therapies used in cancer and beyond, we also discuss possible therapeutic implications in RA, in particular the combination of targeted immunotherapies with anti-angiogenic molecules.

Contents

1. Introduction

Rheumatoid arthritis (RA) is the most common cause of chronic inflammatory arthritis with a prevalence ranging from 0.5% to 1% of the adult population worldwide [1,2].

The synovium is the primary site of the inflammatory process in RA. The synovium becomes inflamed, with infiltration of blood-derived inflammatory cells at the interface between cartilage and bone. This invasive and destructive front (termed 'pannus') promotes the development of the erosions observed in RA. Progressive destruction of the articular cartilage, subchondral bone and periarticular soft tissues results in deformities that characterize long-standing RA. These deformities lead to functional deterioration and long term profound irreversible disability.

An important feature of RA is the role of vascular structures in these invasive and destructive processes. Indeed, there are increased number

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* Corresponding author at: Service de Rhumatologie A, Hôpital Cochin, Université Paris Descartes, 27 rue du Faubourg Saint-Jacques, 75014, Paris, France.
E-mail address: jerome.avouac@aphp.fr (J. Avouac).

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and density of synovial blood vessels in RA, which are required to supply the expansion of synovial tissue and to develop the hyperplasic and invasive nature of RA synovium. Endothelial cells (ECs) lining the blood vessels also appear to be an active target for the action of cytokines, growth factors, permeability factors, and matrix-degrading enzymes. EC response to these factors both maintain and promotes RA. Thus, neoangiogenesis appears to be central to maintaining and promoting RA. It is also possible that a potential method of attenuating the development of the pannus is to interfere with its blood supply. This possibility is supported by several studies in animal models of arthritis which have suggested that blocking angiogenesis during the course of RA might actually be of therapeutic benefit.

The aim of this review is to summarize the current understanding of synovial neoangiogenesis in RA and its regulation. We are also giving a focus on the application of angiogenesis inhibitors in animal models of arthritis, and on the potential for development of new vascular-targeted therapies for treatment of RA.

2. Increased vascular density in RA synovium and the contrast with tissue hypoxia

The synovium is normally a physiologically relatively paucicellular structure with a delicate intimal lining between macrophage-like and fibroblast-like synoviocytes. This lining region is one or two cells deep and is highly vascularized. Synovial blood flow provides oxygen and nutrients to the synoviocytes and to the avascular articular cartilage.

RA is first characterized by a transitory pre-vascular highly inflammatory stage, followed by a prominent vascular stage with a strong increase in vessel growth.

The pre-vascular stage is characterized by a marked hyperplasia of macrophage-like and fibroblast-like synoviocytes in the lining layer. In parallel, the sublining layer is infiltrated by CD4+ T cells, B cells and macrophages, leading to the formation of an invasive and destructive front, called the synovial pannus. This pannus acts like a local tumor that invades and damages cartilage and bone [2] (Fig. 1).

Then, the vascular stage rapidly arises and is usually set at the time of RA clinical diagnosis. In this stage, capillary density is increased in the RA synovium, with a more deeply distribution as compared with normal tissue (Fig. 2) [3,4]. Increased density of sublining blood vessels perpetuates synovitis by increasing the delivery of nutrients and oxygen to the proliferating pannus, and allows immune cells to emigrate from the blood into inflamed synovium where they highly produce a network of pro-inflammatory cytokines and chemokines [5]. The increased number of blood vessels correlates with synovial hyperplesia, mononuclear cell infiltration and tender/swollen joint counts [6]. Vascular proliferation is usually primarily detected in inflamed joints, whereas mononuclear cell infiltration and increased thickness of the synovial lining layer are observed both in inflamed and non-inflamed joints [3].

Despite increased vessel density related to active endothelial proliferation and increased EC survival, synovium in RA is chronically hypoxic, particulary in the lining layer [3] (Fig. 1). The presence of reduced oxygen levels in the RA synovium was demonstrated by direct measurements of the oxygen tension and more indirectly by an increase of hypoxic metabolites in the synovium [7]. This observation is not unexpected given the raise in synovial cell proliferation and the consequent increase in the distance between the proliferating cells and the nearest blood vessels. This leads to a growing metabolic demand for oxygen and nutrients resulting in local hypoxia and relative hypoperfusion. Moreover the vasculature of RA synovium is compromised by movement and accumulation of synovial fluid, thus exacerbating hypoxia in an already ischemic environment. Such a combination of increased metabolic demand and hypoxia is a potent signal for new vessel formation.

3. Source of new synovial blood vessels

The recruitement of ECs is required to form new vascular structures. ECs can be recruited locally through angiogenesis, defined by the capillary sprouting of resident ECs. Circulating bone marrow-derived endothelial progenitor cells (EPCs or hemangioblasts) are a second potential source of ECs.

3.1. Angiogenesis

Angiogenesis is the growth of new blood vessels from existing ones and is an important aspect of new tissue development, growth and repair. The numerous proangiogenic signals that target ECs derive from cells primed in an abnormal environment, where the proliferation rate exceeds the supply of nutrients and oxygen [8]. Angiogenic stimulation is triggered in RA synovium by the proinflammatory and hypoxic miceoenvironment, with production of a large array of growth factors, cytokines, and chemokines. These factors induce the sprouting of ECs from preexisting vessels, their proliferation and migration into inflamed sites, launching the vascular stage of the disease (Fig. 1). This sequence is not specific to RA and is observed in other diseases with angiogenic compentent including cancer, diabetes, and other chronic inflammatory conditions. However, specific cells from the synovium are also able to early drive angiogenenis together with ECs. Indeed, local synovial inflammation drives resident stromal synovial cells to acquire a pro-angiogenic profile. Synovial fibroblast from RA synovium are sufficient under hypoxic conditions to induce angiogenesis, when used in a matrigel plug system engrafted in immunodeficient mouse [9,10]. In addition, these cells express growth factors (VEGF, b FGF, TGFβ), cytokines (IL-6, IL-8), chemokines (CXCL12), adhesion molecules (ICAM-1, VCAM-1) and matrix remodeling enzymes (MMP1, 2, 3 and 9) that regulate angiogenesis.

Infiltrating macrophages are also a major source of pro-angiogenic molecules producing a broad range of mediators including growth factors, chemokines and matrix-remodeling enzymes [11].

In RA, increased angiogenesis is associated with morphological alterations of new formed vessels. This fraction of neoangiogenic immature, dilated and leak vessels lacks α-smooth muscle actin (α-SMA) positive mural cells. Chronic VEGF overexpression is implicated in this imbalance between EC proliferation and the lack of concomitant development of pericyte coverage. These small size vessels are preferentially located in sublining layer and are surrounded by inflamatory infiltrates [12] (Fig. 1). Interestingly, disease progression and activity are related to the density of immature vessels, which is the sole vessel fraction to regress in response to anti-TNFα therapy [12].

3.2. Vasculogenesis

EPCs, first described by Asahara and al [13], are a population of bone marrow-derived cells characterized by the presence of surface markers such as CD34, VEGF receptor-2 (VEGFR-2 or kinase-insert domain receptor, KDR) and CD133, able to differentiate into mature endothelial cells and to participate in the formation of new blood vessels [14] (Fig. 1).

Two studies have reported the presence of endothelial precursor cells in the synovial tissue of RA patients. In a first study [15], a population of cells expressing CD34 on their surface was found in the synovial tissue of 18 RA patients. These cells were detected in close proximity to CD133+ cells, forming cell clusters in the area under the synovial membrane. CD34+ precursor cells produced high levels of the chemokine receptor CXCR4, and VEGFR-2 was expressed on CD34+ and CD133+ cells. In the second study [16], CD34+ cells, purified from the bone marrow of 13 patients with active RA and 9 control subjects, were cultured in the presence of stem cell factor and GM-CSF. Significantly more von Willebrand factor-positive cells (vWF+) and CD31+/vWF+ cells were generated from RA bone marrow-derived CD34+ cells for RA