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Author: Mathieu Ferrari Shimobi C. Onuoha Costantino Pitzalis

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Going with the flow: harnessing the power of the vasculature for targeted therapy in rheumatoid arthritis

Mathieu Ferrari*, Shimobi C. Onuoha*, and Costantino Pitzalis

[1]William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK

*These authors contributed equally.

Corresponding author: Ferrari, M. (m.ferrari@qmul.ac.uk)

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Teaser: Angiogenesis has been shown to exacerbate rheumatoid arthritis, yet a great therapeutic potential lays in harnessing the vasculature for tissue-targeting drug delivery approaches. The most promising strategies are described in this review.

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease that leads to excessive joint inflammation and is associated with significant morbidity and mortality. Although much is still to be learned about the aetiology RA, a growing body of evidence suggests that an altered vascular environment is an important aspect of its pathophysiology. In this context, RA shares many similarities with cancer, and it is expected that several angiogenic targets in cancer might be relevant to the treatment of RA. Here, we discuss how these targets can be combined with advances in drug development to generate the next generation of RA therapeutics.

Introduction

RA is a chronic, systemic, autoimmune disease that is considered one of the most common and severe forms of inflammatory arthritis, associated with significant morbidity and mortality [1,2]. Although its aetiology is poorly understood, the pathogenesis and the role of the immune system in disease progression are well defined. Clinically, RA is characterised by swelling of the small diarthrodial joints, stiffness, and pain that can lead to profound disability in the long run. At a cellular level, the hypertrophic and hyperplastic synovial membrane, assisted by pro-inflammatory cytokine expression and proteolytic enzymes, forms an aggressive pannus lesion at the cartilage–bone interface, mainly comprising macrophages, fibroblasts, and osteoclasts, which infiltrate the adjoining articular cartilage, promoting joint destruction. Systemic involvements of RA include cardiovascular alterations (e.g., pericardial inflammation and vasculitis), pulmonary, psychological, and skeletal disorders, and is generally associated with increased disability and shortened life expectancy [1,3].

An important aspect of the pathophysiology of RA is the presence of an altered vascular environment. In this context, although different for various disease aspects, RA shows similarities with cancer, because both are characterised by a hyperproliferative cellular environment with elevated metabolic demand and extensive angiogenesis in a pro-inflammatory milieu [4]. Whether angiogenesis is a concurrent cause or a consequence during RA onset is still under debate; however, it is now clear that inflammation and angiogenesis are two intertwined events that both have a pivotal role in disease progression and perpetuation [4,5] (Figure 1).

The role of angiogenesis in RA

Similar to the well-characterised phenomenon in cancer tissues, the hyperproliferation and expansion of the synovial tissue in RA results in increased metabolic demand and oxygen consumption, where oxygen tension levels can drop from 9% to 12% in normal joints to 2–4% in arthritic joints [6]. This hypoxic condition leads to the activation of hypoxic-inducible factors (HIF) that are responsible for the regulation of approximately 1% of all human genes. HIF-β is constitutively expressed in the nucleus, whereas HIF-α subunits are oxygen regulated and require active translocation to the nucleus to dimerise with the β subunit and activate the hypoxia-responsive elements (HRE) in the target genes. In RA tissues, the presence of HIF-1α and HIF-2α has been confirmed, suggesting a role for HIF in synovial angiogenesis [7,8]. The most well-known pro-angiogenic factor, vascular endothelial growth factor (VEGF), with the VEGF-121 and VEGF-165 isoforms expressed in RA synovium [9], is one protein regulated through HRE. It exerts its effects on the proliferation and migration of endothelial cells via interaction with two tyrosine-kinase receptors: VEGF receptor 1 and 2 (VEGFR-1 and VEGFR-). Upregulation of stromal cell-derived factor 1, proinflammatory cytokines, such as interleukin (IL)-6 and IL-8, and matrix metalloproteinases (MMPs) have also been associated with HIF activation in RA synovium [10,11], suggesting a direct role of hypoxia in synovial angiogenesis, inflammation, and cartilage degradation. Interestingly, proinflammatory cytokines, such as IL-1β and tumour necrosis factor (TNF), are able to directly stimulate HIF expression in normoxia, further strengthening the relation between inflammation and hypoxia [12]. More recently,