Autoimmunity Reviews 16 (2017) 951–962

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Endothelial cells: From innocent bystanders to active participants in immune responses☆

A. Al-Soudi [1], M.H. Kaaij [1], S.W. Tas *

Amsterdam Rheumatology and Immunology Center, Department of Clinical Immunology & Rheumatology and Laboratory for Experimental Immunology, Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 3 June 2017
Accepted 5 June 2017
Available online 8 July 2017

Keywords:
Inflammation
Endothelial cells
Angiogenesis
Immune regulation
Endothelial-to-mesenchymal transition (EndMT)
Targeted therapies

ABSTRACT

The endothelium is crucially important for the delivery of oxygen and nutrients throughout the body under homeostatic conditions. However, it also contributes to pathology, including the initiation and perpetuation of inflammation. Understanding the function of endothelial cells (ECs) in inflammatory diseases and molecular mechanisms involved may lead to novel approaches to dampen inflammation and restore homeostasis. In this article, we discuss the various functions of ECs in inflammation with a focus on pathological angiogenesis, attraction of immune cells, antigen presentation, immunoregulatory properties and endothelial-to-mesenchymal transition (EndMT). We also review the current literature on approaches to target these processes in ECs to modulate immune responses and advance anti-inflammatory therapies.

Contents

☆ Declaration of interest: none

* Corresponding author at: Department of Clinical Immunology & Rheumatology, Academic Medical Center/University of Amsterdam, Meibergdreef 9, 1105AZ Amsterdam, PO. Box 22600, The Netherlands.
E-mail address: S.W.Tas@amc.uva.nl (S.W. Tas).

[1] These authors contributed equally.

http://dx.doi.org/10.1016/j.autrev.2017.07.008

1. Introduction

As our knowledge of the human immune response increases, many cell types first thought to be mere bystanders have shown to play crucial roles in inflammatory processes. Inflammation is highly dependent on interactions between immune cells and stromal cells. Recently, the role of stromal cells, including endothelial cells (ECs), is more and more appreciated. ECs form the vascular endothelium and under homeostatic conditions conduct several essential processes such as maintenance of vessel integrity, the supply of oxygen and nutrients to underlying tissues and patrolling immune cell trafficking. However, in pathologic circumstances such as auto-immune diseases, ECs contribute to inflammatory responses and play an important role in perpetuation of inflammation through processes such as angiogenesis and immune cell recruitment. The goal of this article is to review the many faces of the ECs and their role in chronic inflammatory diseases, with a focus on rheumatoid arthritis (RA) as a model disease. We will elaborate on the plethora of EC functions involved in inflammation and highlight processes like pathological angiogenesis, immune cell attraction, antigen presentation, and endothelial-to-mesenchymal transition (EndMT), as well as certain immunoregulatory properties (see Fig. 1 for overview). In addition, we will discuss potential therapeutic interventions to block inflammatory responses or normalize EC function and limit inflammation.

2. Pathological angiogenesis

2.1. General principles of angiogenesis

Angiogenesis is a complex and highly coordinated process that ultimately leads to the formation of new blood vessels from pre-existing vasculature. In essence, the endothelial basement membrane of existing vessels, mostly microvessels, is degraded by proteases produced by other stromal cells such as fibroblasts or immune cells, resulting in generation of capillary sprouts that enable ECs to migrate into surrounding interstitial tissue and form a new vessel wall [1,2]. Under physiological conditions, angiogenesis is important in development and in tissue repair (i.e. wound healing), but in pathologic circumstances, such as RA or other chronic inflammatory diseases, angiogenesis is essential in initiation and maintenance of inflammation by supporting expanded stromal cell populations and tissue-resident or accumulated immune cells via supply of oxygen and nutrients, as well as enabling new immune cells to reach the site of inflammation by formation of new vascular routes and expression of homing molecules such as chemokines and adhesion molecules [3]. In many rheumatologic diseases, including several types of arthritis, angiogenesis is observed from the earliest phases of the disease and is an essential component contributing to synovial inflammation (reviewed in [4]). Newly formed blood vessels offer an entrance for inflammatory cells to the synovial membrane, leading to perpetuation of inflammation and pannus formation, eventually resulting in cartilage and bone destruction [5]. Despite continued angiogenesis, the inflamed joint is hypoxic and hypoperfused due to a high cellular proliferation rate in the synovium. The resulting deficit in oxygen and nutrients acts as an extra stimulus for angiogenesis, leading to a vicious cycle of inflammation and tissue destruction [6]. Recent studies have shown that, in addition to proinflammatory stimuli and growth factors, oxygen metabolism might be one of the most important driving forces behind angiogenesis in inflammatory arthritis [7]. In a setting of tissue hypoxia, oxygen-sensing propyl hydroxylases are able to hydroxylate the hypoxia-inducible factor (HIF) proteins, HIF-1 and HIF-2, ultimately resulting in gene transcription and production of proteins that stimulate expression of vascular endothelial growth factor (VEGF). The HIF-pathway is also actively involved in inflammation via interaction with the nuclear factor-κB (NF-κB) family of transcription factors and is able to stimulate adaptive and innate immune responses [8]. Of note, HIF proteins, VEGF and NF-κB signaling components are abundantly expressed in the inflamed synovial tissue in humans and in animal models of arthritis [9–12].

2.2. Growth factors

VEGF is the chief growth factor involved in angiogenesis, but it is certainly not the only one [13]. Basic fibroblast growth factor (bFGF) stimulates EC differentiation and proliferation [14]. Platelet derived growth factor (PDGF) promotes recruitment of pericytes to the angiogenic sprouting ECs and is involved in synovial angiogenesis [5]. VEGF family members are able to activate the angiopoietin (Ang)-Tie-2 (Ang-1 receptor) system, which are involved in angiogenesis, both in physiological and in pathological circumstances [5]. Ang-1 is mainly expressed on inactive vasculature, in contrast to Ang-2 that is only expressed when ECs are activated. Both VEGF and HIF are able to upregulate Ang-2, that can antagonize the effects of Ang-1 on Tie2. Ang-1-Tie-2 activation results in pericyte recruitment, EC migration and survival, while Ang-2-Tie-2 activation marks instability and angiogenic potential of the vasculature. During inflammation the balance is in favor of Ang-2-Tie-2, rendering ECs susceptible to inflammatory and proangiogenic cytokines [15,16]. This is well established in RA synovial inflammation, where the number of pericyte-lined blood vessels (as a consequence of Ang-1-Tie-2 activation) is lower than in healthy individuals or in osteoarthritis. Earlier research has demonstrated a direct interaction between tumour necrosis factor (TNF) and the Ang-Tie2 complex, as TNF can stimulate Tie2 expression and thus promote angiogenesis [17]. This association has subsequently been made more plausible by the significant reduction of Tie-2 mRNA and protein expression after anti-TNF treatment [18]. Interestingly, anti-TNF therapy in RA results in vessel stabilization and normalization [19]. Consequently, targeting TNF may also result in ameliorating chronic inflammatory diseases characterized by increased angiogenesis, including RA [4].

2.3. Integrins and endothelial progenitor cells

Another crucial part of neovascularization is tissue remodeling, in which extracellular matrix components, adhesion receptors and proteases are involved. Integrins, including $a_v\beta_3$ expressed on ECs, are involved in pathways regulating tissue remodeling, ultimately leading to activation of tissue degrading enzymes such as matrix metalloproteinases (MMP's) [20]. More recently, $CD34^+$ endothelial progenitor cells (EPCs) have been identified as key players in neovascularization as well. Bone marrow derived EPCs home to inflamed or damaged tissues, where they are able to form a new vessel wall [21]. Tissue resident EPCs in the lung may contribute even more to pulmonary endothelial repair than bone marrow derived EPCs [22].