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Review

The role of monocytes in ANCA-associated vasculitides

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ABSTRACT

The anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) are a heterogeneous group of diseases causing inflammation in small blood vessels and linked by the presence of circulating ANCA specific for proteinase 3 (PR3) or myeloperoxidase (MPO). These antigens are present both in the cytoplasmic granules and on the surface of neutrophils, and the effect of ANCA on neutrophil biology has been extensively studied. In contrast, less attention has been paid to the role of monocytes in AAV. These cells contain PR3 and MPO in lysosomes and can also express them at the cell surface. Monocytes respond to ANCA by producing pro-inflammatory and chemotactic cytokines, reactive-oxygen-species and by up-regulating CD14. Moreover, soluble and cell surface markers of monocyte activation are raised in AAV patients, suggesting an activated phenotype that may persist even during disease remission. The presence of monocyte-derived macrophages and giant cells within damaged renal and vascular tissue in AAV also attests to their role in pathogenesis. In particular, their presence in the tertiary lymphoid organ-like granulomas of AAV patients may generate an environment predisposed to maintaining autoimmunity. Here we discuss the evidence for a pathogenic role of monocytes in AAV, their role in granuloma formation and tissue damage, and their potential to both direct and maintain autoimmunity. ANCA-activation of monocytes may therefore provide an explanation for the relapsing–remitting course of disease and its links with infections. Monocytes may thus represent a promising target for the treatment of this group of life-threatening diseases.

Contents

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1. Introduction

1.1. ANCA-associated vasculitides

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) are a group of rare systemic autoimmune diseases that affect small or medium-sized blood vessels. The term embraces three different nosologic entities: granulomatosis with polyangiitis (GPA, previously Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, previously Churg-Strauss syndrome), all of which are characterized by necrotizing vasculitic lesions with scanty or absent immune deposits and, for GPA and EGPA, by the presence of tissue granulomas, typically in the upper and lower respiratory tract [1]. Whilst there is significant clinical overlap between these diseases, each also demonstrates distinct pathological profiles. Thus, GPA is characterized by disrupting lesions of the upper respiratory tract, lung involvement, and, in approximately 70% of patients, a pauci-immune necrotizing glomerulonephritis (GN) with extra-capillary proliferation [2]. In MPA, the kidney is affected in almost 100% of cases [2], with alveolar hemorrhage affecting one third of patients [3]. In contrast, in EGPA the kidney is not a main target of disease, whilst lung involvement is almost constant. EGPA is commonly associated with asthma and eosinophilia, with eosinophil tissue infiltration contributing to lesion pathogenesis [4].

Despite these clinical disparities, AAV patients are linked by their serological positivity for ANCA. These IgG antibodies target two main proteins in neutrophils and monocytes, namely proteinase 3 (PR3), a serine protease that on immunofluorescence assay shows a granular, cytoplasmic staining pattern (C-ANCA), and myeloperoxidase (MPO), which shows a peri-nuclear staining pattern (P-ANCA) [5]. PR3 seropositivity is typically found in GPA patients (at least in Caucasians) [6], whilst MPA and EGPA are predominantly associated with anti-MPO antibodies [5].

ANCA positivity is not completely diagnostic, and some patients clinically diagnosed with AAV are ANCA negative, while low levels of ANCA can be detected in some healthy individuals [7]. In EGPA only about 40% of patients have ANCA [2], typically those with renal involvement and more vasculitic features [4], compared to 75–95% of active GPA and MPA [2]. On the other hand, there is good scientific evidence to suggest that ANCA are closely linked to disease pathogenesis [8], and variations in ANCA titres are used as a rough tool for monitoring vasculitis activity in clinical practice. However, ANCA titres do not correlate well with disease activity in all reported series, and can be more useful in renal AAV [9].

1.2. Evidence for the pathogenicity of ANCA

Animal models of MPO AAV have been extremely useful and have demonstrated that, in mice and rats, IgG anti-MPO antibodies can cause necrotizing crescentic glomerulonephritis and systemic small vessel vasculitis [10,11]. Attempts to establish an animal model of GPA by the direct injection of anti-PR3 antibodies into mice have been more problematic, and have failed to induce any pathological changes, even after pre-treatment with LPS. Another approach using human-anti-PR3 antibodies in mice with a humanized immune system, generated mild pulmonary capillaritis and glomerulonephritis, but did not reproduce the GPA phenotype and, in particular, failed to induce granulomatous lesions [12].

In humans, PR3-ANCA may appear before sub-clinical and clinical GPA [13], and their production is also associated with the development of drug-induced systemic vasculitis [9]. There is a correlation between ANCA titre and specificity with disease activity and phenotype respectively. ANCA pathogenicity is also demonstrated by the clinical benefit observed in AAV with treatment strategies aimed at removing circulating antibodies, such as plasmapheresis [14], or at hindering antibody production by depleting B lymphocytes, eg. rituximab [15], and this approach forms a valuable part of AAV treatment today. Direct evidence for the pathogenic nature of ANCA in humans has also been provided by a sporadic case of transplacental MPO-ANCA transfer from mother to baby, with the development of pulmonary and kidney vasculitis in the newborn [8].

1.3. ANCA can activate neutrophils

The ANCA antigens MPO and PR3 are expressed in the azurophilic granules of neutrophils and the lysosomes of monocytes, but can also be expressed on the cell surface. Expression can be up-regulated, at least in vitro, by priming with tumor necrosis factor α (TNFα) [16,17]. TNFα-primed neutrophils respond to ANCA stimulation by releasing their granules and reactive-oxygen-species (ROS), producing pro-inflammatory cytokines and increasing the expression of adhesion molecules on their surface, and they have been shown to activate and damage endothelial cells [18]. Moreover, ANCA induce neutrophils to release DNA, histones and proteins into the extracellular space as neutrophil extracellular traps (NETs), a phenomenon known as NETosis. This is primarily a mechanism of defense against infections, but could also be implicated in tissue injury and in the onset of autoimmunity in AAV, through PR3 and MPO presentation by antigen presenting cells [19]. The response of neutrophils to ANCA and their role in AAV has been discussed in many excellent reviews [19]. For the purpose of this review we will concentrate on the role of monocytes in AAV, an area of research which, to date, has received significantly less attention.

2. Monocytes in inflammation and autoimmune diseases

As one of the cell types expressing ANCA antigens, monocytes are prime candidates for mediating many of the systemic inflammatory effects seen in AAV. Their potential role in disease pathogenesis is only beginning to be elucidated, but a number of key observations suggest that these cells play an important part in AAV. Monocytes represent approximately 10% of human leucocytes in the blood stream and originate from the bone marrow. Although they have traditionally been regarded as the progenitors of tissue macrophages, recent studies have revealed that, at least during homeostasis, many tissue-resident macrophage populations are maintained by a process of self-renewal [20]. In conditions of tissue insult, these cells undergo further rounds of proliferation, but their numbers are also boosted by the recruitment of monocytes from the circulation. Once recruited, monocytes can differentiate into macrophages and are able to mediate a wide range of immunologic processes [20].

Monocytes are now recognized as a heterogeneous population, and can be divided into three sub-types, according to the level of expression of two cell surface antigens, CD14 (the co-receptor for Toll-Like-Receptor (TLR)-4), and CD16 (FcγIIIR). Thus, monocytes are described as classical ($CD14^{++}/CD16^{-}$), intermediate ($CD14^{++}/CD16^{+}$), or non-classical ($CD14^{dim}/CD16^{+}$) [21]. The distinctions between these groups are not completely defined, and they may represent a maturation continuum rather than clear-cut divisions [22]. Nevertheless, these sub-types are backed-up by differences in phenotype, in cytokine production at homeostasis or in response to infections, in phagocytosis