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Mechanisms of Vessel Wall Necrosis in ANCA-associated Vasculitis: Beyond Autoantibodies

Haines Ren*

Department of Immunology & Vascular Biology, Karolinska Institute, Solna, Stockholm, Sweden

Introduction

Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis (AAV) comprises a group of small-vessel vasculitides including Granulomatosis with Polyangiitis (GPA), Microscopic Polyangiitis (MPA) and Eosinophilic Granulomatosis With Polyangiitis (EGPA). These syndromes are characterized by necrotizing inflammation of blood vessels and are commonly associated with circulating ANCAs directed against Myeloperoxidase (MPO) or Proteinase 3 (PR3), enzymes present in neutrophil azurophilic granules. Traditionally, ANCAs have been considered central to the pathogenesis of AAV, responsible for activating neutrophils and causing vascular injury. However, emerging evidence suggests that the pathophysiology of vessel wall necrosis in AAV extends far beyond the direct effects of ANCAs, involving a complex interplay of immune cells, inflammatory mediators, genetic susceptibility, complement activation, endothelial dysfunction and tissue-resident immune mechanisms. Understanding these multifactorial processes is essential to unravel the full spectrum of vascular injury in AAV and to develop more targeted therapeutic interventions [1].

Description

Although ANCAs play a crucial initiating role, their mere presence does not fully account for disease severity, organ specificity, or clinical heterogeneity. Studies have shown that ANCAs can exist in asymptomatic individuals without active vasculitis, indicating that additional factors are necessary to precipitate vessel wall injury. Neutrophils, when primed by inflammatory cytokines such as TNF-α or IL-1β, translocate MPO and PR3 to their cell surface, making them accessible to circulating ANCAs. The complement system, especially the alternative pathway, has emerged as a central player in the amplification of vascular damage in AAV. Activation of this pathway leads to generation of C3a and C5a, potent anaphylatoxins that promote leukocyte recruitment, vascular permeability and inflammation. C5a, in particular, acts as a priming agent for neutrophils and augments ANCA-induced activation. The C5a receptor (C5aR) on neutrophils creates a positive feedback loop, further fueling the inflammatory cascade. Animal models of AAV have demonstrated that blockade of C5aR can abrogate disease features even in the presence of ANCAs, highlighting the importance of complement-mediated amplification. The therapeutic efficacy of complement inhibitors, such as avacopan, in clinical trials lends further credence to this paradigm [2,3].

Another pivotal mechanism involves endothelial cell dysfunction and injury, which primes the vascular niche for necrosis. Activated neutrophils adhere to endothelial surfaces through upregulation of adhesion molecules such as ICAM-1 and VCAM-1. They release reactive oxygen species, elastases and proteases that compromise endothelial integrity. NETs and degranulation products also initiate direct cytotoxicity, leading to apoptosis or necrosis of endothelial cells. The loss of endothelial barrier function allows infiltration of immune cells into the vessel wall, setting the stage for full-thickness necrotizing inflammation. Moreover, endothelial injury leads to the exposure of normally sequestered antigens and Damage-Associated Molecular Patterns (DAMPs), perpetuating autoimmunity and inflammation. Beyond neutrophils, monocytes and macrophages play significant roles in orchestrating tissue destruction and remodeling in AAV. These cells infiltrate perivascular tissues and release matrix metalloproteinAses (MMPs), cytokines like IL-6 and IL-1β and procoagulant factors that exacerbate necrosis and thrombosis. They contribute to the formation of granulomatous inflammation, especially in GPA, where necrotizing granulomas can be found in the respiratory tract. Macrophages also produce TNF-α and IL-23, sustaining Th17 cell responses that drive chronic inflammation. Importantly, tissue-resident macrophages and dendritic cells may be involved in the early sensing of neutrophil-derived DAMPs, contributing to the local immune activation independent of systemic ANCA levels [4].

Finally, coagulation pathways and thrombosis are intimately linked to vessel wall necrosis in AAV. Endothelial injury activates tissue factor and exposes subendothelial collagen, triggering the coagulation cascade. Neutrophil-derived products such as NETs serve as a scaffold for thrombus formation. Concurrently, a reduction in anticoagulant mechanisms, including protein C and antithrombin, promotes a prothrombotic state. Microvascular thrombosis, in conjunction with inflammation, leads to ischemic injury and tissue necrosis. This thromboinflammatory axis is increasingly recognized as a therapeutic target, with potential roles for anticoagulants and antiplatelet agents in selected patients [5].

Conclusion

In summary, the mechanisms underlying vessel wall necrosis in ANCA-associated vasculitis extend significantly beyond the direct effects of ANCAs. Neutrophil activation, NET formation, complement amplification, endothelial injury, monocyte and T-cell-mediated inflammation, genetic susceptibility and prothrombotic pathways all converge to produce the characteristic necrotizing vasculitis seen in AAV. Understanding these multifaceted processes is crucial for developing targeted therapies that go beyond immunosuppression to modulate specific elements of the disease cascade. As insights into these mechanisms deepen, they promise to reshape diagnostic approaches, risk stratification and personalized treatment strategies for this complex and potentially life-threatening group of diseases.

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Conflict of Interest

None.

***Address for Correspondence:** Haines Ren, Department of Immunology & Vascular Biology, Karolinska Institute, Solna, Stockholm, Sweden, E-mail: ren.haines@karolinska.sw*

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