Novel territory for neutrophils in the pathogenesis of ANCA-associated vasculitides

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Summary of key findings of the article

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) are a group of autoimmune disorders characterized by necrotizing small-vessel vasculitis and frequently affecting the kidneys. The pathogenesis of AAV has not been fully elucidated, but neutrophils play an important role. Kessenbrock et al. start to uncover a novel role of neutrophils in the pathogenesis of AAV, namely, the formation of neutrophil extracellular traps (NETs) induced by ANCA [1]. NETs are chromatin fibres released by neutrophils. They can kill invading microbes extracellularly [2]. In sepsis, they can also stick to the endothelium and cause vascular damage [3]. Kessenbrock et al. found that ANCA-mediated activation of neutrophils induces the formation of NETs, which contain the ANCA-targeted autoantigens proteinase-3 (PR3) and myeloperoxidase (MPO). The typical components of NETs, that is DNA–histone complexes and neutrophil granule proteins, are located in close proximity to neutrophil infiltrates in affected glomeruli and in the interstitium. NETs were prominent in specimens with strong neutrophil infiltration, suggesting that NET formation occurs predominantly during active disease. These NETs may damage the glomeruli, so triggering vasculitis. Furthermore, the anti-microbial neutrophil protein LL37 is present on NETs and acts upon self-DNA in chromatins, which then activates plasmacytoid dendritic cells (pDC) and autoreactive B cells. In the presence of the DNA-complexed autoantigens PR3 and MPO on NETs, this promotes the autoimmune response to ANCA antigens in patients with AAV resulting in a vicious circle of tissue damage (Figure 1).

Review of the field

Although the pathogenesis of AAV has not been fully elucidated, many experimental data have shown that ANCA and neutrophils play a pivotal role.

Xiao et al. have shown that mice injected with mouse anti-MPO developed AAV [4], which is the most convincing argument for a pathogenetic role of ANCA. However, similar procedures have not resulted in a relevant animal model of PR3–ANCA-associated vasculitis [5,6]. Depletion of neutrophils in the recipient mice could ameliorate anti-MPO-antibody-induced glomerular vasculitic lesions, suggesting that neutrophil activation is involved in the pathogenesis of AAV [7]. In another model of vasculitis induced in rats by immunization with human MPO, Little et al. found that ANCAs induce leucocyte–vessel wall interaction and leucocyte-mediated vascular damage [8].

In vitro studies suggest that neutrophils stimulated by pro-inflammatory cytokines, such as tumour necrosis factor (TNF)-α or IL-18, translocate the target antigens of ANCA to their surface, thereby allowing binding by circulating autoantibodies. When exposed to ANCA IgG, neutrophils could undergo a respiratory burst and release free oxygen radicals and various proteases, which could play a direct pathogenic role in vasculitic lesion development [9]. Moreover, circulating levels of certain neutrophil degranulation products can be considered a useful biomarker for assessing disease activity of AAV [10]. The presence of membrane-bound PR3 (mPR3) is a prerequisite for ANCA binding and ANCA-mediated vessel damage. Neutrophils from patients with PR3–ANCA-associated vasculitis and some other chronic inflammatory diseases show higher levels of mPR3 expression than those from healthy controls [11,12], and the presence of a high proportion of mPR3-expressing neutrophils is associated with more frequent relapse of Wegener granulomatosis (WG) [13]. Whether MPO–ANCA-mediated neutrophil activation involves MPO translocation to the surface of primed neutrophils has yet to be resolved. ANCA could also affect the interaction between neutrophils
Novel territory for neutrophils in AAV

Fig. 1. Pathophysiological model of neutrophil extracellular traps (NETs) in ANCA-associated vasculitis. ANCA can induce TNF-α-primed neutrophils to produce NETs. The deposition of NETs may activate plasmacytoid dendritic cells that produce large amounts of interferon-α, driving the autoimmune response. In this context, NETs may activate autoreactive B cells to the production of ANCA, which results in a vicious circle of NET production that maintains the delivery of antigen–chromatin complexes to the immune system. Moreover, NETs may also stick to the endothelium and cause endothelial damage.

and endothelial cells. In the presence of pro-inflammatory cytokines, such as TNF-α, anti-MPO antibodies induced leucocyte adhesion and transmigration across the endothelium mediated by Fcγ receptors and β2 integrins in an in vitro system [14]. Administration of anti-MPO in vivo also led to the recruitment of leucocytes preferentially to the kidney and lung [8], sites that are often affected in human ANCA-associated vasculitis.

The study by Kessenbrock et al. [1] has added a novel piece to the role of neutrophils in the pathogenesis of AAV. Other than the well-known ANCA-mediated neutrophil respiratory burst, which results in the release of free oxygen radicals and various proteases, it reveals a new pathway of neutrophil-induced vasculitic lesion development in AAV. ANCA can lead TNF-α-primed neutrophils to produce NETs. Besides the damaging effects of NETs to the endothelium, deposition of NETs may activate plasmacytoid dendritic cells that produce large amounts of interferon-α, and so activating autoimmunity [15]. In this milieu, NETs, containing the targeted autoantigens PR3 and MPO, may activate autoreactive B cells to the production of ANCA, which in turn maintain the delivery of the antigen–chromatin complexes to the immune system via NET formation.

What is in it for the practising nephrologist

For practising nephrologists, three issues of clinical relevance could be deduced from this article. Firstly, since in renal histopathology NET formation occurs predominantly during active disease, NET might be considered a pathological biomarker of active disease in ANCA-associated glomerulonephritis. Secondly, as previous studies have shown that NETs can also be formed during infections [2,3], neutrophils might be more likely to form NETs in patients with AAV encountering an infection [16], further supporting a role for infection in disease activation (reviewed by Kallenberg et al. [17]). Thirdly, this study, by suggesting that NET-induced interferon-α production by pDC maintains the autoimmune response in AAV, opens the way for anti-interferon-α treatment in AAV.

Take home message

The discovery of NETs has extended the territory for neutrophils in the pathogenesis of ANCA-associated vasculitides and may open new ways of treatment.

Conflict of interest statement. None declared.

References

Immune complex formation in IgA nephropathy: a case of the ‘right’ antibodies in the ‘wrong’ place at the ‘wrong’ time?*

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Review of the field

One of the most striking findings in IgAN is an increase in the circulating levels of poorly galactosylated IgA1 O-glycoforms (Figure 1B). This has been observed in patient populations from North America, Europe and Asia, using a variety of techniques [1–3]. Importantly, two studies of IgA1 eluted from isolated glomeruli have shown that mesangial IgA1 is enriched with poorly galactosylated IgA1 O-glycoforms, strongly implicating the composition of IgA1 hinge region glycans in the mechanism of IgA1 deposition [4,5]. Novak and colleagues have also reported that these poorly galactosylated IgA1 O-glycoforms are predominantly found in circulating high molecular weight IgA-IC in IgAN [6]. IgA1 is one of the very few serum proteins to have O-linked sugars. The 18-amino acid hinge region of IgA1 can carry from zero to six O-glycan moieties, each of which is a relatively short and simple sugar chain (Figure 1A). An IgA1 monomer, consisting of two α1 heavy chains, therefore carries multiple closely adjacent O-linked sugars in the hinge region, providing a tight clustering of sialic acid (NeuNAc), galactose (Gal) and N-acetylgalactosamine.