

Commentary

***Staphylococcus aureus* and Wegener's granulomatosis**

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Abstract

Wegener's granulomatosis (WG) is a form of systemic vasculitis. It is characterized by granulomatous inflammation in the upper and lower airways, vasculitis and necrotizing glomerulonephritis, and is strongly associated with antineutrophil cytoplasmic antibodies against proteinase 3. Since the etiology of the disease is not clear, treatment, consisting of corticosteroids and immunosuppressives, is nonspecific and associated with severe side effects. Pinpointing the trigger(s) of the disease would highly improve treatment. Clinical evidence shows that an infectious agent, the bacterium *Staphylococcus aureus*, is a risk factor for disease relapse, suggesting its involvement in the pathogenesis of WG. Here we review both clinical and experimental data that either indicate or support a role for *S. aureus* in WG.

Keywords: autoimmunity, co-trimoxazole, *Staphylococcus aureus*, superantigens, Wegener's granulomatosis

Introduction

Wegener's granulomatosis (WG) is a form of systemic vasculitis that predominantly affects small- and medium-sized blood vessels. Frequently commencing with general, aspecific symptoms, the disease is frequently hallmarked by the presence of autoantibodies (antineutrophil cytoplasmic antibodies [ANCA]) [1,2] directed predominantly against the myeloid enzyme proteinase 3 (in 80% of WG patients) and, in a minority of cases, against myeloperoxidase [3,4]. Manifestations of granulomatous inflammation in the upper and lower airways, vasculitis and necrotizing glomerulonephritis characterize the classical clinical picture of WG [5].

In WG, respiratory tract infections frequently precede or accompany initial symptoms [6,7]. Moreover, treatment of WG limited to the airways with the antibiotic co-trimoxazole often leads to achievement of stable remission [8]

and prophylactic treatment with this drug reduced the incidence of disease relapses [9]. Although the beneficial effect of co-trimoxazole may also be explained by its immunosuppressive effect [10] and although a bacterial agent was originally not pinpointed [9,11], these findings were taken as indications that bacterial infections may be essentially implicated in the pathogenesis of WG. In search of a specific pathogenic bacterial agent we have shown that chronic nasal carriage of *Staphylococcus aureus* is approximately three times higher in WG patients than in healthy individuals [11], which may, at least in part, be due to hospitalization and/or immunosuppressive treatment. In contrast to healthy individuals who are frequently exposed to *S. aureus* (e.g. hospital personnel), but for whom carriage of this bacterium remains inconsequential, in WG patients *S. aureus* constitutes a risk factor for disease exacerbation [11]. This may possibly be due to a

dysregulated immune system and frequent nasal lesions present in these patients. Thus, these data ask for exploration of the potential mechanisms mediating staphylococcal pathogenicity. Recently obtained data supporting various pathogenic mechanisms related to *S. aureus* will be reviewed below.

Staphylococcal superantigens and WG

In vitro and in animal models *S. aureus* acts as a potent immunostimulator, effecting polyclonal proliferation of T- and B cells, secretion of immunoglobulins, and cytokine production. The main influence of *S. aureus* on immunocompetent cells is exerted by its exotoxins. Three classes of staphylococcal exotoxins have been described so far: the staphylococcal enterotoxins, exfoliative toxins, and the toxic-shock-syndrome-toxin-1 (TSST-1) [12]. Based on their exceptionally strong capacity to stimulate T cells in a nonantigen specific way, exotoxins were termed 'superantigens' (SAg) [13]. Moreover, staphylococcal protein A (SpA), a common component of the staphylococcal cell wall, has been recognized as a B-cell SAg [14].

T-cell SAg

T-cell SAg can simultaneously bind to MHC class II molecules outside the peptide-binding groove and to conserved regions of specific families of T-cell receptor V-beta chains (TCR V β) [13], independently of ligand specificity of T cells. As a consequence, virtually all T cells expressing a SAg-reactive TCR V β chain are stimulated to proliferate.

In the absence of more formal proof, exaggerated proliferation of SAg-specific T-cell subsets has been regarded as an indicator of SAg involvement in disease. Indeed, the presence of abnormal expansions of V β 2-expressing T cells during the active phase of Kawasaki disease (a form of large- to medium-size vessel vasculitis) together with the detection of TSST-1-producing *S. aureus* in this disease, strongly suggested a causal link between immune dysbalance, disease activity and SAg [15–18]. In WG, several groups have reported expansions of various T-cell subsets but they found no obvious preferential skewing of any particular V β subset [19,20]. Moreover, we were unable to demonstrate a link between staphylococcal SAg and peripheral blood T-cell expansions in patients with WG, since expansions of peripheral blood T-cell subsets were not associated with the simultaneous presence of SAg-positive *S. aureus* strains (Popa *et al.* manuscript in preparation).

These findings, however, do not exclude a pathophysiologic role for staphylococcal SAg in WG. In a study including 709 *S. aureus* strains (isolated from nasal cultures from 63 WG patients followed over a time period of 6 years) we screened for genes encoding the staphylococcal enterotoxin SAg SEA-E, exfoliative toxin A and TSST-1. We assessed the risk for development of a

disease relapse within three months from the appearance of one of these SAg. We again confirmed the association of the presence of *S. aureus* with a risk for relapse of WG. In addition, we found that the risk for relapse was modulated according to the presence and type of SAg, with *tsst-1* being associated with a higher risk for relapse (relative risk 14.5, 95% confidence interval 2.4–85.4). In WG, a pathogenic role for *S. aureus* in general, and the SAg TSST-1 in particular, thus cannot be excluded and the mechanisms of pathogenicity should be investigated further. An important goal for investigation will be the demonstration of SAg in the blood stream and lymphoid organs of WG patients.

B-cell SAg

The B-cell SAg, SpA, is a component of most clinical strains of *S. aureus*. The superantigenic activity of SpA is induced after binding to membrane immunoglobulin heavy chains encoded by V μ 3 family genes [14], which constitute 15–50% of total human IgM, IgG and IgA, and effects mitogenicity and induction of polyclonal antibody responses.

In WG, the possible implication of SpA can be conjectured from the amino acid sequence of WG-associated ANCA. Thus, the presence of ANCA with a V μ 3-encoded heavy chain would indicate potential binding capacity of SpA. Based on an anecdotic report of V μ 3-encoded ANCA [21] it is conceivable that, in the presence of SpA, ANCA-producing B cells could be induced to proliferate, resulting in an amplification of the pool of autoantibodies. The fact that carriage of *S. aureus* in patients with WG was associated with increased ANCA positivity during follow-up [11] supports this potential mechanism.

Staphylococcal acid phosphatase

In patients with *S. aureus*-associated glomerulonephritis, high levels of circulating immune complexes are present which decrease during antibiotic treatment [22,23]. These findings raise the possibility that specific staphylococcal molecules may be nephritogenic. One of these molecules is the cationic acid phosphatase, SAcP [24], which has a high affinity for the glomerular basement membrane and can induce glomerulonephritis when perfused in the kidney of naïve rats [25] or rats immunized with SAcP [26]. Based on these data, we hypothesized that, in WG, SAcP may act as a planted antigen by binding to glomerular basement membrane and vascular endothelium, thus initiating glomerulonephritis and vasculitis. We found that SAcP can bind to human umbilical vein endothelial cells and glomerular endothelial cells *in vitro* [27] in a charge-dependent manner, since binding can be blocked by the negatively charged heparin. Moreover, sera of WG patients were able to bind SAcP bound to endothelial cells *in vitro* [27]. Together with our finding that antibodies to SAcP are present in WG patients who are *S. aureus* carriers, these data suggest that, *in vivo*, the presence of

SACp in conjunction with anti-SACp antibodies may be nephritogenic and vasculitogenic in WG patients. Moreover, in the presence of SACp-anti-SACp immune complexes in the kidney, ANCA may be able to aggravate glomerulonephritis, as suggested by our studies on the effect of myeloperoxidase-specific autoantibodies on anti-glomerular-basement-membrane-mediated glomerular injury in the rat [28].

Conclusion

To date, despite clinical evidence suggesting that *S. aureus* may be implicated in the pathophysiology of WG, laboratory investigation of the possible mechanisms by which *S. aureus* is involved in WG is still scarce. Besides staphylococcal SAg and SACp, which have received some attention, other staphylococcal molecules, such as hemolysins, teichoic acid, proteoglycans and DNA-containing CpG motifs, to name only a few, are currently known as immunomodulators and certainly deserve further investigation in the context of vasculitis. Moreover, there are ample *in vitro* and *in vivo* data available on the effect of *S. aureus* on immunocompetent cells, such as B and T cells, monocytes and neutrophilic granulocytes, but also on other cell types, such as endothelial and epithelial cells. Keeping in mind that in WG, immune dysbalance can eventually lead to vascular damage, *S. aureus* as a trigger and mediator of various pathophysiologic mechanisms is a very attractive target for investigation.

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