

Editorial

Mast cells can be commandeered for staphylococcal pathogenicity in patients with chronic rhinosinusitis with nasal polyposis

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Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a prevalent condition and a substantial cause of morbidity. It frequently recurs after surgical resection and can be refractory to local and systemic glucocorticoid therapy. In Western countries CRSwNP is most typically associated with eosinophilic inflammation accompanied by epithelial hyperplasia and infiltration and activation of mast cells (MCs). Several factors, including functional alterations of the epithelium, allergic sensitization,¹ and genetic susceptibility,² have been implicated in the pathogenesis of the disease and its associated inflammation. It is likely that these and other factors explain the onset, persistence, and recalcitrance of the immunopathology leading to CRSwNP.

CRSwNP is linked to high rates of tissue colonization with *Staphylococcus aureus* potentially associated with reduced microbial diversity.³ Although *S aureus* does not spread beyond the sinus tissue in patients with CRSwNP, it can contribute to local immunopathogenesis through several potential mechanisms, including secretion of toxins that can serve as immune superantigens. One of these, staphylococcal enterotoxin B (SEB), has been implicated as a potentially important factor in the pathogenesis of CRSwNP.

SEB can directly stimulate T cells to produce type 2 cytokines (IL-5 and IL-13) that contribute to the development of eosinophilic inflammation.⁴ SEB can also alter mucosal barrier function through cytopathic effects on epithelial cells and can elicit local IgE formation.⁵ Although these studies are compatible with a direct pathogenic role for *Staphylococcus* in general and SEB in particular in patients with CRSwNP, the precise mechanisms remain to be proven.

MCs are powerful effector cells in both IgE-driven adaptive immunity and antimicrobial innate immunity. They abound in tissue from patients with CRSwNP, being distributed in both the intraepithelial and submucosal compartments and in association with mucus-producing glands.⁶ Activated MCs release proteases,

cytokines, chemokines, and lipid mediators of inflammation that are thought to contribute to the immunopathogenesis of CRSwNP, although the precise mechanisms that drive MC activation in this context are unknown. Consistent with their role in innate immunity, MCs are endowed with an array of pattern recognition receptors, permitting their activation in response to direct encounters with pathogens. Such encounters result in MC-dependent recruitment of granulocytes to the tissue, a feature that is essential in models of bacterial sepsis in the lung and in the peritoneal cavity.

No studies to date have directly addressed the potential role of MCs in functional responses to *S aureus* and its constituents in patients with CRSwNP. Given the prominence of MCs in patients with CRSwNP and the association of *S aureus* colonization with disease pathogenesis, it seems possible that an MC–*S aureus* interaction could be a component of the immunopathogenesis of CRSwNP.

In the current issue of the *Journal*, Hayes et al⁷ present strong evidence for a *S aureus*–MC interaction in CRSwNP pathogenesis and propose its potential consequences. After an earlier study in which these investigators observed viable *S aureus* within polyp MCs,⁸ they sought to explore the potential biological significance. Using explants of inferior turbinate tissues excised from patients with CRSwNP and nondiseased control subjects, the investigators demonstrated that MCs in turbinate tissue samples from patients with CRSwNP engulf *S aureus* (grown from a patient with CRSwNP) provided in the culture medium. As assessed by using immunohistochemistry, both the numbers of *S aureus*–containing MCs and overall numbers of MCs in the polyp epithelium increase in response to incubation of the tissues with *S aureus* in combination with concomitant exposure to exogenous SEB. The increases were paralleled by increases in the numbers of *S aureus*–positive and total MCs in the subepithelial area of the mucosa. The authors demonstrated a sharp increase in the numbers and percentages of MCs in the tissue, demonstrating extracellular tryptase and indicating degranulation in the samples treated with *S aureus* plus SEB. In a separate set of experiments, the authors showed that *S aureus* can enter the MC line HMC1, which is used as a surrogate for human MCs; can replicate intracellularly; and induce cell lysis. The authors concluded that intraepithelial MCs can encounter *S aureus* at the epithelial surface, transport them to the subepithelial compartment, and undergo cytolytic degranulation, thus promoting both replication of *S aureus* and release of proinflammatory MC products.⁷

The study by Hayes et al⁷ suggests that *S aureus*, once engulfed, are able to survive and replicate within MCs. This interaction and its potential consequences (cell activation, cytolysis, or both) are potentiated by SEB, at least in the *ex vivo* system used. The authors conclusively demonstrate that distribution of MCs in the inferior turbinate tissue changes in response to exposure to *S aureus* and SEB, presumably reflecting either

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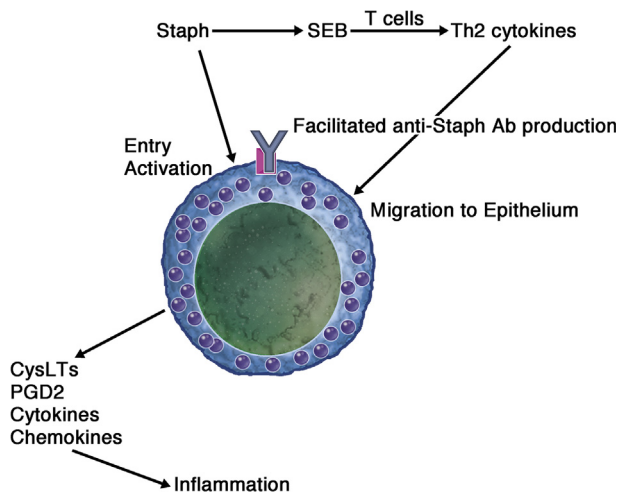


FIG 1. Potential mechanisms by which *Staphylococcus aureus* (Staph), through MCs, can augment inflammation in patients with CRSwNP. Ab, Antibody; CysLTs, cysteinyl leukotrienes; PGD₂, prostaglandin D₂.

redistribution of mature MCs from other parts of the tissue, induced *in situ* maturation from resident committed progenitors, or both. Release of granule contents and replicating organisms from the infected MCs into the tissue could promote mediator release through a cytolytic mechanism, promoting both inflammation and persistence of colonization.

The study by Haynes et al⁷ also leaves some key questions unanswered. The mechanisms that account for the *S aureus*-induced accumulation of MCs both within and beneath the epithelium are not clear. In experimental model systems the appearance of MCs in epithelial surfaces is typically associated with (and likely driven by) local expression of type 2 cytokines, particularly IL-4/IL-13, which provide signals essential for recruitment, proliferation, or both.⁹ Therefore the requirement for SEB to promote relocation of MCs could reflect its ability to induce type 2 cytokine production by lymphocytes that in turn instruct MCs to proliferate, migrate, or both (Fig 1).

Although the authors clearly demonstrate lysis of HMC1 cells after *S aureus* plus SEB exposure *in vitro*, it is not clear that this cytolytic mechanism also occurs in tissue MCs that have taken up

S aureus (the figure provided suggests a process of limited degranulation). It seems equally possible that encounters with *S aureus* in the context of SEB might promote a physiologic activation, resulting in an innate response. In some systems MC uptake of bacterial antigens is followed by their migration to regional lymph nodes, where the antigens can initiate an adaptive immune response.¹⁰ Because CRSwNP is associated with robust local production of IgE and other antibodies, some of which are directed against SEB, it is tempting to speculate that MCs can function to amplify local anti-*S aureus* immune responses that are both protective and pathogenic in patients with CRSwNP.

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