

CORRESPONDENCE

Staphylococcus aureus and primary lysis of eosinophils

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I read with interest the comprehensive report by Minai-Fleminger *et al.* [1] on eosinophil activation by *Staphylococcus aureus* (*S. aureus*). The authors focus on possible involvement of CD48 in eosinophil activation and forward the possibility that blocking CD48 is of therapeutic interest. One part of their study concerns so-called eosinophil extracellular DNA traps (EETs). They speculate that EETs have antibacterial functions. Accordingly, there is some promise in the authors' statement: 'blocking CD48 increased EETs formation'. This effect adds to the data suggesting that blocking CD48 attenuates eosinophil degranulation [1]. However, increased EETs and reduced eosinophil degranulation may not be fully compatible in vivo events.

Careful experiments by Ueki *et al.* [2] have now demonstrated that EETs emerge as a natural consequence of primary lysis of eosinophils [2, 3]. Distinct from apoptosis, primary lysis (regulated necrosis) of eosinophils involves chromatolysis and cell membrane disruption as typical features [2, 3]. As evidenced by electron microscopy analysis, the occurrence of primary lysis may dominate the diseased tissue scene with more than 80% of eosinophils exhibiting cytolysis (reviewed in 3). Primary eosinophil lysis causes spilling of nuclear and cytosolic DAMPs as well as extracellular tissue deposition of specific granules (free eosinophilic granules: FEGs). In turn, the FEGs release their toxic proteins and cytokines [2, 3]. Importantly, this ultimate mode of eosinophil activation agrees with in vivo observations in human diseased tissues in asthma and atopic dermatitis, the two conditions discussed by Minai-Fleminger *et al.* [1].

Primary lysis (determined as FEGs and released cationic proteins), rather than numbers of eosinophils,

has been demonstrated to associate with severity of asthma [4]. Primary lysis, but not eosinophil counts, has further associated with a major pathogenic feature of this disease, epithelial derangement [4, 5]. These observations suggest that a drug should probably not increase EETs in inflammatory eosinophilic diseases. Contrasting the nuclear DNA released by primary lysis-associated chromatolysis of eosinophils [2], the occurrence of 'mitochondrial DNA-containing traps', discussed by Minai-Fleminger *et al.* [1], may remain to be confirmed. For example, is there any in vivo evidence on occurrence of EETs without being associated with other signs of primary lysis such as FEGs and released cationic proteins? I don't think so. It would also be of interest to learn whether primary lysis of eosinophils occurred in the experiments where Minai-Fleminger *et al.* [1] detect EETs.

Interestingly, supernatants from cultured *S. aureus* clearly evoke primary lysis of human eosinophils [6]. This is a rapid cytolysis detectible within 15 min. The response appears specific to eosinophils because neutrophils are little affected [6]. *S. aureus*-induced primary lysis of eosinophils agrees with possible roles at exacerbations of eosinophilic diseases [3, 5]. *S. aureus*-derived alpha-haemolysin has been intriguingly implicated in the primary lysis effect; yet it induces apoptosis in addition to mimicking the primary lysis of eosinophils that is produced by *S. aureus* supernatants [6]. Irrespective of which cytolysin, superantigen and/or other exotoxins are causatively involved, primary lysis of eosinophils and its consequences need consideration in a discussion of *S. aureus*-eosinophil interactions.

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