学 位 論 文 の 要 旨

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主論文の題名

Staphylococcus aureus directly activates eosinophils via platelet-activating factor receptor

主論文の要旨

Colonization by *Staphylococcus aureus* (SA) is associated with exacerbation of atopic dermatitis (AD). Eosinophilic inflammation is a cardinal pathological feature of AD, but little is known about possible direct interaction between SA and eosinophils. PAF receptor (PAFR) appears to be involved in phagocytosis of Gram-positive bacteria by leukocytes. The objective of this study was to investigate if SA directly induces eosinophil effector functions via PAFR in the context of AD pathogenesis. Peripheral blood eosinophils were cultured with heat-killed SA, and eosinophil-derived neurotoxin (EDN) release, superoxide generation and adhesion to fibronectin-coated plates were measured. Cytokines released in the supernatants were quantified by multiplex bead immunoassays. FISH-labeled SA was incubated with eosinophils and visualized by confocal laser scanning microscopy. Platelet-activating factor receptor (PAFR)-blocking peptide and PAFR antagonists were tested for inhibitory effects on SA-induced reactions. SA induced EDN release and superoxide generation by eosinophils in a dose-dependent manner. IL-5 significantly enhanced SA-induced EDN release. IL-5 and IL-17A significantly enhanced SA-induced superoxide generation. SA enhanced eosinophil adhesion to fibronectin, which was blocked by anti-CD49d, and induced eosinophil secretion of various cytokines/chemokines (IL-2R, IL-9, TNF-R, IL-1ß, IL-17A, IP-10, TNF-α, PDGF-bb, VEGF and FGF-basic). After incubation of eosinophils with SA, FISH-labeled SA was visualized in the eosinophils' cytoplasm, indicating phagocytosis. A PAFR-blocking peptide and two PAFR antagonists completely inhibited those reactions. In conclusion, SA directly induced eosinophil activation via PAFR. Blockade of PAFR may be a novel therapeutic approach for AD colonized by SA.