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Anaphylatoxins in the pathogenesis of asthma

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Keywords

Anaphylatoxin C3a, asthma, C3a-receptor, guinea pig model of asthma

Context

The complement system forms a central core of the innate immune defence against a wide range of pathogens. Complement activation leads to a proteolytic cascade whereby the anaphylatoxins C3a and C5a are liberated as activation byproducts. By binding to their specific cell surface receptors C3aR and C5aR, respectively, they mediate bronchoconstriction, edema formation and leucocyte activation. An inbred guinea pig strain has been previously described as non-responsive to C3a, though the molecular nature of this defect remained obscure. Guinea pigs are very sensitive to airway antigen challenge and therefore represent a suitable animal model of allergic asthma. The authors used the C3a unresponsive strain to analyse the pathophysiological role of C3a in a model of experimental ovalbumin (OVA)-induced allergic asthma.

Significant findings

Molecular analysis of the guinea pig strain unresponsive to C3a revealed a point mutation within the coding region of the C3aR creating a premature stop-codon and thus effectively deleting one third of the receptor. To confirm the functional importance of the deletion of the distal one third in the C3aR protein, human HEK 293 cells were transiently transfected with the wild-type and the mutant genes. A minor expression of the mutant C3aR was found by flow cytometry, however, no binding of C3a to the truncated receptor could be detected. When challenged by OVA inhalation, sensitized animals with the defective gene for C3aR showed a significantly decreased bronchoconstriction in comparison to the corresponding wild-type strain. In contrast, no difference in IgG titres was observed between both groups and the eosinophil influx as well as the amount of eosinophil peroxidase in lung homogenates were equal in both strains.

Comments

Similar observations have been published very recently underscoring the importance of the complement-derived anaphylatoxins in the pathogenesis of asthma (see Additional information). One study found decreased bronchial hyperresponsiveness in C3aR knockout mice compared to wild-type mice, but also no effect on eosinophil influx. Furthermore, complement factor 5 has been identified as a susceptibility locus for experimental allergic asthma in mice. Taken together these three studies provide for the first time substantial evidence for complement factors modulating susceptibility to asthma. They strongly suggest that, in addition to well known acquired immune response mechanisms, the innate immune system and in particular complement are involved in the pathogenesis of asthma in animal models. If these results were confirmed in humans this pathway could provide a novel target for drug intervention strategies in human asthma.

Methods

Guinea pigs (wildtype and C3a unresponsive), transfection of HEK 293 cells, flow cytometry, C3a binding assays, whole-body phlethysmography, histochemistry, IgG ELISA, eosinophil peroxidase assay

Additional information

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