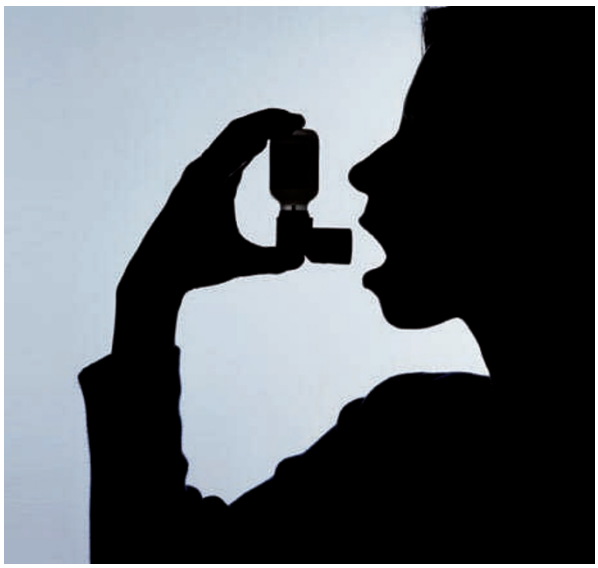
ASTHMA AND ALLERGY

A breathtaking chemokine

Allergic asthma is a chronic inflammatory lung disease that is thought to be driven by T helper 2 (T_H2) cells, but our understanding of the mechanisms responsible for T cell recruitment and activation in the allergic lung remains limited. A new study in *Nature Medicine* now shows that CX_3C-chemokine receptor 1 (CX_3CR1) and its ligand, CX_3C-chemokine ligand 1 (CX_3CL1), exacerbate allergic airway disease by promoting the survival of effector T cells in the inflamed lung.

Previous studies showed that the expression of CX_3CL1 increases in asthmatic lungs following allergen exposure; therefore, the authors explored the functions of the CX_3CL1–CX_3CR1 axis during allergic airway inflammation in mice.



They found that in various models of allergic airway inflammation, CX_3CR1-deficient mice developed less severe airway disease than wild-type controls. This was characterized by reduced airway hyperreactivity and mucus secretion, fewer inflammatory lung infiltrates and lower levels of T_H2-type cytokines. Wild-type mice treated with CX_3CR1-blocking antibodies or the CX_3CL1 antagonist FKN-AT before allergen challenge also developed less severe airway disease. Importantly, intranasal administration of FKN-AT was also effective therapeutically in mice with pre-established airway inflammation.

The authors showed that few T cells from naive mice expressed CX_3CR1, but up to one-third of T_H2 cells in the inflamed airways expressed this chemokine receptor. $CD4^+$ T cells purified from draining lymph nodes of allergen-sensitized CX_3CR1-deficient mice produced similar levels of T_H2-type cytokines to those from wild-type mice. However, only transfer of wild-type $CD4^+$ T cells and not CX_3CR1-deficient T cells could restore airway inflammation to wild-type levels in CX_3CR1-deficient mice. Furthermore, if wild-type allergen-specific T_H2 cells were treated with FKN-AT before transfer, they could no longer promote increased airway inflammation in CX_3CR1-deficient mice.

Competition assays revealed that CX_3CR1 was not necessary for the differentiation of T_H2 cells or for their recruitment to the inflamed lung following allergen challenge. However, compared with wild-type T cells, CX_3CR1-deficient T cells showed increased rates of apoptosis in the inflamed lung, and *in vitro*, CX_3CL1 was shown to promote the survival of wild-type but not CX_3CR1-deficient T_H2 cells. Expression of CX_3CR1 also increased the survival of allergen-specific T_H1 cells that were transferred to the inflamed lung, but CX_3CR1 did not increase T_H2 cell survival in resting or inflamed popliteal lymph nodes.

Finally, the authors showed that CX_3CR1-deficient T cells that were transfected with the anti-apoptotic protein B cell lymphoma 2 (BCL-2) were maintained in inflamed lungs at similar frequencies to wild-type cells. Furthermore, BCL-2-transfected CX_3CR1-deficient T_H2 cells could promote airway inflammation in CX_3CR1-deficient mice as effectively as wild-type T_H2 cells. These data highlight a previously unappreciated role for the CX_3CL1–CX_3CR1 axis in promoting allergic airway inflammation; the authors suggest that intranasal delivery of CX_3CL1 antagonists could be an effective new therapy for patients with corticosteroid-resistant asthma.

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ORIGINAL RESEARCH PAPER Mionnet, C. *et al.* CX3CR1 is required for airway inflammation by promoting T helper cell survival and maintenance in inflamed lung. *Nature Med.* **16**, 1305–1312 (2010)
FURTHER READING Lloyd, C. M. & Hessel, E. M. Functions of T cells in asthma: more than just T_H2 cells. *Nature Rev. Immunol.* **12**, 838–848 (2010)