CHEMOKINES

A class apart — uncovering a role for the C-chemokine

Chemokines are well known to have an important role in driving the migration and activation of cells of the immune system. Members of the chemokine family are classified on a structural basis into the CXC-, CC-, CX₃C- and C-chemokine subfamilies; to date, the function of the C-chemokine subfamily has remained a mystery. Now,

in a recently published study in *Immunity*, Dorner *et al.* reveal a role for XC-chemokine ligand 1 (XCL1; also known as lymphotactin), in promoting the cross-presentation of antigen to CD8⁺ T cells by CD8⁺ dendritic cells (DCs).

The authors began their study by examining the expression of XC-chemokine receptor 1 (XCR1), the only known C-chemokine receptor, by various leukocyte populations. Contrary to earlier findings, which reported widespread expression of XCR1 in the immune system, Dorner *et al.* used highly specific intron-spanning quantitative PCR to show that this chemokine receptor is selectively expressed by CD8⁺ DCs. Furthermore, only CD8⁺ DCs showed evidence of Ca²⁺ mobilization and specific chemotaxis in response to the XCR1 ligand, XCL1. By conducting histochemical analyses of genetically modified mice in which *Xcr1* was replaced with a LacZ reporter construct, the authors showed that the distribution of LacZ⁺ cells corresponded to the localization of CD8⁺ DCs in the spleen and lymph nodes. In addition, the authors used these XCR1-reporter mice to confirm that XCL1 functions exclusively through XCR1 to chemoattract CD8⁺ DCs.

Previous studies from the same research group had shown that activated CD8⁺ T cells are a source of XCL1. Therefore, the authors next examined the *in vivo* kinetics of XCL1 production by T cell receptor-transgenic CD8⁺ T cells, which had

been activated by cross-presentation following the targeting of their cognate antigen to CD8⁺ DCs. Notably, the peak production of XCL1 by activated CD8⁺ T cells occurred at 12 hours following antigen delivery, a time point at which prolonged interactions between CD8⁺ T cells and DCs are known to occur. This suggested that XCL1–XCR1 interactions could be involved in supporting crosstalk between CD8⁺ T cells and CD8⁺ DCs. The authors tested this hypothesis by targeting immunogenic antigen complexes to CD8⁺ DCs and comparing the specific activation of wild-type and XCL1-deficient CD8⁺ T cells *in vivo*. In support of a role for XCL1–XCR1 in aiding cross-presentation, XCL1-deficient CD8⁺ T cells were found at lower frequencies in the spleen and also showed lower cytotoxic activity than their wild-type counterparts.

A novel function for XCL1 and XCR1 in facilitating CD8⁺ DC cross-presentation ”

Overall, these findings point to a novel function for XCL1 and XCR1 in facilitating CD8⁺ DC cross-presentation of antigen to CD8⁺ T cells. Furthermore, the restricted expression of XCR1 suggests that targeting this receptor could promote antigen delivery to CD8⁺ DCs and thus serve as a new vaccination strategy.

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ORIGINAL RESEARCH PAPER

Dorner, B. G. *et al.* Selective expression of the chemokine receptor XCR1 on cross-presenting dendritic cells determines cooperation with CD8⁺ T cells. *Immunity* **31**, 823–833 (2009)

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