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IMMUNE REGULATION

Tripping a tissue-specific switch

Different organs of the body have tissue-specific mechanisms in place to regulate the threshold of immune responses and resolve inflammation. A recent study in *Nature Immunology* has now shown that a homeostatic loop involving CD200 and its receptor (CD200R) is an important regulator of steady-state immune homeostasis and inflammation in the airways.

Ligation of CD200R, which is expressed almost exclusively by myeloid cells, triggers negative regulatory pathways in the cells that express it. In this study, Snelgrove *et al.* first showed that alveolar macrophages that were isolated from normal mice have a higher basal expression level of CD200R than macrophages that were isolated from other tissues. The exposure of nonmucosal splenic macrophages to the immunosuppressive cytokines interleukin-10 (IL-10) or transforming growth factor-β was found to upregulate the expression of CD200R, thereby linking CD200R-mediated inhibition with other negative regulatory pathways. When cultured *in vitro* with $CD200^+$ epithelial cells, alveolar macrophages isolated from CD200R-deficient mice were found to produce increased amounts of the pro-inflammatory cytokines IL-6 and tumour-necrosis factor (TNF) compared with wild-type macrophages, in which the CD200–CD200R axis was intact. In addition, the lungs of mice that lacked CD200 expression were found to contain increased numbers of $CD11c^+$ macrophages that were hyperresponsive to activation *ex vivo*, which demonstrates the importance of CD200–CD200R interactions for maintaining the steady-state homeostasis of macrophages in the airways *in vivo*. Although many different cell types express CD200, including haematopoietic cells, the authors showed that the epithelial cells of the airway lumen are most likely to modulate the responses of $CD200R^+$ alveolar macrophages.

The same mechanisms that maintain immune homeostasis are commonly involved in the resolution of inflammation. Indeed, disabling CD200–CD200R interactions led to more severe immunopathology and increased mortality following influenza virus infection. Interestingly, heightened immunopathology in CD200-deficient mice corresponded with a lower viral load compared with that of wild-type mice, which indicates that the hyperresponsiveness of macrophages in CD200-deficient mice led to more efficient viral clearance but also to more severe 'collateral damage'. The authors went on to demonstrate that the treatment of wild-type mice with a CD200R agonist decreased influenza virus-induced immunopathology, which indicates that this regulatory pathway could be a relevant therapeutic target for inhibiting inflammation in the lung.

These findings provide evidence of a non-redundant role for CD200 in modulating the function of alveolar macrophages and illustrate a new tissue-specific means of immune modulation in the airways. Whether this mechanism of myeloid-cell restraint also operates in other mucosal tissues remains an open question.

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ORIGINAL RESEARCH PAPER Snelgrove, R. J. *et al.* A critical function for CD200 in lung immune homeostasis and the severity of influenza infection. *Nature Immunol.* 27 July 2008 (doi:10.1038/ni.1637)