IMMUNE TOLERANCE

Present and clear danger

Several studies have suggested a role for plasmacytoid dendritic cells (pDCs) in tolerogenic immune responses, but whether this is due to innate functions of pDCs or is a result of their antigen-presenting role has remained unclear. Irla *et al.* now show that pDCs can expand regulatory T (T_{Reg}) cells in an antigen-specific manner and ameliorate inflammation during myelin oligodendrocyte glycoprotein (MOG)-induced experimental autoimmune encephalomyelitis (EAE).

Initial experiments indicated that EAE development was exacerbated in mice when pDCs and B cells were unable to express MHC class II molecules, and additional work suggested that MHC class II-expressing pDCs, rather than B cells, were most important for alleviating inflammation. In further support of this, transfer of MOG peptide-loaded pDCs, but not MHC class II-deficient pDCs, ameliorated EAE disease in wild-type recipients.

Next, the authors examined whether pDCs affected T cell priming in the draining lymph nodes. During EAE, increased frequencies of MOG-specific interferon- γ - and interleukin-17-producing T cells were detected in lymph node cultures from mice with MHC class II-deficient pDCs. Histological analyses indicated that pDCs were recruited to the T cell zone of draining lymph nodes and could interact in an antigen-specific manner with $CD4^+$ T cells. Lack of MHC class II expression did not prevent pDCs from localizing to the T cell zones of draining lymph nodes during EAE, but resulted in pDCs establishing fewer antigen-specific contacts with $CD4^+$ T cells.

One possible explanation for these findings was that pDCs were promoting T_{Reg} cell functions in an antigen-specific manner. Indeed, during EAE induction the frequency of proliferating forkhead box P3 (FOXP3) $^+$ T_{Reg} cells increased in the draining lymph nodes of wild-type

mice, but remained constant in mice with MHC class II-deficient pDCs. Additional experiments suggested that pDCs promoted tolerogenic responses by expanding pre-existing natural T_{Reg} cell populations, rather than by inducing *de novo* FOXP3 expression.

Finally, the authors showed that the transfer of $CD4^+CD25^+$ T cells from mice with EAE could decrease EAE induction in recipient animals, but no protective effect was seen if $CD4^+CD25^+$ T cells were transferred from diseased mice with MHC class II-deficient pDCs. Taken together, these data show that pDCs can act as antigen-presenting cells during adaptive immune responses and promote tolerance by expanding T_{Reg} cell populations.

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ORIGINAL RESEARCH PAPER Irla, M. *et al.* MHC class II-restricted antigen presentation by plasmacytoid dendritic cells inhibits T cell-mediated autoimmunity. *J. Exp. Med.* 9 Aug 2010 (doi:10.1084/jem.20092627)