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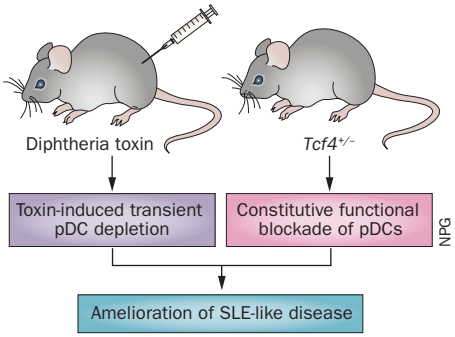
CONNECTIVE TISSUE DISEASES

Depleting plasmacytoid dendritic cells: a new therapeutic approach in SLE?

Plasmacytoid dendritic cells (pDCs), a distinct subtype of dendritic cells that specialize in the secretion of high levels of IFN-α and IFN-β in response to viral nucleic acids, have frequently been implicated in the pathogenesis of systemic lupus erythematosus (SLE). To date, however, the supporting evidence has been correlative and circumstantial. By depleting or inactivating pDCs in mouse models of the disease, two new studies in *The Journal of Experimental Medicine* now provide evidence of the direct involvement of pDCs in SLE pathogenesis and propose pDCs as potential therapeutic targets in this disease.

Sisirak *et al.* used haplodeficiency of the transcription factor Tcf4 to study the effect of constitutive functional blockade of pDCs in two different genetic models of SLE. "We previously identified Tcf4 as a 'master regulator' of pDC development, and used conditional *Tcf4* targeting to create mice that specifically lack pDCs," explains co-author Boris Reizis. Haplodeficient animals have only partial reduction and functional impairment of pDCs, which Reizis contends "better recapitulates the potential therapeutic targeting of pDCs, which is unlikely to be absolutely efficient."

In the *Tlr7* transgenic model, a monogenic model of SLE based on overexpression of Toll-like receptor 7 (Tlr7), mice haplodeficient for *Tcf4* showed improved survival and reduced splenomegaly, immune activation and autoreactivity-driven kidney inflammation in comparison with *Tcf4*-sufficient littermates. Conditional knockout of *Tcf4* using an *Itgax-cre* deleter strain confirmed that these effects were specific to pDCs. In the B6.*Sle1.Sle3* model, a polygenic model that more closely reflects the complex nature of human SLE, *Tgc4* haplodeficiency in essence abolished the key pathological features of disease, including autoantibody production and glomerulonephritis. "The results in the multigenic model were particularly striking and far exceeded our expectations," recounts Reizis. "The fact that even partial pDC ablation had such a profound effect attests to the fundamental role of pDCs in SLE pathogenesis."



The study by Sisirak *et al.* also revealed a relationship between pDC function and autoreactive B cells. Microarray expression analysis of splenocytes from B6.*Sle1.Sle3* mice showed that *Tcf4* haplodeficiency did not affect the SLE-associated gene-expression profile but several genes related to germinal centre B cells and plasma cell differentiation were downregulated; the germinal centre B-cell reaction observed in the spleens of B6.*Sle1.Sle3* mice was also abrogated by *Tcf4* haplodeficiency.

Rowland *et al.* took a different approach to studying the role of pDCs in SLE pathogenesis, using a novel transgenic mouse strain in which administration of diphtheria toxin (DT) specifically depletes pDCs *in vivo*. The new strain, termed BXSB.DTR, was generated by backcrossing trangenic mice expressing the DT receptor (DTR) under the control of *CLEC4C*, a highly specific human pDC promoter, to autoimmune-prone BXSB mice. The investigators demonstrated that administration of DT led, within 24 h, to the depletion of more than 95% of pDCs in BXSB mice that expressed the DTR (BXSB.DTR^{+}), thus enabling the direct study of the contribution of pDCs to lupus pathogenesis.

Early ablation of pDCs in BXSB.DTR^{+} mice from age 8 to 11 weeks, before the onset of disease, led to reduced symptoms at age 19 weeks in comparison with pDC-sufficient BXSB.DTR^{-} littermates. Expansion and activation of T cells, autoantibody production, glomerulonephritis and expression of IFN-inducible genes were all inhibited by depletion of pDCs. Notably, by age 19 weeks pDC populations were comparable in BXSB.DTR^{+} and BXSB.DTR^{-} mice, indicating that the effects of early, transient pDC depletion persist even when populations of these cells have recovered.

As co-authors Sarah Rowland and Marco Colonna explain, these results indicate pDCs are probably most important during the initiation of disease and could shape, or delay, the activation of other innate and adaptive immune cells that have a greater role during established disease. They furthermore suggest that early, short-term depletion of pDCs might represent an attractive therapeutic approach for the early treatment of SLE. "Based on our study, we would expect this treatment to prevent, or significantly delay, the progression to overt lupus," says Colonna.

Chak-Sing Lau of The University of Hong Kong, who was not involved with either study, agrees the results are interesting but sounds a note of caution. "Compared with the human counterpart, mouse pDCs have more ambiguous cell markers and TLR expressions, and thus they may have different responses and extended functions," he explains. "Also, most spontaneous lupus mouse models do not have a strong interferon signature association. We need more studies to better understand the characteristics of pDCs and hence their physiological function in mice."

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Original articles Sisirak, V. *et al.* Genetic evidence for the role of plasmacytoid dendritic cells in systemic lupus erythematosus. *J. Exp. Med.* doi:10.1084/jem.20132522 | Rowland, S. L. *et al.* Early, transient depletion of plasmacytoid dendritic cells ameliorates autoimmunity in a lupus model. *J. Exp. Med.* doi:10.1084/jem.20132620