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AUTOIMMUNITY

Increased PGD_2 signalling in lupus pathogenesis

In systemic lupus erythematosus (SLE), basophils amplify the synthesis of circulating autoreactive antibodies by accumulating in secondary lymphoid organs (SLOs). However, the mechanism by which basophils are recruited to SLOs has remained elusive. Now, Nicolas Charles and colleagues demonstrate in both humans and mice that prostaglandin D_2 (PGD_2) induces CXC-chemokine receptor 4 (CXCR4) externalization on basophils via autocrine signalling through both PGD_2 receptors, which drives their accumulation in SLOs.

The researchers found that basophil surface expression levels of PGD_2 receptors and CXCR4 are increased in patients with active SLE compared with healthy controls, and they subsequently investigated PGD_2 signalling in mouse models of SLE. "We show that repeated PGD_2 injections into lupus-prone mice before disease manifestation accelerated lupus nephritis development by inducing CXCR4-dependent basophil accumulation in SLOs, where they amplify autoantibody production," says Charles. Moreover, targeting of PGD_2 receptors using specific antagonists — which are in clinical use already, for example, for the treatment of allergic rhinitis and niacin-induced flushing — inhibits basophil redistribution to SLOs and dampens lupus-like disease in two distinct mouse models of SLE. "PGD_2 receptor antagonists may represent a new, safe and ready-to-use therapeutic modality in SLE by potentially preventing disease flares that are due to the basophil-dependent amplification loop of autoantibody production," explains Charles.

The researchers now plan to study whether the manifestation of lupus-like nephritis in lupus-prone mice can be prevented using PGD_2 receptor antagonists, an approach that aims to assess whether these antagonists may prevent the development of lupus nephritis in patients with SLE. "Furthermore, we plan to set up clinical trials and develop bispecific antagonists targeting both PGD_2 receptors," concludes Charles.

Jack M. Heintze

ORIGINAL ARTICLE Pellefigues, C. et al. Prostaglandin D_2 amplifies lupus disease through basophil accumulation in lymphoid organs. *Nat. Commun.* **9**, 725 (2018)

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