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TRANSPLANTATION

Pro-tolerogenic properties of erythropoietin

> EPO induces and stabilizes human and murine regulatory T cells

Erythropoietin (EPO) has immunomodulatory effects that promote tolerance to kidney allografts, say researchers. EPO is predominantly produced by renal pericapillary fibroblasts and is required for the differentiation of red blood cells in the bone marrow, but also has non-erythropoietic effects. In particular, reports that EPO can improve kidney transplant outcomes independent of anaemia correction in humans and mice have led to the hypothesis that it might have an immunosuppressive role.

Paolo Cravedi and colleagues previously showed that EPO directly inhibits conventional T cells by uncoupling IL-2 signalling. Now they report that EPO induces and stabilizes human and murine regulatory T (T_{reg}) cells *in vitro* and *in vivo* via a mechanism involving augmentation of IL-2Rγ signalling and stimulation of local TGFβ production.

In mouse transplant models, spontaneous kidney graft acceptance and induction of T_{reg} cells was abrogated by pharmacological inhibition of EPO production in the transplanted kidney. Moreover, treatment with recombinant EPO prolonged the survival of heart grafts and of EPO-deficient kidney grafts, suggesting that EPO is a crucial mediator of allograft tolerance in mice.

"Our findings extend the knowledge that EPO has immunoregulatory properties beyond erythropoiesis and provide proof-of-principle that these effects could be leveraged to improve outcomes in transplant recipients and in patients with autoimmune diseases," says Cravedi. "They also support the fascinating idea that EPO synthesis within the kidney has been evolutionarily conserved as a mechanism of peripheral immune tolerance."

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ORIGINAL ARTICLE Purroy, C. *et al.* Erythropoietin receptor-mediated molecular crosstalk promotes T cell immunoregulation and transplant survival. *J. Am. Soc. Nephrol.* http://dx.doi.org/10.1681/ASN.2016101100 (2017)