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TRANSPLANTATION

CXCL10 linked to poor outcomes

Early loss of graft function after islet transplantation could be prevented by therapeutically targeting 'isletokines' — cytokines produced by donor islet cells as opposed to those produced by classical host immune cells — according to new research.

"Islet transplantation is a promising cell-replacement therapy to prevent or reverse diabetes mellitus, but as with other organ and tissue transplants, islet grafts are subject to an acute, innate immune response within hours of infusion," explains study lead Michael Lawrence. "As up to 50% of the islet graft is lost during this period, new strategies are urgently required to improve patient outcomes and reduce donor tissue requirements."

Having previously shown that cytokine gene expression is activated in β cells purified from islets, the team investigated whether the β cells (rather than resident macrophages) were contributing to inflammation by producing cytokines that mediate or exacerbate the harmful immune response in the early stages of the transplantation process. "We found that the pro-inflammatory chemokine CXCL10 (also known as IP10) was markedly released by islets upon transplantation and that high levels of this protein correlated with poor transplant outcomes in a clinical islet transplant setting." Using a transgenic mouse model, the researchers went on to confirm that islet-derived CXCL10 contributed to loss of graft function. Moreover, loss of graft function could be prevented by supplementing donor islet infusions with a neutralizing CXCL10 monoclonal antibody.

Although targeting isletokines is a promising strategy to protect transplanted islets, Lawrence acknowledges that not all isletokines are likely to be innately harmful to the transplantation process. "We plan to test combinations of monoclonal antibodies that selectively target damaging isletokines while sparing ones that might be beneficial."

David Holmes

ORIGINAL ARTICLE Yoshimatsu, G. *et al.* Pancreatic beta cell-derived IP-10/CXCL10 isletokine mediates early loss of graft function in islet cell transplantation. *Diabetes* http://dx.doi.org/10.2337/db17-0578 (2017)