Islet-released mediators impact transplant outcome

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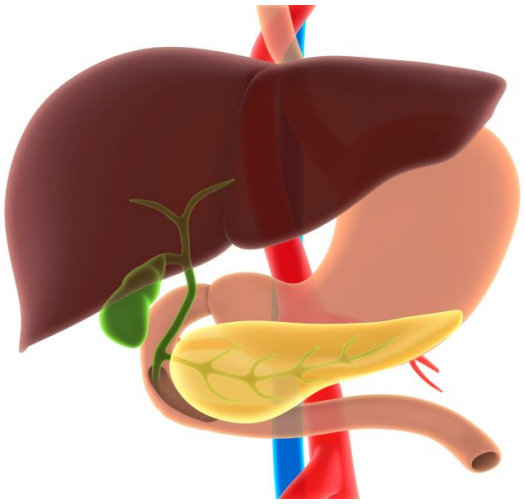

(HealthDay)—Cytokines and chemokines produced by pancreatic islets in response to inflammatory and metabolic stress include interferon gamma-induced protein 10 (IP-10/CXCL10), which is associated with poor islet transplant outcomes, according to a study published in the September issue of *Diabetes*.

Gumpei Yoshimatsu, M.D., Ph.D., from the Baylor Research Institute in Dallas, and colleagues examined the physiological role of "isletokines" produced by pancreatic islets in response to inflammatory and metabolic stress.

The researchers found that for patients undergoing islet transplants, islets released multiple inflammatory mediators within hours of infusion. Among the highest-released was IP-10; high levels correlated with poor islet transplant outcomes. The contribution of donor islet-specific expression of IP-10 to islet inflammation and loss of beta-cell function in islet grafts was confirmed in transgenic mouse studies. Treatment of donor islets and recipient mice with anti-IP-10 neutralizing monoclonal antibody blocked the effects of islet-derived IP-10. IP-10 gene induction was mediated by calcineurin-dependent NFAT signaling in pancreatic beta cells in response to oxidative or inflammatory stress. P38 and JNK MAP kinase (MAPK) activity were required for the sustained correlation of NFAT and p300 histone acetyltransferase with the IP-10 gene, which differentially regulated expression of IP-10 and subsequent release of protein.

"These findings elucidate an NFAT-MAPK signaling paradigm for induction of isletokine expression in beta-cells and reveal IP-10 as a primary therapeutic target to prevent beta-cell-induced inflammatory loss of graft function after islet cell transplantation," the authors write.

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More information: Abstract
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