Immune-repelling protein prolongs function, survival of human stem-cell-derived beta cells

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Encapsulating human stem-cell-derived beta cells in microcapsules made with a protein that repels key immune cells restored glucose metabolism in diabetic mice and protected the cells from immune system attack, preventing the buildup of inflammatory fibrotic tissue that has plagued previous trials of encapsulated beta cells. A team of Massachusetts General Hospital (MGH) investigators reports the results of their study in the *American Journal of Transplantation*.

"When islets are encapsulated in standard gel capsules, the inflammatory foreign body response causes a cellular overgrowth that 'suffocates' the encapsulated cells, leading to their failure," says lead author David Alagpulinsa, Ph.D., of the MGH Vaccine and Immunotherapy Center. "We found that mixing the immune-repellent protein CXCL12 into the capsule gel prevents this overgrowth from happening, prolonging the survival and function of the cells."

A 2015 study led by Vaccine and Immunotherapy Center director Mark Poznansky, MD, Ph.D. - senior author of the current report—described how CXCL12-containing capsules protected islet beta cells obtained from nondiabetic mice or pigs from immune system rejection after implantation into diabetic mice. The encapsulated islets restored long-term blood sugar control to the animals, and the presence of CXCL12 was shown to repel T cells associated with the rejection process while attracting regulatory T cells that can suppress the immune response at the site of transplantation.

The current study used insulin-producing beta cells generated from human pluripotent stem cells using a protocol developed by Harvard Stem Cell Institute investigators led by Douglas Melton, Ph.D., a co-author of the current study. These human SC-beta cells were encapsulated with either low or high levels of CXCL12 prior to being transplanted into diabetic mice. The animals did not receive immunosuppressive drugs throughout the study period.

Among mice receiving low-dose CXCL12 microcapsules, blood sugar levels became normal in two days, while animals receiving high-dose CXCL12 microcapsules did not reach normal glucose levels for an average of seven days. However, low-dose CXCL12 microcapsules either failed or were rejected by day 100 after transplantation, on average, while human SC-beta cells in high-dose CXCL12 microcapsules survived and continued fully functioning up to 154 days post-transplantation, when the experiment was terminated. Examination of microcapsules removed at that time found functional SC-beta cells and virtually no cellular overgrowth on capsules containing high CXCL12 doses. In contrast, low-dose CXCL12 capsules had significant overgrowth and no remaining functional SC-beta cells; the greatest amount of overgrowth was seen on capsules containing no CXCL12.

"High levels of CXCL12 supported beta cell function and protected against both the immune response and the foreign body response significantly longer than did the lower CXCL12 concentration," says Poznansky, an associate professor of Medicine at Harvard Medical School. "We previously explored the concentration dependence of this effect and showed how it can be related, in part, to differential activation of specific signaling pathways in immune and inflammatory cells by different levels of CXCL12 or similar proteins. Through the consistent support of the Juvenile Diabetes Research Foundation, we are currently exploring this mechanism and novel therapeutic approach in large animal models of type 1 diabetes."

Alagpulinsa adds, "Unlike the previous study, this study uses human beta cells, and all the elements are biocompatible, which should facilitate the development of a clinical version of this product. The stem-cell-derived beta cells can be generated in unlimited quantities from both individuals with and without type 1 diabetes, and CXCL12 is a protein that is normally produced in pancreatic islets in the body."

More information: David A. Alagpulinsa et al, Alginate-microencapsulation of human stem cell–derived β cells with CXCL 12 prolongs their survival and function in immunocompetent mice without systemic immunosuppression, *American Journal of Transplantation* (2019). DOI: 10.1111/ajt.15308

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