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Engineering cells and tissues with exogenous immunomodulatory proteins for the induction of tolerance to auto and alloantigen's

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Abstract

Type 1 diabetes (T1D) is a chronic autoimmune disease that targets the destruction of insulin-producing beta cells, leading to insulin deficiency and hyperglycemia. Exogenous insulin treatment is the standard of care for type 1 diabetic patients. However, daily insulin treatment not only negatively affect the quality of life, but is also often ineffective in preventing recurrent hyperglycemic episodes with consequent development of micro- and macroangiopathic lesions and the development and progression of chronic complications. Allogeneic islet transplantation has proven effective in improving metabolic control/quality of life and in preventing severe hypoglycemia in patients with T1D. However, broad application of clinical allogeneic islet transplantation is limited by immune rejection despite the chronic use of immunosuppression and its sequelae. Therefore, novel approaches that control rejection in the absence of chronic immunosuppression will have significant impact on the field of islet transplantation. Allogeneic islet rejection in diabetic individuals are primarily initiated and perpetuated by recipient T cells. Control of T cell responses has the potential to induce tolerance and treatment of T1D. T cells upregulate Fas receptor and become sensitive to Fas/FasL-mediated killing. Therefore, we have recently developed a novel form of FasL protein and displayed it on the surface of pancreatic islets in a rapid and efficient manner without any detrimental effect on the function of islets. Transplantation of FasL-engineered islets into allogeneic diabetic recipients resulted in tolerance and treatment of diabetes. Apoptosis of pathogenic T cells followed by a circuit of regulatory mechanisms were responsible for the induced tolerance. Therefore, the direct display of immunological ligands on the surface of islets serves as a rapid, efficient, and clinically applicable approach for immunomodulation with implications in clinical islet transplantation.

Biography

Dr. Shirwan is Dr. Michael and Joan Hamilton Endowed Chair in Autoimmune Disease, Professor of Microbiology and Immunology, Director of Molecular Immunomodulation Program at the Institute for Cellular Therapeutics. He conducted his graduate studies at the University of California in Santa Barbara, CA, and postdoctoral studies at California Institute of Technology in Pasadena, CA. He joined the University of Louisville in 1998 after holding academic appointments at various institutions in the United States. Dr. Shirwan's research focuses on the modulation of immune system for the treatment of immune-based diseases with particular focus on type 1 diabetes, transplantation, and vaccines. Dr. Shirwan is an inventor on 16 worldwide patents, widely published, lectured at numerous national/international conferences, served on study sections for various federal and non-profit funding agencies, and is on the Editorial Board of 16 scientific journals. He is member of several national and international societies and recipient of various awards.