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Engineering pancreatic islets with exogenous immunomodulatory proteins for the induction of allogeneic tolerance

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Abstract

Type I diabetes mellitus is an immune-mediated disease and characterized by loss of insulin producing beta cells in pancreas leading to insulin deficiency. Autoreactive T cells play a key role in beta-cell destruction during the disease progression. Selective elimination of autoreactive T cells and replacement of destructed islet cells are the ultimate goal for treatment of type 1 diabetes. Allogeneic islet transplantation may be considered as a therapeutic approach for the treatment of type 1 diabetes. However clinical application of this approach is limited by allograft rejection. The rejection is initiated by alloreactive T cells beside long-term use of immunosuppressive medications which are associated with a broad range of side effects. Therefore, novel approaches that control rejection in the absence of chronic immunosuppression will have significant impact on the field of islet transplantation. Activated T cells up-regulates Fas and FasL on their cell surface and upon re-activation with same antigen they become sensitive to FasL-mediated apoptosis. Therefore, selective elimination of alloreactive T cells will not only eliminate the need to use of immunosuppressive drugs but also protects allogeneic islet graft from rejection with intact immune response to unrelated antigens or pathogens. Towards this end, we have constructed and produced a novel form of FasL protein which is chimeric with streptavidin (SA-FasL). We have engineered pancreatic islets using biotin as a bridge to display SA-FasL chimeric protein on the surface of allogeneic islets in a rapid and efficient manner without any unfavorable effect on the function of islets. Transplantation of SA-FasL-engineered islets into diabetic allogeneic recipients resulted in tolerance and treatment of diabetes. 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

Esma S. Yolcu is Assistant Professor of Microbiology and Immunology, Director of Imaging Facility at the Institute for Cellular Therapeutics, and member of James Brown Cancer Center, University of Louisville, Louisville, KY. After receiving her Ph.D. from University of Ankara, Turkey, she joined the Institute for Cellular Therapeutics at the University of Louisville to pursue her postdoctoral training followed by promotion to a faculty position in the Department of Microbiology and Immunology. Dr. Yolcu's research focuses on the modulation of the immune system for the treatment of autoimmunity and graft rejection. Her work has been funded by various federal and nonfederal funding agencies, including NIH, American Heart Association, and American Diabetes Association. Dr. Yolcu is the recipient of several awards, member of various national and international societies, serves on Editorial Board of scientific journals, and published over 67 peer-reviewed papers, abstracts, and review articles in high ranking journals, such as Immunity, Circulation, and Journal of Immunology.