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Negative vaccination with donor splenocytes engineered with FasL as an effective mean of inducing transplantation tolerance

Esma S. Yolcu

University of Louisville, *USA*

Abstract

FasL is a member of TNF ligand superfamily and plays an essential role in immune homeostasis. This critical role played by FasL renders this molecule as an attractive target for immunomodulation to achieve tolerance to auto and transplantation antigens. Immunomodulation of immune system with genetically modified cells expressing FasL was shown to induce tolerance to alloantigens. However, genetic modification of primary cells in a rapid, efficient, and clinically applicable manner proved challenging. Therefore, we developed a protein display technology that allows efficient engineering of donor splenocytes with a novel form of FasL protein (SA-FasL) and tested the efficacy of engineered cells as a negative vaccination strategy to induce tolerance to cardiac allografts. Intraperitoneal injection of ACI rats with WF splenocytes displaying SA-FasL on their surface resulted in tolerance to donor, but not F344 third party, cardiac allografts. Tolerance was associated with apoptosis of donor reactive T effector cells and induction/expansion of CD4+CD25+FoxP3+ T regulatory (Treg) cells. Treg cells played a critical role in the observed tolerance as adoptive transfer of sorted Treg cells from long-term graft recipients into naïve unmanipulated ACI rats resulted in indefinite survival of secondary WF grafts. Immunomodulation with allogeneic cells rapidly and efficiently engineered to display on their surface SA-FasL protein provides an effective and clinically applicable means of cell-based therapy with potential applications to regenerative medicine, transplantation, and autoimmunity.

Biography

Esma S. Yolcu is Assistant Professor of Microbiology and Immunology and the Director of Imaging Facility at the Institute for Cellular Therapeutics and member of James Brown Cancer Center, University of Louisville, Louisville, KY. Dr. Yolcu received her Ph.D. degree from University of Ankara, Ankara, Turkey and joined the University Of Louisville School Of Medicine in Louisville, KY, to pursue her postdoctoral training. Dr. Yolcu's research focuses on novel immunomodulatory approaches for the induction of tolerance to auto and alloantigens for the purpose of treating rejection and autoimmunty. 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, Blood, and the Journal of Immunology.