

Systemic immunomodulation with SA-FasL-engineered donor splenocytes as an effective means of inducing tolerance to cardiac allografts

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Apoptosis induced by the engagement of FasL with Fas receptor on the surface of lymphocytes is an important immune homeostatic mechanism that ensures tolerance to self-antigens under normal physiological conditions. As such, FasL has been extensively tested as a tolerogenic molecule using gene therapy in settings of autoimmunity and transplantation with conflicting outcomes. Although the mechanistic basis of these contradictory observations is largely unknown, the use of wild type FasL and the means by which the gene was expressed may provide an explanation. To overcome these complications, we recently generated a chimeric FasL protein with streptavidin (SA-FasL) having potent apoptotic activity and displayed this molecule effectively and rapidly on biotinylated biological membranes for immunomodulation. In the present study, we displayed SA-FasL on the surface of allogeneic splenocytes and used the engineered cells for systemic immunomodulation of heart graft recipients. This protocol was effective in inducing tolerance to cardiac allografts in a significant percentage of graft recipients. To improve the efficacy of this tolerance protocol, we used rapamycin as a clinically approved immunosuppression to control initial immune reactions as well as to synergize with SA-FasL for tolerance induction. Immunomodulation with SA-FasL-engineered splenocytes under the cover of a short course of rapamycin resulted in 100% graft survival. Taken together, these results establish immunomodulation with SA-FasL-engineered donor splenocytes under transient cover of rapamycin as an effective regimen in preventing cardiac allograft rejection in rodents with important implications in the field of solid organ transplantation.

Biography

Haval Shirwan is Dr Michael and Joan Hamilton Endowed Chair in Autoimmune Disease, Professor of Microbiology and Immunology and the Director of the 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 development of vaccines against infections and cancer. Dr Shirwan is widely lectured at various national/international conferences, served on various federal and nonprofit funding agencies and is on the Editorial Board of nine scientific journals. He is a member of several national and international societies and recipient of various awards.

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