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Establishment of allogeneic mixed chimerism using bone marrow cells engineered to display on their surface an exogenous FasL protein with potent apoptotic activity

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Bone marrow transplantation (BMT) as a source of hematopoietic stem cells is perceived as a powerful therapeutic regimen that can potentially treat a variety of inherited and acquired diseases. BMT leading to mixed allogeneic hematopoietic chimerism (MAC) can be used as an immunomodulatory approach to induce tolerance to auto-, allo-, and xeno-antigens for the treatment of autoimmune disorders and prevention of foreign graft rejection. Mixed chimeras are tolerant to both donor and host antigens since i) stem cells in the donor BM give rise to immune cells, such as lymphocytes, that are "educated" in the host immune environment for nonresponsiveness to the host antigens and ii) macrophages and dendritic cells arising from the donor bone marrow serve as antigen-presenting cells in the thymus to eliminate donor reactive host lymphocytes. However, BMT requires conditioning of recipients for effective engraftment and conditioning regimens used to establish MAHC in the clinic are often toxic. The development of nontoxic and effective approaches to induce MAHC in the clinic, therefore, is of great scientific and therapeutic pursuit. Towards this end, we have recently developed a novel approach, called ProtEx™, that allows us effective and rapid engineering of bone marrow cells (BMCs) to display on their surface a modified apoptotic form of FasL protein. Transplantation of these "engineered" cells into allogeneic hosts was effective in establishing MAHC in recipients with minimal conditioning and resulted in durable tolerance to donor grafts. Furthermore, this approach resulted in prevention of graft-vs-host disease (GVHD), a major complication of BMT, by effectively eliminating mature T cells via apoptosis in the transplanted BMCs. Engineering of total BMCs with exogenous immunomodulatory proteins serves as an effective, rapid, and clinically applicable approach for the establishment of MAHC with significant clinical transplantation implications.

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. Yolcu received her Ph.D. degree from the University of Ankara, Ankara, Turkey. She joined the University Of Louisville School Of Medicine to pursue her postdoctoral training. Yolcu is the recipient of several awards, member of various national and international societies, serves on Editorial Boards, and published over 67 peer-reviewed papers, abstracts, and review articles in high ranking journals, such as Immunity, Circulation, and Journal of Immunology.

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