Conference Proceedings

2nd World conference on Ageing and Gerontology

July 14-15, 2025 | Rome, Italy

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Aging-associated changes in lymph node stromal cells regulate transplant immunity

The stromal environment of the aged lymph node (LN), which is central to maintaining transplant immunity has not received significant attention in aged transplant immunity. Aging-associated alterations in stromal cells could be the most important factors that mediate decreased immunity. Our studies have shown that aged transplant recipients are resistant to the effect of anti-CD40L costimulatory blockade, and that aged LNs contain an inflamed microenvironment. Aged LNs contain a high density of extracellular matrix (ECM) and senescent FRCs. We isolated FRCs from LNs of Young and Aged C57BL/6 (B/6) mice. There was a significantly lower expression of suppressive IDO and iNOS in FRCs from Aged LNs compared to Young LNs, while a significantly higher expression of pro-inflammatory IL-6, TGF-b, INF-g and TNF-a. Heart allografts from BALB/c mice were transplanted into Young and Aged B/6 recipients, we found that aged recipients were resistant to the effect of anti-CD40L on prolonging the heart allograft survival. To generate aged FRC, etoposide was used to induce DNA damage and mimic aging-associated FRC senescence. We assessed the effects of intravenous administration of aged FRCs on stromal changes in the LNs and transplant outcomes of young recipients. Notably, treatment of young mice with ex vivo expanded induced aged FRCs abrogated the long-term effect of anti-CD40L treatment. We also noticed an FRCs subtype with LTbR^{+} expressed significantly higher expression of immunoregulatory PD-L1, IDO, iNOS as well as Arg1, IL-10 and TIM3. We then tested the effect of the LTbR agonist on transplant outcome, and we found that the LTbR agonist not only prolonged the heart allograft survival but also ameliorated cardiac allograft vasculopathy. These data demonstrate that LN FRC status is critical in regulating transplant tolerance. We establish the efficacy and feasibility of a therapeutic approach to the LTbR agonist to promote transplant survival by remodeling the LN microenvironment.

Keywords: Aging, stromal cells, Transplant immunity, lymph node, FRC, costimulatory blockade

Biography

My principal effort at Brigham and Women's Hospital and Harvard Medical School is in basic research, with a focus on transplantation immunobiology. As a surgeon-scientist, I aim to be at the forefront in the development of scientific advances that translate into improved health of transplant recipients. I have come to appreciate the need for strategies to minimize the toxicity of immunosuppression while improving its efficacy. I am particularly interested in developing of targeted immunomodulatory agents in solid organ transplantation. We sought to design strategies that targeted lymph node by applying nanotechnology.

ISBN: 978-1-917892-07-0

doi.org/10.51219/URForum.2025.Jing-Zhao