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CXCR3 Regulates CD4+ T Cell Cardiotropism and Maladaptive Cardiac Remodeling Through Mechanisms Involving ICAM1-Mediated Adhesion

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Left ventricular (LV) dysfunction and heart failure (HF) progression are associated in humans and mice with increased levels of circulating chemokines CXCL9 and CXCL10, and increased frequency of T cells expressing their receptor CXCR3. CXCR3 signaling upon chemokine recognition in T cells results in integrin activation and T cell adhesion to endothelial cells. We recently reported that the integrin ligand ICAM1 is significantly upregulated in the LV endothelium of mice with HF, and that *Icam1*$^{-/-}$ mice have decreased LV T cell recruitment and HF. Additionally, we reported that Th1 cells, which highly express CXCR3, are major drivers of maladaptive cardiac remodeling. Thus, we hypothesized that chemokine signaling through CXCR3 regulates integrin dependent adhesion to ICAM1 and contributes to Th1 cell recruitment to the LV and HF. We used the mouse model of Transverse Aortic Constriction (TAC) to induce LV remodeling and HF in WT and CXCR3$^{-/-}$ mice, and *in vitro* adhesion studies to evaluate WT and CXCR3$^{-/-}$ Th1 cell chemokine-mediated integrin-dependent adhesion to ICAM1. WT mice expressed increased levels of CXCL9 and CXCL10 in the LV during the course of TAC. Activation of CD4+ T cells occurred in the mediastinal lymph nodes (mLN), which drain the heart, of both WT and CXCR3$^{-/-}$ mice; however T cell infiltration in the LV only occurred in WT but not CXCR3$^{-/-}$ mice, and heart infiltrated T cells expressed high levels of CXCR3 and the ligand of ICAM-1, LFA1. Moreover, CXCR3$^{-/-}$ TAC mice did not develop cardiac fibrosis, hypertrophy or inflammation and had preserved systolic and diastolic function as compared to WT TAC mice. Mechanistically, both CXCL9 and CXCL10 induced Th1 cell adhesion to ICAM1 under shear flow conditions *in vitro* in a CXCR3-dependent manner. Our data support a CXCL9/CXCL10-CXCR3-ICAM1 axis regulating CD4+ T cell LV recruitment, and may represent a novel pathway potentially targetable in non-ischemic HF.

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