ABSTRACT FORM DEADLINE: DECEMBER 1, 2018

Association of University Cardiologists

January 23-25, 2019

Grand Beach Hotel, Surfside Surfside Beach, Miami, FL

Macrophages as Potential Therapeutic Targets in Pressure-Overload Heart Failure

Sumanth D. Prabhu, MD; Bindiya Patel, PhD; M. Ameen Ismahil, PhD; Tariq Hamid, PhD; Shyam S. Bansal, PhD; Gregg Rokosh, PhD; Matthias Mack, MD*

University of Alabama at Birmingham, Birmingham, AL, and *University Hospital Regensburg, Regensburg, Germany

Background. Although monocytes and macrophages are known key contributors to left ventricular (LV) remodeling and heart failure (HF) after myocardial infarction, their role in the pathogenesis of HF after pressure-overload is unclear. Our objective was to define the temporal profile of cardiac immune cells during the development of pressure-overload remodeling, and to test the hypothesis that monocyte-derived infiltrating macrophages are required for the progression of LV remodeling, chronic inflammation, and the transition to HF following pressure-overload.

Methods and Results. C57BL/6 mice were subjected to transverse aortic constriction (TAC) or sham operation, and assessed for alterations in mononuclear phagocytes (MPs). Ly6C^{hi} monocyte-derived macrophages were identified by the expression of C-C chemokine receptor 2 (CCR2). As compared with sham, TAC mice exhibited robust expansion of circulating LyC6^{hi}CCR2^{+} monocytes, and pro-inflammatory CD206^{-} and CCR2^{+} cardiac macrophages early (1 w) after pressure-overload, along with increased cardiac expression of CCL2, CCL7, and CCL12 (chemokine ligands for CCR2), during the compensated hypertrophy phase, with subsequent decline during chronic HF. Classical dendritic cells (DCs) were expanded in the heart in a biphasic manner, with peaks both early, analogous to macrophages, and late (8 w), during established HF. There was no significant expansion of circulating DCs, or Ly6C^{+} monocytes and DCs in the spleen. Periodic systemic and non-targeted MP depletion from 2 to 16 w after TAC in macrophage Fas-induced apoptosis (MaFIA) transgenic mice did not alter cardiac remodeling progression, nor did splenectomy in mice with established HF after TAC. In contrast, early and circumscribed CCR2 inhibition, using either a CCR2 small molecule antagonist or MC21, a specific anti-CCR2 antibody, ameliorated pathological LV remodeling and dysfunction, hypertrophy, and interstitial fibrosis in mice 4 w post-TAC. Furthermore, MC21 suppressed late cardiac CD4^{+} T-cell recruitment and T-cell expansion in heart-draining mediastinal lymph nodes.

Conclusions. Mononuclear phagocytes populations expand in a phasic manner in the heart during pressure-overload. CCR2^{+} macrophages are recruited to the heart in a demarcated fashion early during compensated hypertrophy, and this early recruitment is required for long-term pathological remodeling, subsequent cardiac T-cell expansion, and the transition to failure. Hence, CCR2^{+} monocytes/macrophages may represent key targets for immunomodulation to delay or prevent HF in pressure-overload states.

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