Abstract: P498

Myocarditis-induced heart failure is caused by the cytokine midkine mediating neutrophil recruitment and NET formation

Authors:
L Weckbach¹, U Grabmaier², A Uhl¹, A Zehrer², R Pick², K Klingel³, U Eriksson⁴, S Massberg¹, S Brunner¹, B Walzog², ¹University Hospital of Munich, Medizinische Klinik und Poliklinik I - Munich - Germany, ²Ludwig-Maximilians University, Walter Brendel Center of Experimental Medicine - Munich - Germany, ³Eberhard-Karls-Universitätsklinikum Tübingen, Kardiopathologie, Institut für Pathologie und Neuropathologie - Tübingen - Germany, ⁴University of Zurich, Cardioimmunology, Center of Molecular Cardiology - Zurich - Switzerland,

Topic(s):
Basic Science - Cardiac Diseases:Heart Failure

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S121

Funding Acknowledgements:
Sonderforschungsbereich 914 (DFG), FöFoLe program (LMU), Deutsche Gesellschaft für Kardiologie, LMUexcellent (LMU)

Background: Myocarditis evolving into heart failure belongs to the most common causes for heart transplantation in young adults. While the pathogenesis of myocarditis has been studied for decades, the contribution of the innate immune system remains incompletely understood.

Purpose: To study the role of Neutrophil Extracellular Traps (NETs) and the cytokine MK for cardiac inflammation during myocarditis.

Methods: Sections of endomyocardial biopsies from patients with myocarditis or from mice after induction of Experimental Autoimmune Myocarditis (EAM) were stained for NETs. Cardiac inflammation was assessed in mice with EAM after blocking NETs or the cytokine midkine (MK). Hoxb8-SCF cell-derived neutrophils generated from mice lacking the MK receptor Low Density Lipoprotein Receptor-Related Protein 1 (LRP1) or control animals were used to study the role of the MK-LRP1 axis during neutrophil recruitment steps in microflow chambers in vitro. NET formation of isolated neutrophils was investigated in the presence of MK.

Results: Here, we report for the first time the presence of NETs in cardiac tissue of patients and mice with myocarditis. Inhibition of NET formation in EAM substantially reduced cardiac leukocyte infiltration as well as compensatory cardiac hypertrophy in the acute phase of the disease. Inhibition of the cytokine MK attenuated NET formation as well as leukocyte infiltration, reduced fibrosis and preserved systolic function during EAM. Using Hoxb8-SCF cell-derived neutrophils we demonstrated that LRP1 represents the central receptor triggering MK-induced neutrophil recruitment. Moreover, mice lacking LRP1 on blood cells revealed reduced immune cell adhesion and extravasation, suggesting that MK mediates PMN recruitment and activation via LRP1. Furthermore, MK directly triggered NET formation via LRP1 in primary murine and human as well as Hoxb8-SCF cell-derived neutrophils.

Conclusion: In summary, NETosis substantially contributes to the pathogenesis of myocarditis and MK drives cardiac inflammation by mediating NETosis and neutrophil trafficking. Targeting MK as well as NETs represents a novel therapeutic strategy for the treatment of myocarditis.