Infinite Science Publishing

First results of the prospective ETiCS-study: acute (microbial-associated) inflammation rather than (infarction-associated) myocardial ischemia triggers the development of cardiac GPCR autoantibodies

Valérie Boivin-Jahns[a], Chistina Zechmeister[a], Claudia Schuetz[a], Niklas Beyersdorf[b], Stefan Stoerk[c], Roland Jahns[d,*]

[a] *Institute of Pharmacology and Toxicology, University Wuerzburg, Germany*
[b] *Institute of Immunobiology, University Wuerzburg, Germany*
[c] *Comprehensive Heart Failure Center, University Hospital Wuerzburg, Germany*
[d] *Interdisciplinary Bank of Bio-materials and Data Wuerzburg , University and University Hospital Wuerzburg, Germany*
[*] *Corresponding author, email: Jahns_r@ukw.de*

Introduction: Heart failure (HF) is the leading cause of mortality and morbidity in developed countries. In the past decade evidence for a clinical relevance of GPCR-autoimmunity in human HF has substantially increased. Stimulating autoantibodies targeting the second extracellular loop (ECII) of the cardiac beta1-adrenoceptor (beta1-aabs) have been claimed to be involved in the pathogenesis of HF and to increase the risk of cardio-vascular death by three-fold. Still, the events triggering the formation of beta1-aabs and their impact on HF-progression are unknown.

Methods: Based on the rationale that presentation of beta1-adrenoceptors and other cardiac membrane antigens following inflammation or necrosis may induce the formation of beta1-aabs, in total 13 University Hospitals (12 in Germany, 1 in Serbia) prospectively recruited 226 patients with a first acute myocardial infarction (FAMI), and 140 pts with acute (biopsy- or cMRI-proven) myocarditis (AMitis) into the Etiology, Titer-Course and effect on Survival of cardiac autoantibodies-study (ETiCS-study). At baseline (BL) and three follow-up visits (Fup1-3) blood was sampled to follow the time-course of various GPCR-aabs. Beta1-aabs were assessed by using Dynabeads® M-270-Epoxy coated with increasing amounts of beta1-ECII-peptides (2.5-100 µg/ml). As control, beads were coated with a peptide comprising same amino-acids, but in a scrambled order. After reacting with the beads (15min on ice) the samples were measured on a FACScan flow-cytometer. Data were analyzed using FlowJo (Treestar); when half-maximal binding was calculable the serum was classified beta1-aab-positive.

Results: From n=366 pts (226 FAMI/140 AMitis) recruited into the ETiCS-study 45 pts had to be excluded because of unperformed cMRI's; 46 pts stopped the study before Fup-1 (month 3). Only 180/226 FAMI- and 98/140 AMitis-pts had complete Fup1-3 (after 3, 6, and 12 months, including clinical evaluation, echocardiograms, and cMRI's at BL & Fup-3). All valid ETiCS-pts (197 FAMI-/123 AMitis-pts) were assessed for the formation of beta1-aabs, and then compared focussed on the development of echo-LVEF. In the course of the study relevant (high-affinity) beta1-aab-titres were detected in ~31% (37/123) of the AMitis-pts compared to only ~21% (42/197) of the FAMI-pts. In aab-positive AMitis-pts echo-LVEF did not recover and was always significantly inferior to aab-negative AMitis-pts (BL: 38 vs. 49% LVEF; Fup-3: 49 vs. 64% LVEF) whereas such a difference was not noted in FAMI-pts. In addition, aab-positive AMitis-pts had higher NT pro-BNP-, renin-, and aldosterone-levels than aab-negative AMitis-pts.

Conclusion: These first results from the ETiCS-study suggest that acute microbial-induced rather than post-infarction myocardial inflammation triggers the formation of clinically relevant beta1-aabs. AAb-positive AMitis-patients might profit from early intensification of standard HF-therapy (including early beta-blockade) and/or novel antibody-directed experimental therapies which are currently under development.