AIM2-driven inflammasome activation in chronic heart failure

M. Ruppert[1], Z.S. Onodi[2], P. Leszek[3], V.E. Toth[2], G. Koncsos[2], B. Merkely[1], P. Ferdinandy[2], T. Radovits[1], Z. Varga[2]

[1]Semmelweis University Heart and Vascular Center, Budapest, Hungary; [2]Semmelweis University, Department of Pharmacology and Pharmacotherapy, Budapest, Hungary; [3]Institute of Cardiology, Department of Heart Failure and Transplantology, Warsaw, Poland

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Background: Inflammation and cytokine release have been implicated in the pathogenesis of chronic heart failure (CHF). Of particular interest, Canakinumab, a monoclonal antibody against interleukin-1b (IL-1β), had provided benefit against cardiovascular events, suggesting that blockade of IL-1β secretion and signaling might be a promising new therapeutic target. Although, recent studies have provided evidence that inflammasome activation is the main contributor to IL-1β maturation, the role of inflammasome activation in CHF remains unknown.

Objective: Therefore, we aimed to assess inflammasome activation in myocardial samples from end-stage failing hearts.

Methods: Inflammasome activation was assessed by immunoblotting in left ventricular myocardial specimens harvested from patients with end-stage CHF. Furthermore, immunoblot measurements were also performed on translational animal models of CHF (e.g. rat models of permanent coronary artery ligation and transverse aortic constriction). Left ventricular monocyte and macrophage infiltration was detected by immunohistochemistry. To investigate the molecular background of inflammasome activation, a series of cell culture experiments were performed on AC16 human cardiomyocytes and THP-1 human monocytic cell lines.

Results: Out of the 4 major inflammasome sensors tested, expression of the inflammasome protein absent in melanoma 2 (AIM2) and NLR family CARD domain-containing protein 4 (NLRC4) increased in human CHF while the NLRP1 and NLRP3 (NLR family, pyrin domain containing 1 and 3) inflammasome showed no change. A similar expression pattern in AIM2 and NLRC4 was also noted in CHF animal models. Furthermore, robust infiltration of Iba1+ monocytes/macrophages was observed in human failing hearts as well as in different animal models of CHF. In vitro AIM2 inflammasome activation, as induced by transfection with double-stranded DNA [poly(deoxyadenylic-deoxythymidylic)] was reduced significantly by the pharmacological blockade of pannexin-1 channels.

Conclusions: AIM2 and NLRC4 inflammasome activation might contribute to chronic inflammation in CHF. Our findings suggest that pannexin-1 channels might be a promising novel target to reduce inflammasome activation.

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