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Identification and characterization of the NLRP3 inflammasome in cardiac fibroblasts

Sandanger Ø [1,4,5], Ranheim T [1], Vinge LE [1,3,5], Florholmen G [2,5], Christensen G [2,5], Dahl CP [1,5], Askevold E [1,5], Finsen AV [1,3,5], Rashidi A [1], Espevik T [4], Aukrust P [1], Yndestad A [1,5]

1 Research Institute for Internal Medicine, Oslo University Hospital Rikshospitalet, Oslo, Norway
2 Institute for Experimental Medical Research, Oslo University Hospital Ullevål, Oslo, Norway
3 Department of Cardiology, Oslo University Hospital Rikshospitalet, Oslo, Norway
4 Department of Cancer Research and Molecular Medicine, NTNU, Trondheim, Norway
5 Centre for Heart Failure Research, University of Oslo, Norway

Purpose: The innate immune system is based on highly conserved pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and NOD-like receptors (NLRs) that instantly recognize molecular patterns released by pathogens, injured cells and damaged extracellular matrix. Activation of PRRs leads to acute inflammatory responses, including release of inflammatory cytokines such as IL-1β and TNF-α. IL-1β-release from cells depends on activation of caspase-1, which cleaves pro-IL-1β into its active form. NOD-Like Receptor with a PYD-domain (NLRP) 3 is an innate immune receptor which activates caspase-1 through the assembly of an inflammasome, consisting of NLRP3, ASC and caspase-1. Many noxious mediators released by tissue injury and stress seem to activate NLRP3, including monosodium urate crystals, H_2O_2 and extracellular ATP. Although probably a crucial sensor of cellular danger/damage, the role of NLRP3 in acute and chronic cardiac disease is not characterized. The aim of this study was to characterize the role of the NLRP3 dependent inflammasome in cardiac fibroblasts.

Methods and results: Our main findings were that: (1) Myocardial NLRP3 gene expression was markedly increased in mice with myocardial infarction and aortic banding. (2) In adult mouse ventricular fibroblasts, NLRP3 and pro-IL-1β expression, as determined by RT-PCR and western blot, were induced by TLR ligands, and the induction was dependent on NFKB. (3) Confocal imaging of NLRP3 and ASC showed that inflammasome aggregation could be induced by NLRP3 ligands. (4) NLRP3-ligand induced release of active IL-1β from cardiac fibroblasts required pre-treatment with TLR ligands.

Conclusion: IL-1β release from cardiac fibroblasts requires two signals: 1) activation of NFKB, which induce NLRP3 and pro-IL-1β synthesis; 2) activation of the inflammasome. The first signal can be delivered through Toll-like receptors, the second through NLRP3. Even though activation of NFKB is not necessary for the NLRP3β induced inflammasome aggregation, it is necessary for IL-1β release.

8th Annual CHFR Symposium
September 31 – October 01, 2010
Holmenkollen Park Hotel Rica
Oslo, Norway