Role of NLRP3 inflammasome in a mouse model of diet-induced exacerbation of myocardial ischemia/reperfusion injury

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Cardiovascular disorders associated with metabolic diseases are referred to as cardiometabolic diseases (CMD). CMD describe a spectrum of interconnected pathobiological alterations in organs involved in metabolic and cardiovascular functions, that alone and in concert increase disease burden. However, the identification of common mechanisms of disease are far from clear [1]. A growing body of evidences indicates that diet-induced metabolic overload initiates a low-grade, chronic inflammatory response, known as metaflammation, which promotes CMD development [2]. One of the most recently identified pathways involved in metaflammation is the NLRP3 inflammasome, a large multimeric danger-sensing platform that promotes autocatalytic activation of the cysteine protease caspase-1 and mediates the cleavage of inactive pro-IL-1β, among other proteins, into its active form [3]. We have recently demonstrated that a fructose-enriched diet evokes upregulation of renal NLRP3 expression, which contributes to the development of the diet-related renal dysfunction [4]. Similarly, we documented a key role of NLRP3 inflammasome activation in hepatic lipotoxicity evoked by hepatic cell exposure to high concentration of the saturated fatty acid palmitic acid [5].

The aim of the present study is the identification of the potential role of NLRP3 inflammasome complex within the heart of C57Bl/6 male mice fed a standard diet (SD) or a high fat high fructose diet (HFHF) for 12 weeks and exposed to cardiac *ex vivo* ischemia/reperfusion (I/R) injury. Western blot analysis on heart homogenates demonstrated that dietary manipulation evoked the shift of myosin heavy chain isoform content from α to β and an increased expression of markers of oxidative metabolism, CPT-1m and SDH. These effects, suggestive of a diet-induced maladaptive response in heart mice, were associated with increased intramyocellular lipid accumulation in HFHF mice, as shown by Oil Red O staining. Immunohistochemistry analysis showed that HFHF reduced translocation of GLUT-4 from cytosol to membranes, paralleled by increased phosphorylation rate of IRS-2 that inactivates insulin signaling, thus indicating a diet-induced insulin resistance of the cardiomyocytes. When exposed to I/R, HFHF mice hearts showed greater infarct size and lactic dehydrogenase release in comparison with SD mice.

Interestingly, I/R induced a strong upregulation of both NLRP3 inflammasome and activated caspase-1 either in hearts from mice fed SD or in those from mice fed HFHF. However, basal expression levels of NLRP3 inflammasome and activated caspase-1 (before the induction of I/R injury) were already drastically higher in HFHF mouse hearts in comparison to those recorded in SD hearts.

This is, to the best of our knowledge, the first study demonstrating that the upregulation of NLRP3 protein evoked by I/R injury is drastically higher in the presence of a diet-induced metabolic derangement. These findings suggest a potential association between increased activity of NLRP3 inflammasome following metabolic derangements and enhanced susceptibility to a myocardial ischemic insult, thus suggesting a potential role of the NLRP3 inflammasome as innovative pharmacological target to counteract the development of cardiovascular disorders associated with metabolic diseases.

References

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