

RIP2 plays a role in cardiac Ca²⁺ mishandling prompted by chronic kidney disease

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Background: Chronic kidney disease (CKD) is a multifaceted disease that contributes to cardiac dysfunction. However, the mechanisms underlying the complex relationship between CKD and cardiac impairment remains almost completely unknown. Inflammation is a major player in both CKD and cardiovascular disease (CVD) and, in this context, nucleotide-binding oligomerization domain-containing protein 1 (NOD1) is a newly recognized innate immune receptor involved in both CKD and CVD independently. NOD1 activation is due to the recruitment of the receptor-interacting-serine/threonine-protein kinase 2 (RIP2), which induce NOD1 oligomerization and promotes the inflammatory response, being RIP2 a key partner in the NOD1 activation. Unpublished data from our group has demonstrated that genetic deletion of NOD1 prevents Ca²⁺ mishandling associated to CKD, next step will be to determine whether the absence of its specific adaptor; RIP2 can also mediate these effects.

Purpose: The main aim of this study was to determine whether NOD1-RIP2 axis impairs cardiac dysfunction and Ca²⁺ mishandling prompted by CKD induced by 5/6 nephrectomy (5/6Nx) in a mice model.

Methods and results: We have analysed intracellular Ca²⁺ handling in

cardiomyocytes obtained from Wild type (Wt), Nod1^{-/-} and Rip2^{-/-} sham operated or nephrectomised mice. Compared with Wt-5/6Nx, cardiomyocytes obtained from Nod1^{-/-}-5/6Nx and Rip2^{-/-}-5/6Nx mice showed a significant improvement of Ca²⁺ mishandling, mainly by preventing: i) the reduction in [Ca²⁺]_i transients amplitude; ii) the rise in their decay time; and iii) the lower cell contraction. The lack of NOD1 and RIP2 also prevents the reduced sarcoplasmic reticulum (SR) Ca²⁺ load and the augmented diastolic Ca²⁺ leak induced by 5/6Nx. Furthermore, the increased diastolic Ca²⁺ leak (Ca²⁺ sparks, spontaneous [Ca²⁺]_i transients and waves) induced by 5/6Nx were also significantly prevented in absence of NOD1 and RIP2. Genetic deletion of NOD1 or RIP2 did not induces any improvement of several markers associated with renal dysfunction (urea, phosphate or fibroblast growth factor-23).

Conclusions: Our results confirmed that the absence of both NOD1 and RIP2 prevents the intracellular cardiac Ca²⁺ mishandling in experimental CKD. NOD1 and RIP2 emerge as novel targets for the development of innovative therapeutic strategies for the cardiac remodelling in CKD subjects.