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Manuscript Title:

Lp-PLA2 inhibition prevents Ang II–induced cardiac inflammation and fibrosis by blocking macrophage NLRP3 inflammasome activation

Date of Revision:

May 19, 2021

Abstract:

Macrophage-mediated inflammation plays an important role in hypertensive cardiac remodeling, whereas effective pharmacological treatments targeting cardiac inflammation remain unclear. Lipoprotein-associated phospholipase A2 (Lp-PLA2) contributes to vascular inflammation-related diseases by mediating macrophage migration and activation. Darapladib, the most advanced Lp-PLA2 inhibitor, has been evaluated in phase III trials in atherosclerosis patients. However, the role of darapladib in inhibiting hypertensive cardiac fibrosis remains unknown. Using a murine angiotensin II (Ang II) infusion-induced hypertension model, we found that Pla2g7 (the gene of Lp-PLA2) was the only upregulated PLA2 gene detected in hypertensive cardiac tissue, and it was primarily localized in heart-infiltrating macrophages. As expected, darapladib significantly prevented Ang II-induced cardiac fibrosis, ventricular hypertrophy, and cardiac dysfunction, with potent abatement of macrophage infiltration and inflammatory response. RNA sequencing revealed that darapladib strongly downregulated the expression of genes and signaling pathways related to inflammation, extracellular matrix, and proliferation. Moreover, darapladib substantially reduced the Ang II infusion-induced expression of ...

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