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Newly experimental designed CTPR390-488 biosynthetic nanoparticle as a potential biomarker-drug of myocardial fibrosis

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Background:
Myocardial fibroblast activation coupled with extracellular matrix production is a pathological signature of myocardial fibrosis and is governed by the Transforming Growth Factor (TGFβ)-Smad2/3 signalling. Targeting TGFβ itself carries cellular homeostasis deregulation with adverse consequences and its signalling cascade presents some cofactors that helps the pro-fibrotic proteins production. One of these cofactors is the Heat Shock Protein 90 (Hsp90) that participates in TGFβ signalling cascade as a positive regulator. We utilised a new biotechnological Hsp90 inhibitor, CTPR390-488 nanoparticle, with specific Hsp90 binding properties and a fluorophore attached to be tracked.

Purpose:
Our goal is to describe the potential of the experimental designed CTPR390-488 nanoparticle as a biomarker/drug for the myocardial fibrotic disease, analysing its molecular mechanism of action as well as the ultrastructural features in fibroblasts and its in vivo response in a mouse fibrotic model.

Methods:
Immunofluorescence assays, western blot, cell viability assays, transmission electronic microscopy were performed in primary and stable fibroblasts. The simulations of protein-protein interactions were done using Z Dock, ClusPro and ROSIE Docking servers. For the mice studies, we proceeded to the subcutaneous implantation of angiotensin osmotic minipumps, and the histological assessment of myocardial fibrosis was detected through the Masson trichrome assay.

Results and Conclusions:
CTPR390-488 nano-particle co-localised with Hsp90 in fibroblasts and promoted collagen reduction without cell toxicity (not significant differences in cell viability compared to controls). Previously we showed that Hsp90 binds TGFβ-receptor I at the plasma membrane playing a role in TGFβ-Smad2/3 signalling cascade. The inhibition of Hsp90 through the nanoparticle CTPR390-488 lead to a reduction of collagen production and ultrastructural changes in the fibroblasts treated. The in vivo experiments showed that the CTPR390-488 treated pro-fibrotic mouse model exhibited lessened myocardial collagen deposition where the CTPR390-488 was detected. Moreover, the in silico prediction of the mechanism of action indicated a displacement of the Hsp90-TGFβ-receptor I interaction upon CTPR390-488 binding.

We conclude that the biosynthetic CTPR390-488 nanoparticle exhibited anti-fibrotic behaviour both in vitro and in vivo with a high potential of becoming the first anti-fibrotic drug/biomarker with a predicted mechanism of action that is capable of reducing collagen formation and being tracked in pathological hearts.
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