Abstract: 24O

Inactivation of the local cardiac renin angiotensin system improves cardiac performance after myocardial infarction

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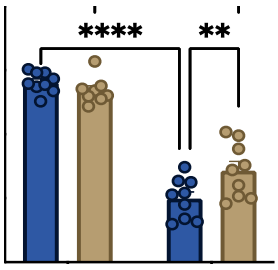
Reasons for the work. The renin-angiotensin system (RAS) regulates blood pressure via angiotensin II (Ang II), which is generated in blood from angiotensinogen (AGT). In addition to the blood borne RAS, a local cardiac RAS has been identified that is activated following heart injury, but its contribution to the cardiac recovery process post injury is controversial. Based on RNAseq data from isolated cardiac cells (1), AGT is primarily expressed from cardiomyocytes. We aimed to examine the role of the local cardiac RAS in the remodelling process post-myocardial infarction (MI) by specifically deleting AGT from adult cardiomyocytes to prevent local activation of the RAS.

Methods. $AGT^{wt/wt}$ and $AGT^{fl/fl}$ mice were injected with $2x10^{11}$ vg adeno-associated virus (AAV9) through the tail vein, which drives the expression of Cre enzyme specifically in cardiomyocytes. Mice received MI surgeries by ligating the left anterior descending artery (anaesthetized by inhaled isoflurane) 4 weeks after virus administration The expression of transgenes and AGT deletion were confirmed by RT-qPCR; fibrosis was analysed by histological staining and cardiac function post MI was assessed by echocardiography.

Results. Angiotensinogen expression was restricted to cardiomyocytes and increased 6-fold in whole heart, 24h post-MI. The AAV-Cre approach successfully deleted AGT in cardiomyocytes. This AGT knockdown reduced MI-induced inflammatory, hypertrophic, and fibrotic responses at 7 days after MI. At 4 weeks after MI, control mice ($AGT^{wt/wt}$) showed profound impairment of cardiac output, stroke volume and ejection fraction (see figure), whereas AGT deleted $AGT^{fl/fl}$ mice showed significantly improved systolic cardiac function.



Conclusion. These results indicate a functional, local cardiac RAS, which is active following myocardial infarction and contributes to the fibrosis and functional impairment associated with cardiac damage/repair. The findings of this study provide fundamental insights into the contribution of the local RAS in the setting of cardiac pathology and may have clinical relevance when considering local versus systemic RAS inhibition.

1.Quaife-Ryan Gregory A, Sim Choon B, Ziemann M, Kaspi A, Rafehi H, Ramialison M, et al. Multicellular Transcriptional Analysis of Mammalian Heart Regeneration. *Circulation*. 2017;**136(12)**:1123-39.