RGS5 and cardiac pericytes during ageing

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Ageing is one of the main risk factors of cardiovascular disease (CVD). In the heart, it induces hypertrophy and fibrosis and has profound effects on the microvascular bed. Pericytes are capillary-associated mesenchymal mural cells involved in the maintenance and stability of the vascular network. Although the phenotypes that arise from cardiac remodelling have been well studied in cardiomyocytes, endothelial cells and fibroblasts, the effect of ageing on pericytes remain largely unknown. In this study, we have characterised pericyte responses to cardiac ageing.
Histological analysis of 12-week- and 18-month-old murine hearts showed reduced pericyte coverage in the aged heart. To understand the effects of ageing on cardiac pericytes, we performed single-nuclei-RNA sequencing comparing young and old hearts and we observed an age-dependent downregulation of the expression of Regulator of G-protein signalling 5 (*Rgs5*), a repressor of GPCRs (G-protein coupled receptors) signalling and a known pericyte marker. Moreover, the specific deletion of *Rgs5* in pericytes showed a reduction in classical pericytes markers such as PDGFRβ and NG2 in the heart. Interestingly, it induced systolic dysfunction as the mutant mice showed reduced ejection fraction.
To study the cell-specific effects of RGS5 knockdown, we used human primary pericytes in vitro. *RGS5* knockdown induced a contractile (*ACTA2*), pro-inflammatory (*IL7R*, *IL6R*) and pro-fibrotic (*FN1*, *TGFB2*, and different collagens like *COL1A1* and *COL3A1*) gene expression profile in pericytes. Furthermore, it reduced pericytes proliferation and migration, but increased cell death. We have demonstrated that RGS5 interacts with PDGFRβ, a crucial tyrosine kinase receptor for pericyte recruitment and proliferation. RGS5 knockdown reduced the expression of PDGFRβ at the protein level, but not at the gene expression level, indicating a post transcriptional regulation of the receptor. In addition, it reduced the phosphorylation of AKT, a downstream target of PDGFRβ, suggesting that the regulation of this signalling pathway may be RGS5 mechanism of action.
Together these data define RGS5 as an active player in regulating pericyte function. Given the importance of pericytes keeping vessel homeostasis, targeting pericyte function could be a valid approach to reduce the malignant effects of cardiac remodelling related to ageing.