Tbx20 is a repressor of pericyte PDGFRβ during cardiac ageing

Guillermo Luxán[1,4,5], Anita Tamiato[1,4,5], Lukas Tombor[1,4,5], Marie C. Hartmann[1], Alisha Haug[2], Jun Xu[3], Nathan J. Palpant[3], Simone F. Glaser[1,4,5], David John[1,4,5], Andreas M. Zeiher[1,4,5], Julian U.G. Wagner[1,4,5] and Stefanie Dimmeler[1,4,5]

[1] Institute of Cardiovascular Regeneration, Goethe-University Hospital, Theodor Stern Kai 7, Frankfurt am Main, Germany
[2] Department of Cardiology, Internal Medicine III, Goethe-University Hospital, Theodor Stern Kai 7, Frankfurt am Main, Germany
[3] Institute for Molecular Bioscience, University of Queensland. 306 Carmody Rd, St Lucia QLD 4072, Australia
[4] Cardiopulmonary Institute, Frankfurt am Main, Germany
[5] German Center of Cardiovascular Research (DZHK), Frankfurt am Main, Germany

Ageing leads to the progressive deterioration of cardiac function and structure. Although the relationship of age-related remodelling with cardiomyocyte hypertrophy, fibrosis, and endothelial cell dysfunction is well documented, its effects on cardiac pericytes have not been studied.

Here, we have combined single-nucleus-RNA-sequencing, imaging, and molecular biology approaches to describe the effects of age on cardiac pericytes. We show that ageing leads to a dilation of cardiac capillaries and a reduction of pericyte coverage. The analysis of differentially expressed regulatory genes revealed that the expression of the cardiogenic transcription factor Tbx20 is increased in cardiac pericytes of aged mice hearts. To do so, we have used TRIAGE, a method that uses epigenetic data from diverse cell types to identify cell-type specific genes controlling cell differentiation and function from single-cell- or single-nucleus-RNA-sequencing. We show that Tbx20 acts as a repressor of Platelet Derived Growth Factor Receptor Beta (PDGFRβ), a classical pericyte marker, which is essential for pericyte function. The overexpression of Tbx20 is sufficient to inhibit *PDGFRB* expression, while its silencing enhances the expression of *PDGFRB* in pericytes in vitro. Furthermore, the expression of Tbx20 regulates pericyte adhesion in a similar manner: the upregulation of Tbx20 reduces pericyte adhesion and its silencing increases cell adhesion supporting our primary observation in which aged hearts show a reduction of pericyte coverage. We could not detect any effect on the expression of extracellular matrix genes upon Tbx20 overexpression and the regulation of Tbx20 did not contribute to cellular senescence supporting that *PDGFRB* regulation may be the major mechanism of action.

These results identify the increased expression of Tbx20 as a feature of aged pericytes in the heart, which could represent a potential therapeutic strategy to treat age related cardiac microcirculatory dysfunction and maintain pericyte function and coverage in the aged heart.