BRUNO BUCHHOLZ

Matrix metalloproteinases as potential targets to treat vascular ageing

Diaz-Canestro C, Puspitasari YM, Liberale L, Guzik TJ, Flammer AJ, Bonetti NR, Wüst P, Costantino S, Paneni F, Akhmedov A, Varga Z, Ministrini S, Beer JH, Ruschitzka F, Hermann M, Lüscher TF, Sudano I, Camici GG. MMP-2 knockdown blunts age-dependent carotid stiffness by decreasing elastin degradation and augmenting eNOS activation. **Cardiovasc Res. 2022;118:2385-96. https://doi.org/10.1093/cvr/cvab300.**

The great elastic arteries, as the aorta and carotids, absorb the pulsatile force of ventricular systole and distally protect the more rigid muscular arteries from the damage produced by the transmission or energetic oscillations. Cardiovascular risk factors, such as diabetes, hypertension, smoking and the metabolic syndrome generate loss of the elastic properties of these arteries, leading to vascular stiffness and its ensuing complications. Arterial stiffness, produced by the loss of elasticity in the great arteries, can be measured through pulse wave velocity, which is an independent predictor of cardiovascular risk and death. Increased pulse wave velocity as a consequence of vascular stiffness is also associated with progressive age, even in the absence of cardiovascular risk factors, thus allowing the estimation of vascular ageing. Extracellular matrix remodeling, with elastin and collagen deposit degradation, among other factors, has a pathophysiological participation in age-dependent vascular stiffness. A large group of enzymes called matrix metalloproteinases (MMP) contribute to the extracellular matrix remodeling of several cardiovascular diseases.

In this study, Díaz Canestro et al. aim to study the role of MMP-2 in age-dependent carotid stiffness, using small-interfering ARN (siRNA) to blunt the MMP gene expression in mice from different age groups. Intravenous siRNA reduced the increase of pulse wave velocity produced by age and circulating and carotid wall MMP-2 levels after a 4-week treatment. At the histological and molecular level, older mice treated with siRNA evidenced increased elastin vs. collagen relationship in the carotid wall and reduced desmosine plasma levels, a marker of elastin degradation. Moreover, the treatment was associated with increased direct protein-protein interaction between MMP-2 and endothelial nitric oxide synthase (eNOS), in addition to eNOS phosphorylation and higher cyclic guanosine-monophosphate (cGMP) levels. Interestingly, they also observed a statistical correlation between circulating desmosine levels and vascular stiffness assessed by pulse wave velocity in elderly patients. They thus conclude that attenuation of MMP-2 expression using siRNA reduces carotid stiffness caused by ageing by decreasing elastin degradation and increasing endothelial nitric oxide bioavailability.

At this stage of our knowledge, it is not a novelty that experimental expression and activity blunting of some MMP types has beneficial effects on different cardiovascular diseases. It is neither new that selective gene expression modulation through RNA silencing has contributed to the understanding of multiple physiological and pathophysiological mechanisms in different organs, generating great expectancy in the last decades. In this study, Díaz Canestro et el. make an interesting contribution to the knowledge of arterial stiffness mechanisms and open a highly relevant pathway for potential clinical trials using selective gene expression modulation technologies to delay or reverse age-dependent vascular damage. It is estimated that in the next three decades the world population over 65 years of age could be more than 15%. This demographic ageing is added to the increased comorbidities emerging from lifestyle and climate change modifications. Taken as a whole, these variables are frequently linked in several shared pathophysiological mechanisms, evidencing the growing need of their deeper study to find more effective solutions in the immediate future.