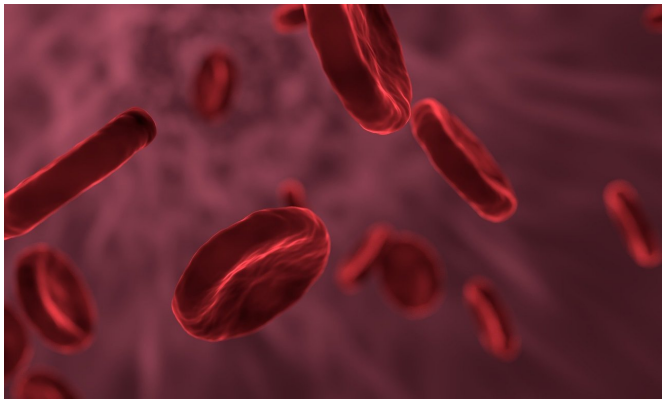
The biomechanics of vascular aging

8 January 2019



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Cardiovascular diseases (CVD) lead to atherosclerosis and heart failure and are prevalent age-related illnesses in humans. In a new study, published in the renowned journal *JCI*, scientists from Roland Foisner's group at the Max F. Perutz Laboratories of the University of Vienna and the Medical University of Vienna, together with scientists from the Ludwig Boltzmann Cluster for Cardiovascular Research at the Center for Biomedical Research, Medical University of Vienna and from the BOKU, Vienna describe the molecular mechanism behind CVD in the premature aging disease Hutchinson-Gilford progeria syndrome (HGPS). The findings could also help understand normal aging processes in the cardiovascular system.

Cardiovascular diseases remain one of the major causes for death in modern society, and are also a typical symptom in HGPS, a genetic defect characterized by progressive premature aging. The exact mechanisms of CVD on a molecular level are unclear, yet dysfunction of the endothelium, a cell layer lining the inner surface of blood vessels is known to be a prominent initiating event. These endothelial cells are under constant mechanical shear stress caused by blood flow. In normal cells a protein meshwork inside the cell called the nuclear lamina and the cytoskeleton provide stability and stiffness, ensuring that changes in mechanical forces from blood pressure do not cause cellular harm.

The scientists now report how this cellular scaffolding is impaired in progeria model organisms, causing the cell to activate abnormal mechanoresponsive mechanisms that produce excessive connective tissue in blood vessels, a condition called fibrosis. First author and senior associated scientist Selma Osmanagic-Myers explains in detail: "In fact, the accumulation of the disease-causing mutant protein in endothelial cells makes the lamina extremely stiff and undynamic, thereby exerting high intracellular mechanical stress, so that the endothelium cannot respond properly to shear stress changes of the blood flow anymore. This in turn hyper-activates mechano-sensitive signalling pathways that lead to fibrosis, vessel stiffening, and cardiac overload."

The results were based on studies in HGPS model organisms. CVD is the most severe, life-threatening symptom in progeria. It is caused by mutations in the LMNA gene that lead to the production of a mutant lamin protein, called progerin. Roland Foisner explains further: "Understanding the molecular defects leading to CVD in progeria will tremendously help to develop new promising effective therapeutic strategies that can significantly improve life conditions of patients and prevent early death due to heart failure. While most previous studies revealed defects of vascular smooth muscle cells in HGPS, we show for the first time that endothelial dysfunction contributes to the severe fibrosis and cardiac impairment in the disease."

"Interestingly, the progeria-causing lamin mutant is also often found in normally aged organisms, yet in lower levels and the CVD pathologies of "normally-aged" people resemble those in progeria. Thus, our study provides an insight into underlying molecular mechanism relevant to defective blood flow sensing occurring at curvatures of aged arteries," adds Bruno Podesser, cardiologist at the Medical

University Vienna.

More information: Selma Osmanagic-Myers et al. Endothelial progerin expression causes cardiovascular pathology through an impaired mechanoresponse, *Journal of Clinical Investigation* (2018). DOI: 10.1172/JCI121297

Provided by Medical University of Vienna