Vulnerability of Progeroid Smooth Muscle Cells to biomechanical forces is mediated by an enzyme

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Hutchinson-Gilford Progeria syndrome (Progeria), a devastating premature aging disease that leads to early death. Smooth muscle cells (SMCs) are the most affected cells in Progeria patients, although the reason for such sensitivity remains poorly understood. We developed an *in vitro* mono-culture cell system to study the vulnerability of Progeria SMCs to arterial flow shear stress using a microfluidic device. Progeria SMCs derived from iPSCs could recapitulate the most important aspect of the disease, i.e., Progeria SMCs loss under flow shear stress. Microarray analysis comparing Progeria SMCs cultured in static conditions and under slow conditions reveals that Progeria SMCs have significant changes in extracellular matrix secretion, specifically an enzyme. Moreover, Progeria SMC detachment is prevented by the inhibition of this enzyme. Finally, double mutant $Lmna^{G609G/G609}$GMmp13$^{-/-}$ mice or $Lmna^{G609G/G609G}$Mmp13$^{+/+}$ mice treated with a MMP inhibitor showed lower SMC loss in the aortic arch than controls. Our results offer a new platform for developing treatments for HGPS patients that may complement previous pre-clinical and clinical treatments. To the best of our knowledge, this is the first study documenting part of the mechanism underlining the sensitivity of HGPS SMCs to arterial flow shear stress.

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