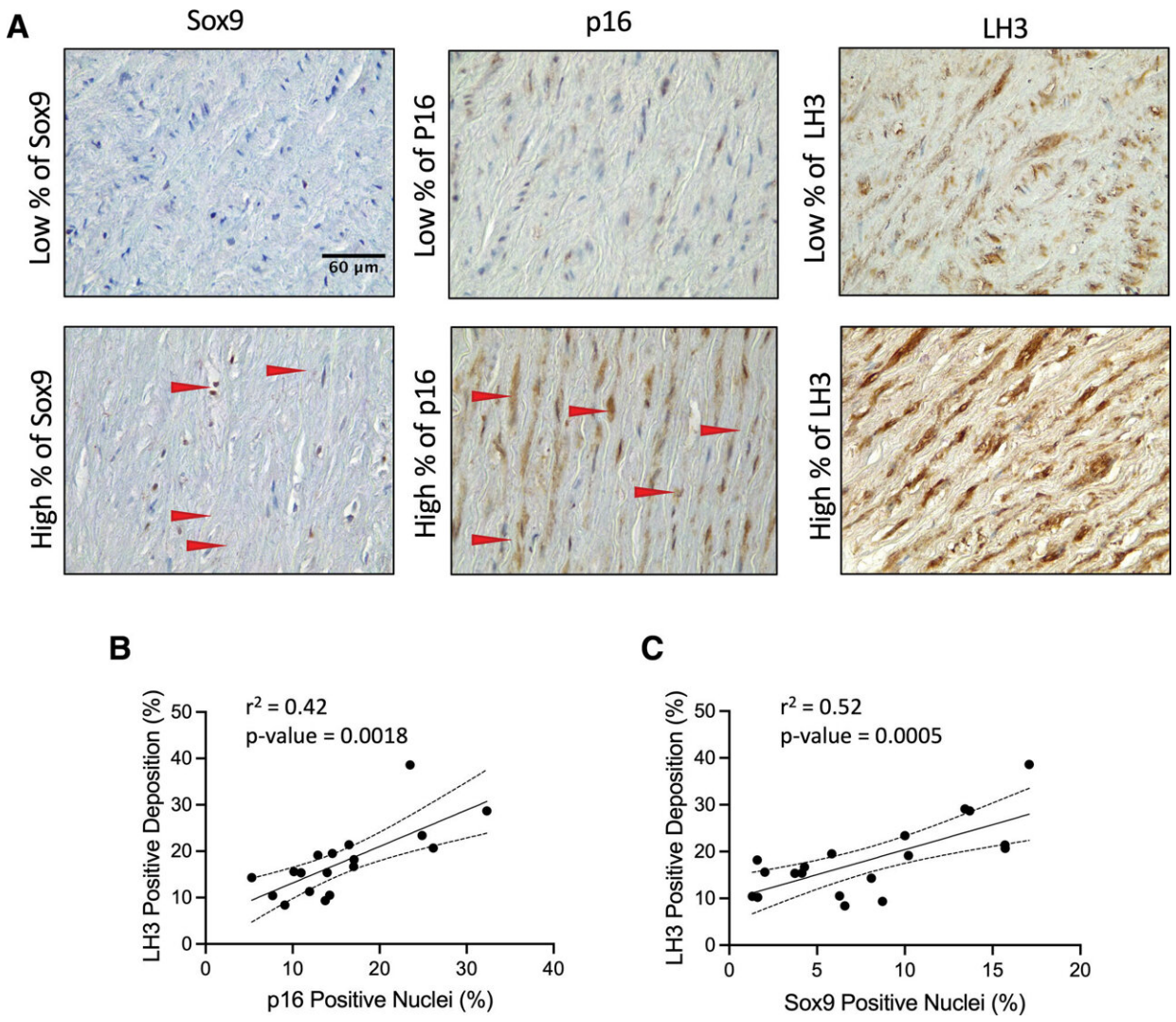
Researchers uncover key molecule influencing vascular aging

February 14 2024



LH3 (procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3) deposition increases in the medial aortic layer with age and Sox9 (SRY-box transcription factor 9) expression. A, Immunohistochemistry of Sox9, p16 (cyclin-dependent kinase

inhibitor 2A), and LH3 staining in the aortic medial layer. Positive staining is shown in brown. Red arrows highlight the positive staining of Sox9 and p16. Correlation of LH3 positive staining (%) with (B) p16 and (C) Sox9 positive nuclei. Normality was validated via the Shapiro-Wilk test, and correlation was determined via the Pearson test (n=16). Credit: *Circulation Research* (2024). DOI: 10.1161/CIRCRESAHA.123.323365

A new study shows how the molecule Sox9 is involved in a positive feedback loop that accelerates the aging of blood vessels, which could be used as a target for new therapies.

King's College London scientists have uncovered a key player in the aging process of blood vessels: the molecule Sox9. These results reveal a positive feedback loop that speeds up cellular senescence; a major culprit behind vascular aging. These insights can help clinicians measure vascular health and to develop new therapies.

"By unraveling the intricate mechanisms driving vascular aging, we are not only shedding light on fundamental biological processes but also paving the way for transformative interventions. Understanding how molecules like Sox9 influence cellular senescence in blood vessels holds the key to developing targeted therapies for age-related vascular diseases and, hopefully, enhance the quality of life for millions worldwide," says King's researcher Dr. Maria Faleeva

Cellular senescence refers to a process where cells lose their ability to divide, halting their growth and replication. It is a pivotal mechanism in the aging process, affecting various cell types, including those composing our blood vessels. Furthermore, the aging of these vessels is often linked to a build-up of calcium, known as calcification, and changes to the extracellular matrix (ECM)- a network of proteins that

surround the vessel's outer layers.

Scientists have long been intrigued by Sox9, a molecule associated with muscle cells within blood vessels, but its role in vessel calcification and aging remained a mystery. A recent paper, published in *Circulation Research* and led by Dr. Maria Faleeva, a former Ph.D. student at King's, investigated this relationship.

Initial analysis of blood vessels taken from patients didn't find a direct connection between Sox9 and calcification. Instead, researchers found that Sox9 correlated with a molecule indicative of senescence, suggesting a link to the process.

Further experiments with cultured human muscle cells from blood vessels highlighted the role of Sox9 in cellular senescence. As the cells underwent senescence, Sox9 expression levels increased and accelerated the process by changing the ECM of proteins surrounding the cells.

The team confirmed the ECM's ability to trigger senescence by introducing young, non-senescent cells into a matrix modified by Sox9, which then resulted in the manifestation of senescence characteristics. Conversely, when senescent cells were grown in an ECM environment lacking Sox9, a remarkable reversal occurred; they resumed proliferation akin to their youthful counterparts.

The observed increase in ECM stiffness within senescent cells was found to promote greater expression of Sox9, which then continued to drive senescence within the vessel's muscle cells. This creates a positive feedback loop that perpetuates cellular senescence and accelerated blood vessel aging.

These results not only shine a light on an important chemical process that drives the aging of blood vessels but also identify important molecular

targets. Sox9, along with other molecules involved in the process, can potentially be used to monitor vascular health and be potential therapeutic targets for combating age-related vascular diseases.

More information: Maria Faleeva et al, Sox9 Accelerates Vascular Aging by Regulating Extracellular Matrix Composition and Stiffness, *Circulation Research* (2024). DOI: 10.1161/CIRCRESAHA.123.323365

Provided by King's College London