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Similarities discovered between vascular calcification and bone growth

University of Tübingen research team observes biochemical process in living cells – indications of new approach to preventing heart attacks and strokes

Real-time observation of certain biochemical processes in blood vessels from mice has revealed a previously unknown similarity between atherosclerosis, also known as vascular calcification, and bone growth. A research team led by Professor Robert Feil at the University of Tübingen's Interfaculty Institute of Biochemistry discovered that a molecular signaling pathway that plays an important role in bone growth can slow down the development of atherosclerosis in blood vessels. In the future, it may be possible to treat atherosclerosis with drugs that were originally developed to treat growth disorders of the bones, such as dwarfism. The study has been published in the journal *Nature Communications*.

Atherosclerosis is a widespread vascular disease that leads to heart attacks and strokes and is the main cause of death worldwide. This disease causes deposits, including fats and various cells, to form in the inner wall layer of blood vessels; these deposits can grow into plaques. The plaques can constrict vessels and lead to blood clots, so that the oxygen supply to the organs via the blood is no longer sufficient and cardiovascular diseases develop.

Blood vessels are mainly made up of smooth muscle, which can increase blood flow by relaxing. "The central signal transmitter for this is the cellular messenger cyclic guanosine monophosphate, or cGMP for short, which is formed in the smooth muscle cells of the blood vessels," explains Dr. Moritz Lehners from the University of Tübingen, the first author of the study. cGMP is found in many human organs and regulates numerous body functions. Interestingly, the signaling molecule may be formed in the vascular cells in several different ways. "Because the overall regulatory process is not yet fully understood, we focused on one of the cGMP production pathways in the current study," says the researcher. To this end, the research team used blood vessel cells from mice in which the cGMP molecule can be detected as a glow under the microscope using a novel fluorescent biosensor. "This enabled us to visualize the signaling molecules and the biochemical processes in which they are involved in individual cells and observe them in real time, at work so to speak," says Lehners. Such single-cell analyses could also be further developed for other areas of vascular biology.

The status of vascular cells is crucial

"The initial situation was confusing," Lehners says. "If we know that several metabolic pathways in the vascular cells can lead to the production of cGMP, the question arises as to whether these different pathways also have different effects." The researchers found that changes in biochemical signaling pathways occur in the vascular cells during the development of atherosclerosis. "As a cell grows into the plaque and stiffens, the cGMP production pathway changes. The pathway we looked at more closely starts up in atherosclerotic plaques and works against the calcification of the vessels," says Lehners. "This mechanism therefore has a vasoprotective function." This result is underpinned by the fact that mice in which this cGMP pathway was blocked, developed more severe vascular calcification.

"Interestingly, precisely this pathway of cGMP formation has long been known in biochemistry and medicine as a promoter of bone growth," says study leader Robert Feil. Genetic variants of the receptors involved in the metabolic pathway lead to anomalies in the human skeleton. "In fact, a new drug, vosoritide, has recently been developed that acts on the cGMP signaling pathway in bone and is used to treat dwarfism in children. The parallels that our study has shown between bone growth and the formation of atherosclerosis in blood vessels could now be used to test whether agents such as vosoritide may also be used in the treatment of atherosclerosis."

Publication:
Moritz Lehners, Hannes Schmidt, Maria T K Zaldivia, Daniel Stehle, Michael Krämer, Andreas Peter, Julia Adler, Robert Lukowski, Susanne Feil, Robert Feil: Single-cell analysis identifies the CNP/GC-B/cGMP axis as marker and regulator of modulated VSMCs in atherosclerosis. *Nature Communications*, https://doi.org/10.1038/s41467-024-55687-9

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