Discovery may illuminate a missing link between atherosclerosis and aging

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Results are published in *Science Translational Medicine*.

"We have identified a new actor in controlling aging in the vessel wall and, surprisingly, it's not a traditional gene or protein. It's part of the non-coding genome. That was unexpected," said Feinberg. "We know a lot about the importance of cholesterol and inflammation in heart disease, but this is a new, additional pathway. We need to think carefully about how it might impact the development of therapeutics for cardiovascular disease."

Feinberg and colleagues used a mouse model of atherosclerosis in which mice begin to develop atherosclerotic lesions at 12 weeks. The investigators isolated RNA from the inner-most lining of the blood vessel wall and looked across the entire genome at all RNAs, searching for which ones had changes in activity during disease progression or regression. One of the most dynamic was SNHG12, a long stretch of RNA that does not code for a protein but is found across multiple species, including humans, pigs and mice.

To better understand SNHG12's role, the researchers conducted experiments in which they either knocked down its activity or ramped it up. They found that less SNHG12 led to a profound increase in atherosclerosis but more SNHG12 dramatically reduced disease progression. To understand what SNHG12 was doing, the team looked for who its partners were. One of them turned out to be a molecule involved with DNA damage repair and aging. Without these partners working together, vessel walls became leaky and permeable to bad cholesterol. The team could reverse this phenomenon by adding a small molecule that promotes DNA damage repair, suggesting a potential therapeutic avenue to pursue.

"What's really exciting is that RNA therapeutics—in
which we deliver RNA molecules or small molecules that can help regulate RNA—is a growing area,” said Feinberg. “Our work helps lay a foundation for pursuing these kinds of therapies for atherosclerosis.”


Provided by Brigham and Women’s Hospital

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