Long non-coding RNA may play a key role in cardiovascular disease

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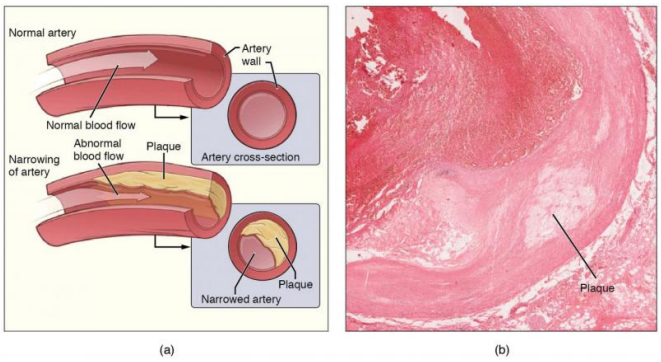

Atherosclerosis is a condition affecting the cardiovascular system. If atherosclerosis occurs in the coronary arteries (which supply the heart) the result may be angina pectoris, or in worse cases a heart attack. Credit: Wikipedia/CC BY 3.0

Atherosclerosis is marked by the buildup of inflammatory cells which narrow arteries to the point of chest pain and muscle weakness. Severe cases result in lesions and internal ruptures of arteries or even thrombosis in coronary arteries. One way that investigators are working to understand how atherosclerosis occurs and progresses is by looking at long non-coding RNAs (lncRNAs), strands of RNA that are not translated into proteins and which may play integral but understudied roles in cell regulation and disease progression.

Through utilization of genetically modified high-risk atherosclerotic mice, a research team from Brigham and Women's Hospital identified and characterized Macrophage-Associated Atherosclerosis lncRNA Sequence (MAARS), which is expressed specifically in macrophages in atherosclerotic plaques and contributes to the progression of the disease. Results are published in *Nature Communications*.

"We hypothesized, given the unknown role of lncRNAs, that some may be highly expressed in the blood vessel wall during the process of atherosclerosis," said Mark Feinberg, MD, senior author and member of the Brigham's Division of Cardiovascular Medicine. "We want to identify who these actors are, what they are doing, and how we can understand their function in a way that provides a foundation for future therapeutic opportunities."

Feinberg and colleagues used genetically modified mice prone to atherosclerosis and placed them on a high cholesterol diet, which boosted their cholesterol to 500-1,000 units, up from a normal level of around 200 units. The mice were observed on their high cholesterol diet for 12 weeks, then placed on a normal diet and observed while their cholesterol levels returned to normal. Researchers isolated the innermost lining of the blood vessel walls of these mice and sent the samples for RNA sequencing to identify the presence of lncRNAs.

Among the list of present lncRNAs was MAARS, which piqued the interest of researchers with its specificity to macrophages and expression pattern. As atherosclerosis developed in the mice over the initial 12 weeks, the presence of MAARS increased 270-fold; once fed normal diets, the presence of MAARS decreased from its heightened expression by 60 percent. Targeted interruption of MAARS's function reduced atherosclerotic lesion formation by 52 percent by decreasing macrophage cell death and increasing efferocytosis—the clearance of dead cellular debris—from these lesions. These effects were largely independent of effects on circulating cholesterol.

Researchers found an important relationship between MAARS and an RNA-binding protein known as HuR. In the vessel wall, MAARS interacts with HuR, which plays a critical role in cell death. If MAARS is deliberately inhibited, HuR is released from the nucleus into the cytoplasm and the macrophages continue their cleaning. This chain of

events leads to more active macrophages able to clean up more plaque and debris produced by atherosclerosis.

"lncRNAs play a really important role in cardiovascular disease," said Feinberg. "We had no idea what we were going to find, and we ended up identifying a lncRNA that has a crucial role in macrophages and pathways that could have therapeutic potential. We are shedding light on new players in old signaling pathways. It is so exciting to add more nuance to this area of research, since that means future studies will have that much more to work with."

More information: Viorel Simion et al, A macrophage-specific lncRNA regulates apoptosis and atherosclerosis by tethering HuR in the nucleus, *Nature Communications* (2020). DOI: 10.1038/s41467-020-19664-2

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