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Atherosclerosis—a short cut to inflammation

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The enzyme Dicer processes RNA transcripts, cutting them into short segments that regulate the synthesis of specific proteins. An Ludwig-Maximilians-Universitaet (LMU) in Munich team has shown that Dicer promotes the development of atherosclerosis, thus identifying a new drug target.

The term atherosclerosis refers to a pathological process in which fat-rich deposits in the walls of major blood vessels, particularly at branch-points of the arterial tree, provoke a localized inflammatory reaction that becomes chronic. The resulting build-up of the atherosclerotic plaque restricts and may ultimately block blood flow, causing a heart attack or a stroke. Local inflammation is initiated by the activation of endothelial cells that make up the inner surface of the blood vessel, which in turn enables specialized immune cells called monocytes to adhere to them. Continuing recruitment of immune cells then promotes the formation of plaques. A team from the Institute for Cardiovascular Prevention at the LMU Medical Center, led by Andreas Schober, has now discovered that an enzyme called Dicer plays a central role in the activation of the endothelial cells. The researchers characterized the mechanism underlying the activation process and identified a new potential target for the therapy of atherosclerosis. The results of the study have been recently published in the journal *Nature Communications*.

The enzyme Dicer is an essential component of the protein complex that generates so-called microRNAs (miRNAs) by cutting these short fragments out of longer precursor molecules. The miRNAs in turn control the expression of specific genes by interfering with the synthesis

of their protein products. MiRNAs are known to be involved in the regulation of a wide range of cellular functions – including the activation of endothelial cells during inflammatory reactions. "However, the impact of Dicer's activity on the development of atherosclerosis, and the nature of the mechanisms that lead to the inflammatory activation of endothelial cells remained unexplored," says Schober.

In order to assess the importance of Dicer, Schober and his colleagues inactivated the Dicer gene specifically in the endothelial cells of atherosclerotic mice. "We found that fewer immune cells attached to the endothelium in these animals, and that the mice exhibited fewer atherosclerotic plaques", Schober explains. "In addition, we noted that loss of Dicer in endothelial cells is associated with a striking reduction in the level of a specific microRNA, referred to as miR-103." The team then showed that miR-103 inhibits synthesis of the KLF4 protein, which is known to be necessary for the induction of mechanisms that restrain inflammation. In other words, in endothelial cells, Dicer is required for the production of a microRNA that promotes the activation of endothelial cells and thus contributes to the development of atherosclerosis.

MiRNAs generally act by binding to messenger RNAs and blocking the synthesis of the proteins they encode. Indeed, when Schober and his team specifically inhibited interaction of miR-103 with the KLF4 mRNA, using a so-called "target site blocker" (TSB), they found that levels of the KLF4 protein increased, and that fewer monocytes bound to the endothelium and fewer atherosclerotic plaques formed. Target site blockers are short synthetic RNAs which have been chemically modified to increase their binding affinity for their target sites in cellular RNAs. In contrast to other types of inhibitors with similar effects, the KLF4 target site blocker does not interact with any of the other genes targeted by miR-103. "With our KLF4-directed TSB, we were able to inhibit the pro-inflammatory effects of miR-103 specifically in endothelial cells,"

Schober explains. "This finding suggests that TSBs could serve as the basis for a novel and promising strategy for the treatment of atherosclerosis."

More information: Petra Hartmann et al. Endothelial Dicer promotes atherosclerosis and vascular inflammation by miRNA-103-mediated suppression of KLF4, *Nature Communications* (2016). DOI: 10.1038/ncomms10521

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