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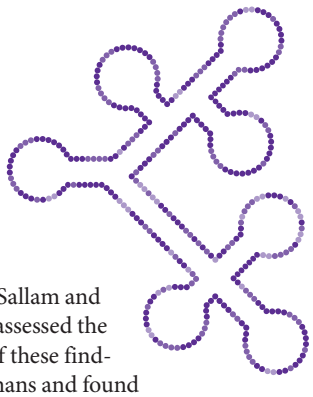
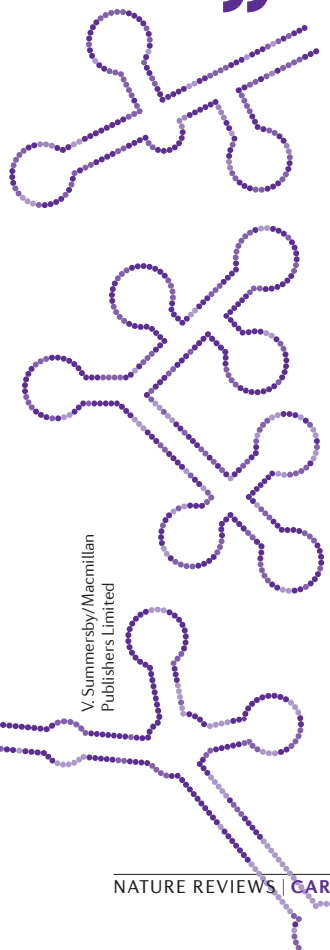
ATHEROSCLEROSIS

A new role for lncRNAs in atherosclerosis



> induction of the long noncoding RNA ... MeXis in response to LXR activation amplifies LXR-dependent *Abca1* transcription in macrophages



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Activation of ligand-dependent liver X receptors (LXRs) promotes cholesterol transport in macrophages through the induction of genes such as *Abca1*, which encodes a cholesterol efflux transporter crucial for the generation of HDL. A new study now shows that induction of the long noncoding RNA (lncRNA) MeXis in response to LXR activation amplifies LXR-dependent *Abca1* transcription in macrophages. This finding provides new insights into the molecular mechanisms controlling cellular cholesterol homeostasis and the pathogenesis of atherosclerosis, and expands our understanding of the cell-type-selective response of LXR.

"We wondered why *Abca1* is very robustly induced with LXR activation in macrophages, but minimally induced in the liver," says study investigator Tamer Sallam. To study the mechanisms regulating LXR-dependent transcription, the researchers first performed genome-wide transcriptional profiling of mouse peritoneal macrophages treated with or without the LXR agonist GW3965. In addition to inducing well-known LXR target genes, LXR activation induced genes encoding lncRNAs. One of the most strongly induced was a gene localized close to *Abca1*, which the investigators named MeXis (for macrophage-expressed LXR-induced sequence).

Next, Sallam and colleagues showed that MeXis regulates *Abca1* expression and function. *In vitro*, siRNA-mediated *MeXis* knockdown or use of an antisense oligonucleotide targeting *MeXis* led to a reduction in *Abca1* expression in mouse peritoneal macrophages. *MeXis* overexpression increased *Abca1* levels and cholesterol efflux capacity. Consistent with these findings, mice with MeXis deficiency fed a Western diet had lower *Abca1* expression than wild-type mice. Loss of MeXis altered *Abca1* expression in a tissue-specific manner: *Abca1* expression was lower in the heart, kidney, and macrophages of MeXis-deficient mice compared with wild-type mice, but liver *Abca1* levels were similar in both groups. Peritoneal macrophages from MeXis-deficient mice fed a Western diet had higher cholesterol levels than those in wild-type mice, with no differences in plasma lipid levels between the groups.

To assess the role of MeXis in atherosclerosis, the investigators reconstituted the bone marrow of irradiated *Ldlr*$^{-/-}$ mice with wild-type or *MeXis*$^{-/-}$ bone marrow cells and analysed the atherosclerotic plaques after 17 weeks of Western diet feeding. Loss of MeXis in bone marrow cells was associated with a significant increase in atherosclerosis burden, with increased macrophage numbers in the plaques and decreased *Abca1* expression in plaque macrophages.

MeXis modulates *Abca1* transcription by altering chromosome architecture at the *Abca1* gene locus. An assay for transposase-accessible chromatin with high-throughput sequencing (ATAC-seq) in peritoneal macrophages showed that MeXis deficiency led to blunted accessibility at multiple sites in the *Abca1* gene locus. Further studies revealed that MeXis interacts with and guides binding of DDX17, a nuclear receptor coactivator, to LXR binding sites in *Abca1* enhancer regions.

Finally, Sallam and colleagues assessed the relevance of these findings in humans and found that the genomic region surrounding the *MeXis–Abca1* locus had a degree of conservation between human and mouse genomes. The investigators identified a noncoding RNA induced in response to LXR activation in a human macrophage cell line. Antisense oligonucleotide targeting of this RNA transcript reduced *ABCA1* levels, whereas lentiviral transduction of *MeXis* increased *ABCA1* expression. A genome-wide association study identified a moderately significant association between a single nucleotide polymorphism in this RNA transcript and coronary artery disease.

"We do not think that MeXis entirely explains why LXRs differentially regulate *Abca1*," points out Sallam, "but our results suggest that lncRNAs play important roles in the context-specific effects of nuclear receptors. We still have a long way to go but, based on the proposed function of MeXis, it is conceivable that figuring out ways to boost MeXis levels within lesions may reduce heart disease burden," concludes Sallam.

Irene Fernández-Ruiz

ORIGINAL ARTICLE Sallam, T. *et al.* Transcriptional regulation of macrophage cholesterol efflux and atherogenesis by a long noncoding RNA. *Nat. Med.* https://doi.org/10.1038/nm.4479 (2018)

FURTHER READING Devaux, Y. *et al.* Long noncoding RNAs in cardiac development and ageing. *Nat. Rev. Cardiol.* **12**, 415–425 (2015) | Greco, C. M. & Condorelli, G. Epigenetic modifications and noncoding RNAs in cardiac hypertrophy and failure. *Nat. Rev. Cardiol.* **12**, 488–497 (2015)