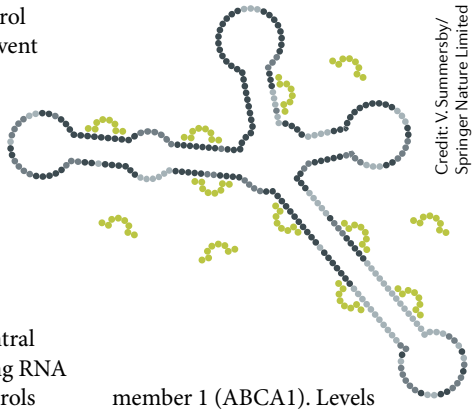
ATHEROSCLEROSIS

The lncRNA CHROME regulates cholesterol homeostasis



Credit: V. Summersby/ Springer Nature Limited

The maintenance of cholesterol homeostasis is critical to prevent atherosclerosis. Cellular cholesterol abundance and availability are regulated by complex feedback processes, including transcriptional and post-transcriptional mechanisms. According to a new study, the long non-coding RNA (lncRNA) CHROME is a central component of the non-coding RNA regulatory network that controls responses to cholesterol excess.

"This [study] adds to our understanding of the multilayered regulatory circuitry that maintains cellular and systemic cholesterol homeostasis," explains lead investigator, Kathryn Moore. CHROME, which is conserved in the genome of primates and absent in other species, is located on human chromosome 2, in a locus that had previously been linked to coronary artery disease (CAD). Analysis of blood and tissue samples from healthy individuals and patients with CAD revealed that CHROME levels were higher in the context of atherosclerosis.

Monkeys fed with a cholesterol-enriched diet had higher levels of CHROME in the liver than monkeys fed with a low-fat chow diet. CHROME expression was also increased in human cultured hepatocytes and macrophages in response to cholesterol overload or after treatment with GW3965, an agonist of liver X receptor (LXR), a nuclear receptor that induces the expression of genes involved in cholesterol efflux. Altogether, these results indicate that CHROME acts downstream of LXR to alter gene expression in response to systemic and cellular cholesterol excess.

CHROME knockdown in human hepatocytes and macrophages reduced cholesterol efflux by 50% and decreased the expression of cholesterol transporter protein ATP-binding cassette subfamily A member 1 (ABCA1). Levels of mature but not nascent *ABCA1* mRNA were reduced after CHROME depletion, suggesting that CHROME regulates *ABCA1* at the post-transcriptional level. Further experiments showed that CHROME knockdown increased the expression of miR-27b, miR-33a, miR-33b and miR-128, a network of miRNAs known to repress the expression of genes mediating cholesterol transport. By contrast, CHROME overexpression reduced miRNA levels and increased *ABCA1* expression. These findings suggest that CHROME antagonizes the repressor activity of miRNAs by sequestering or degrading them.

"The upregulation of CHROME provides a mechanism to coordinately downregulate levels of these miRNAs in the cell and upregulate the cholesterol efflux gene programmes that they control," says Moore, adding that future investigations include evaluating the effect of CHROME depletion in vivo in primates and to assess the diagnostic potential of CHROME. "We showed that [the level of] CHROME is elevated in the plasma and atherosclerotic plaque of individuals with CAD, suggesting that it may have utility as a clinical biomarker," concludes Moore.

Alexandra Le Bras

ORIGINAL ARTICLE Hennessy, E. J. et al. The long noncoding RNA CHROME regulates cholesterol homeostasis in primates. *Nat. Metab.* https://doi.org/10.1038/s42255-018-0004-9 (2018)

IN BRIEF

AORTIC DISEASES

Nanotherapy for abdominal aortic aneurysm

A nanotherapy designed to release rapamycin specifically in response to an inflammatory microenvironment effectively reduces abdominal aortic aneurysm (AAA) expansion in rats. Rapamycin was encapsulated in a biomimetic cloaking of macrophage cell membrane to create a nanoparticle that would release drug molecules in response to high levels of reactive oxygen species (ROS). Peptide ligands were incorporated to target the intravenously injected nanoparticles to aneurysms. The nanotherapy inhibited calcification, oxidative stress and apoptosis in cells associated with the development of AAAs and prevented aneurysm expansion more effectively than a control nanotherapy that was not responsive to ROS. The nanotherapy had a good safety profile in preliminary safety tests and has the potential to be developed into a targeted therapy for other vascular diseases.

ORIGINAL ARTICLE Cheng, J. et al. A targeting nanotherapy for abdominal aortic aneurysms. *J. Am. Coll. Cardiol.* **72**, 2591–2605 (2018)

HEART FAILURE

Benefits of renal denervation in HFrEF

Radiofrequency renal denervation (RF-RDN) inhibits the renin–angiotensin–aldosterone system and improves cardiovascular outcomes in a pig model of heart failure with reduced ejection fraction (HFrEF). Yucatan miniature pigs were subjected to 75 min of left anterior descending coronary artery balloon occlusion to induce a myocardial infarction, followed by 18 weeks of reperfusion. Animals with HFrEF (defined as a left ventricular (LV) ejection fraction <40%) were randomly assigned to receive bilateral RF-RDN ($n = 10$) or a sham procedure ($n = 11$) at 6 weeks after reperfusion. RF-RDN was associated with significant reductions in renal noradrenaline content, circulating angiotensin I and angiotensin II levels, LV end-systolic volume and LV fibrosis compared with controls. RF-RDN was also associated with significant increases in circulating B-type natriuretic peptide levels, LV longitudinal strain and LV ejection fraction. Moreover, RF-RDN improved coronary artery responses to vasodilators.

ORIGINAL ARTICLE Sharp, T. E. III et al. Renal denervation prevents heart failure progression via inhibition of the renin-angiotensin system. *J. Am. Coll. Cardiol.* **72**, 2609–2621 (2018)

VALVULAR DISEASE

Mid-term outcomes with CoreValve versus surgery

Transcatheter aortic valve replacement (TAVI) using the CoreValve System (Medtronic) was associated with reduced 1-year mortality compared with surgical aortic valve replacement (SAVR) in 750 patients at high surgical risk who underwent an attempted implantation procedure in the CoreValve U.S. Pivotal High Risk Trial. In a planned report of 5-year follow-up data, all-cause mortality was 55.3% with TAVI and 55.4% with SAVR, and the rates of major stroke were 12.3% with TAVI and 13.2% with SAVR. Freedom from severe structural valve deterioration was not significantly different between the two groups, and freedom from valve reintervention was 97.0% with TAVI and 98.9% with SAVR. Of note, 33.0% of the TAVI group received a permanent pacemaker, compared with 19.8% of the SAVR group. Overall, mid-term survival and rates of stroke in this population of high-risk patients were similar with TAVI and SAVR, with similar device safety, performance and durability.

ORIGINAL ARTICLE Gleason, T. G. et al. 5-year outcomes of self-expanding transcatheter versus surgical aortic valve replacement in high-risk patients. *J. Am. Coll. Cardiol.* **72**, 2687–2696 (2018)