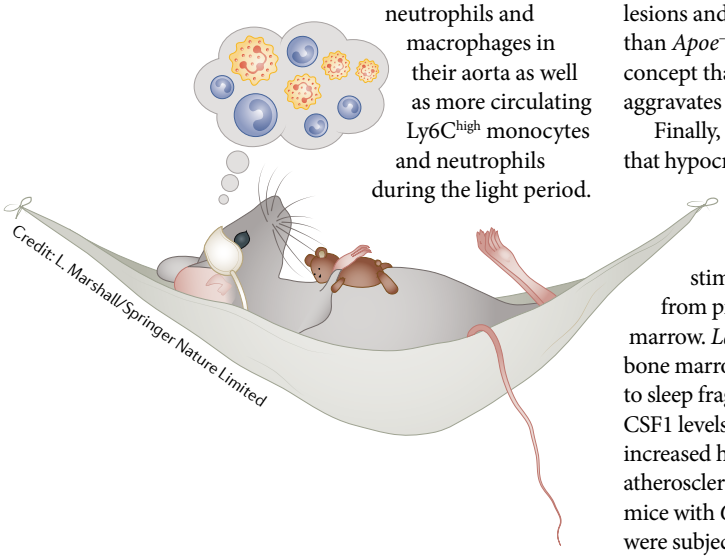
ATHEROSCLEROSIS

Sleep reduces haematopoiesis and atherosclerosis via a neuroimmune axis

> different cardiovascular risk factors alter the haematopoietic system to produce more monocytes

"A neuroimmune axis … directly links a neuropeptide produced in the region of the brain known as the hypothalamus with production of immune inflammatory cells in the bone marrow," comments Filip Swirski about the findings that he and colleagues have published in *Nature*. "Moreover, we have shown that poor sleep interferes with this pathway, leading to increased haematopoiesis and increased atherosclerosis. This convergence of brain and bone marrow is, to my mind, the most exciting part of this study," he adds.

In the study, Swirksi and colleagues fragmented the sleep pattern of *Apoe*$^{-/-}$ mice by moving a bar intermittently across the bottom of the animals' cages during their sleep period. Although these mice developed larger atherosclerotic lesions than control *Apoe*$^{-/-}$ mice with unfragmented sleep, no differences were observed in body weight, plasma cholesterol level or glucose tolerance. However, the mice subjected to sleep fragmentation had more Ly6C^{high} monocytes, neutrophils and macrophages in their aorta as well as more circulating Ly6C^{high} monocytes and neutrophils during the light period.



Credit: L. Marshall/Springer Nature Limited

The investigators went on to show that *Apoe*$^{-/-}$ mice with sleep fragmentation had increased myeloid-biased haematopoiesis in the bone marrow and decreased expression of *Hcrt* (encoding hypocretin, also known as orexin) in the hypothalamus. Accordingly, sleep-fragmented animals had lower levels of hypocretin 1 in the plasma and bone marrow than animals with unfragmented sleep.

Hypocretin is a modulator of metabolism, sleep and appetite. Of note, reduced plasma levels of hypocretin are associated with increased risk of myocardial infarction, heart failure and obesity in humans, and autoimmune destruction of hypocretin causes narcolepsy; patients with narcolepsy have an increased risk of heart disease.

Therefore, the researchers used *Hcrt*$^{-/-}$ mice and found higher numbers of Ly6C^{high} monocytes and neutrophils in the blood, spleen and bone marrow than in wild-type controls. Moreover, *Hcrt*$^{-/-}$*Apoe*$^{-/-}$ mice had larger atherosclerotic lesions and more aortic leukocytes than *Apoe*$^{-/-}$ controls, supporting the concept that hypocretin deficiency aggravates atherosclerosis.

Finally, the investigators showed that hypocretin protects against atherosclerosis by inhibiting the release of macrophage colony-stimulating factor 1 (CSF1) from pre-neutrophils in the bone marrow. *Ldlr*$^{-/-}$ mice with wild-type bone marrow that were subjected to sleep fragmentation had higher CSF1 levels in the bone marrow, increased haematopoiesis and larger atherosclerotic lesions than *Ldlr*$^{-/-}$ mice with *Csf1*$^{-/-}$ bone marrow that were subjected to sleep fragmentation.

Interestingly, *Apoe*$^{-/-}$ mice subjected to sleep fragmentation that received hypocretin 1 delivered to the periphery had reduced numbers of circulating monocytes and neutrophils, lower levels of CSF1 in the bone marrow and smaller atherosclerotic lesions compared with control animals.

Haematopoiesis is emerging as one of the most important processes in the body in the pathogenesis of cardiovascular disease. "[The findings by Swirski and colleagues] contribute to a larger body of work showing how different cardiovascular risk factors alter the haematopoietic system to produce more monocytes," comments Andrew Murphy from the Baker Heart and Diabetes Institute in Melbourne, Australia, and who was not involved in the study. "There is a rationale to directly target the proliferation or lineage selection of the haematopoietic system to tone down the production of monocytes, neutrophils and platelets in people at high risk of a cardiovascular event, but this should be met with caution as we do not want to put patients at risk when the body requires the haematopoietic system to respond, especially in acute situations like infection," warns Murphy. Swirksi and colleagues are now collaborating with clinicians to test this novel neuroimmune pathway in humans.

Gregory B. Lim

ORIGINAL ARTICLE McAlpine, C. S. et al. Sleep modulates haematopoiesis and protects against atherosclerosis. *Nature* 566, 383–387 (2019)

FURTHER READING Tobaldini, E. et al. Short sleep duration and cardiometabolic risk: from pathophysiology to clinical evidence. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-018-0109-6 (2018)