the exercise-induced leptin reduction and effects on niche factors waned but circulating leukocytes remained lower than in sedentary mice, suggesting short-term memory of exercise in haematopoietic cells. Indeed, HSPCs from exercising mice retained their quiescent properties when transferred into sedentary mice. This 'memory' for exercise was linked to epigenetic changes: HSPCs from exercising mice showed reduced overall chromatin accessibility at promoters compared with HSPCs from sedentary mice. Moreover, this reduced chromatin accessibility was even retained in mice that had stopped exercising. The genes that showed reduced accessibility after exercise included those involved in cell cycle regulation and lineage fate decisions.

Although exercise reduced the numbers of circulating leukocytes, emergency haematopoiesis was not compromised: exercising mice responded vigorously to challenge with intraperitoneal lipopolysaccharide and showed lower mortality than sedentary mice in a sepsis model.

Finally, the authors tested whether dampening leukocyte supply through exercise has a beneficial effect on atherosclerosis and plaque inflammation. *Apoe*$^{-/-}$ mice with established atherosclerosis were given access to running wheels, and this led to lower leptin levels, reduced hyperlipidaemia-associated leukocytosis and smaller plaque sizes. The same effects of exercise on atherosclerosis could be achieved by stromal cell-specific deletion of *Lepr*. Importantly, it seems the beneficial effects of exercise on haematopoiesis also apply to patients with existing cardiovascular disease. Patients who exercised four or more times a week had lower plasma leptin levels and lower total leukocyte counts, suggesting that a sedentary lifestyle contributes to cardiovascular risk via oversupply of inflammatory leukocytes.

Lucy Bird

ORIGINAL ARTICLE Frodermann, V. et al. Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells. *Nat. Med.* **25**, 1761–1771 (2019)

Credit: Aleksandr Doodko/Alamy

generate acetyl-CoA to fuel the TCA cycle directly, as well as to activate an alternative pathway of glucose anaplerosis involving pyruvate carboxylase. Moreover, Leone et al. found that the ability of T cells to use acetate to fuel OXPHOS enables them to divert glucose into the pentose phosphate pathway to maintain NADPH/NAD$^+$ homeostasis following glutamine blockade; by contrast, DON-treated cancer cells could not maintain redox homeostasis.

Therefore, activated CD8$^+$ T cells can adapt to glutamine blockade through upregulation of acetate metabolism, whereas cancer cells lack this plasticity and are highly susceptible to glutamine blockade. This previously unappreciated metabolic flexibility of CD8$^+$ T cells suggests that glutamine metabolism could be targeted as a 'metabolic checkpoint' in cancer immunotherapy.

Yvonne Bordon

ORIGINAL ARTICLE Leone, R. D. et al. Glutamine blockade induces divergent metabolic programs to overcome tumor immune evasion. *Science* **366**, 1013–1021 (2019)

Journal Club

LEPTIN: A MISSING PIECE IN THE IMMUNOMETABOLISM PUZZLE

Obesity is characterized by low-grade inflammation, and a growing number of immunologists are devoted to the study of obesity, thus seeding the field of immunometabolism. I entered this field after training in the laboratory that identified the hormone leptin, a key regulator of fat mass. The ground-breaking paper describing the discovery of leptin is a must-read for those new to the field of immunometabolism (Zhang et al., 1994); deservedly, this paper was celebrated in the 2020 Breakthrough Prizes in Life Science.

The *ob*/*ob* mouse line, spontaneously generated in the 1950s by the Jackson Laboratories, showed a Mendelian pattern of inheritance of obesity, which suggested a monogenetic mutation controlling fat mass. Consistent with this idea were Coleman's parabiosis experiments, which indicated that an unknown blood-borne circulating factor normalized the obese phenotype of *ob*/*ob* mice (Coleman, 1978). Using positional cloning technology, Jeffrey Friedman and colleagues mapped the *ob* gene encoding the circulating factor (later named leptin) to chromosome 6 and isolated it by exon trapping, thus identifying the first piece in the puzzle of what regulates whole body fat mass. They also identified adipose tissue as the source of this circulating factor, which informs the brain on the levels of body fat stores via a negative-feedback loop to regulate adipose mass (Halaas et al., 1995).

> "Leptin resistance is the main culprit of common obesity"

The discovery of leptin represented a paradigm shift at a time when mechanistic models of obesity were restricted to voluntary control of food intake and exercise. The identification of leptin also uncovered a novel endocrine system and a better understanding of the pathology of obesity from a biological perspective, similarly to what was accepted for conditions such as cancer, depression and autoimmune diseases.

Leptin resistance is the main culprit of common obesity, yet it is rarely considered in immunometabolism models. I am optimistic that an immunometabolic understanding of leptin resistance could be achieved with a greater appreciation by immunologists of the contribution of leptin.

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ORIGINAL ARTICLE Zhang, Y. et al. Positional cloning of the mouse obese gene and its human homologue. *Nature* **372**, 425–432 (1994)
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