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OBESITY

Specialized macrophages contribute to obesity

Although macrophages are known mediators of adipose tissue inflammation in obesity, their mechanistic involvement in noradrenaline-regulated thermogenesis is unclear. A previously uncharacterized population of specialized macrophages in direct contact with sympathetic neurons that mediate noradrenaline clearance and contribute to obesity in mouse models has now been identified in a new study.

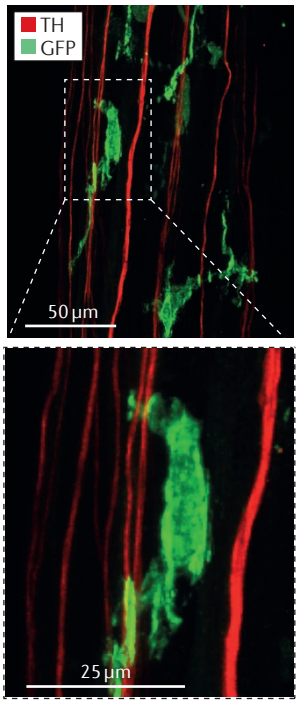
Using two-photon and confocal microscopy in mice, Pirzgalska *et al.* found that sympathetic neuron-associated macrophages (SAMs) exhibited a specialized morphology for neuronal association compared with adipose tissue macrophages (ATMs). Transcriptional profiling revealed that, compared with ATMs, isolated SAMs were the only population that expressed the noradrenaline transporter gene solute carrier family 6 member 2 (*Slc6a2*) and the noradrenaline degradation gene monoamine oxidase A (*Maoa*); indeed, SAMs had relatively higher noradrenaline levels. Notably, SAMs did not express the gene encoding noradrenaline biosynthesis enzyme tyrosine hydroxylase (*Th*), suggesting that SAMs can import and degrade, but not synthesize, noradrenaline.

Optogenetic stimulation of sympathetic nervous system (SNS) explant cultures increased the rate of noradrenaline uptake in SAMs, which was abrogated by pharmacological inhibition of SLC6A2 or MAOA, or by genetic ablation of *Slc6a2*. Intriguingly, flow cytometric analysis revealed that SAM levels were markedly higher in SNS fibres isolated from mouse models of obesity compared with those from lean mice. SAM-specific *Slc6a2* deletion prevented adipocyte hypertrophy and promoted sustained weight loss in obese (*ob/ob*) mice, and, following cold exposure, improved thermoregulation, increased brown adipose tissue content and induced white adipose tissue browning. Finally, human sympathetic ganglia were shown to contain SAMs with noradrenaline clearance capacity.

The findings show that the SNS is populated by specialized SAMs that promote obesity through noradrenaline clearance, suggesting that SAMs and their molecular machinery are therapeutic targets for obesity. Interestingly, SLC6A2 is a molecular target of amphetamines, which are thought to exert their anti-obesity effects via the brain. "Perhaps this model needs an update," explains lead investigator Ana Domingos. "We plan to revisit the mechanism of action of amphetamine to produce a potent weight loss".

Conor A. Bradley

> "the SNS is populated by specialized SAMs that promote obesity"



Confocal microscopy of immunostained sympathetic nerve fibres isolated from the inguinal fat pad of mice, demonstrating contact between neurons (anti-TH; red) and macrophages (anti-GFP; green). Permission obtained from Pirzgalska, R. M. *et al. Nat. Med.* http://dx.doi.org/10.1038/nm.4422 (2017), Macmillan Publishers Limited.

ORIGINAL ARTICLE Pirzgalska, R. M. *et al.* Sympathetic neuron-associated macrophages contribute to obesity by importing and metabolizing norepinephrine. *Nat. Med.* http://dx.doi.org/10.1038/nm.4422 (2017)