COMMENTARY

Countering obesity with eosinophils and sympathetic fat

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In addition to being the main energy storage depot of the body, adipose tissue plays a key role in metabolic homeostasis and hormone production (1). Dysregulation of adipose tissue due to inflammation, obesity, hypoxia, and other conditions results in a host of metabolic alterations that drive the obesity-associated diseases (1). These

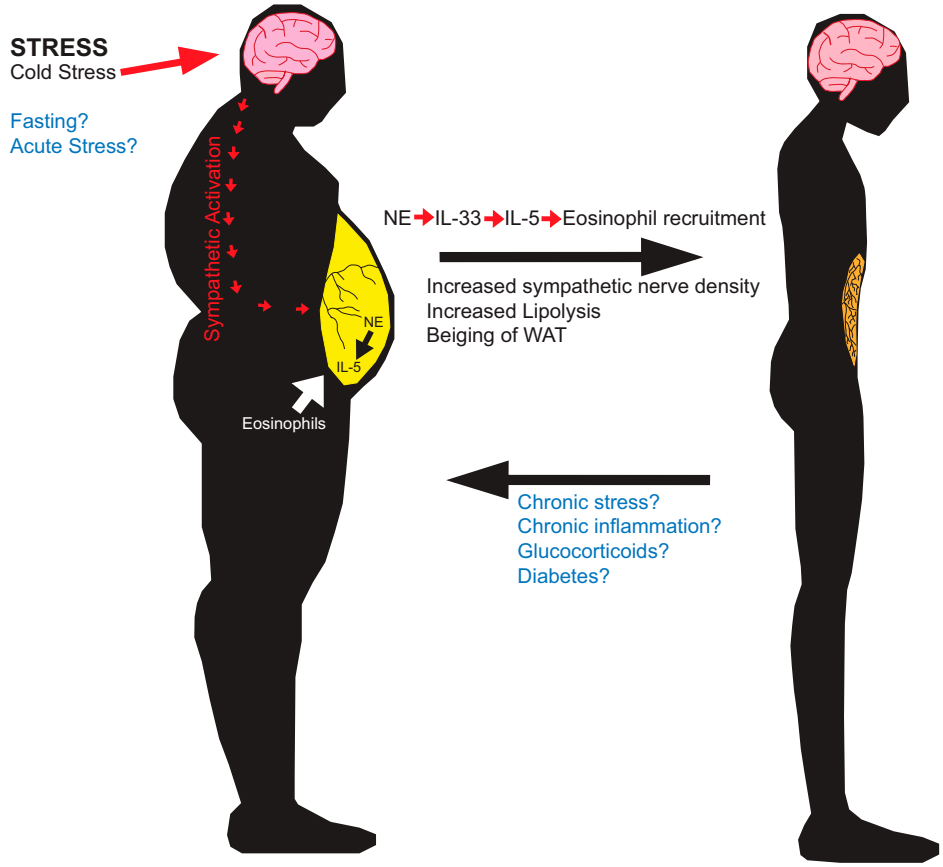

Fig. 1. Stress-induced sympathetic activation results in enhanced neural infiltration and beiging in adipose tissue. Cold stress and potentially other stressors, such as fasting and acute stress, result in activation of the sympathetic nervous system. Sympathetic nerve fibers in the adipose tissue release NE, which acts on stromal cells to drive release of IL-33. This IL-33 acts on tissue-resident ILC2s to drive their release of IL-5 and subsequent recruitment of eosinophils. Eosinophils in adipose tissue release NGF, driving enhanced sympathetic innervation of adipose tissue. This sympathetic signaling in adipose tissue also results in enhanced lipolysis and beiging of the WAT, ultimately resulting in weight loss. Obesity, diabetes, and GC treatment are associated with reduced sympathetic innervation in adipose tissue; however, the mechanism by which this occurs is unknown.

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include type 2 diabetes, fatty liver disease, dementia, and several types of cancer. Understanding how adipose tissue is regulated and the mechanisms to restore healthy metabolic conditions is critical to develop new therapeutic strategies to treat obesity-induced metabolic diseases.

Adipose tissue is highly innervated by the sympathetic nervous system, and the degree of innervation changes in the tissue in different metabolic states. In obese or diabetic mice, sympathetic innervation is decreased, while cold stress (2), prolonged fasting (3), or chronic leptin treatment (4) results in increased sympathetic innervation in the adipose tissue. These sympathetic nerve fibers regulate adipose tissue and upon activation, are sufficient to induce lipolysis (5) and conversion of white adipose tissue (WAT) to brown adipose tissue (BAT). Recent work has found that leptin signaling in the paraventricular nucleus of the hypothalamus can drive increased innervation in the adipose tissue (4); however, the mechanism by which increased innervation in adipose tissue is achieved remained a mystery. Through a series of elegant experiments, Meng et al. (6) have found that eosinophils are singularly responsible for promoting sympathetic axonal branching in adipose tissue in response to cold stress by producing neuronal growth factor (NGF). Cold stress resulted in sympathetic activation and release of norepinephrine (NE) in adipose tissue. This NE then signals to stromal cells, causing the release of interleukin 33 (IL-33) and the activation of type 2 innate lymphoid cells (ILC2s) in adipose tissue (6). These cells then secrete IL-5 to recruit eosinophils, which in turn, release nerve growth factor (NGF) to promote further innervation of the adipose tissue by the sympathetic nerves (6). Significantly, chronic leptin treatment increases sympathetic activation in addition to increased innervation of adipose tissue (4). As prolonged fasting would also raise leptin levels, this suggests that the sympathetic/ILC2/eosinophil neuroimmune feedback loop is also responsible for driving increased innervation after prolonged fasting or leptin treatment. Excitingly, human eosinophils have also been found to produce NGF (7, 8), and the authors found clusters of IL-33+ stromal cells, eosinophils, and sympathetic nerves in human adipose tissue (6), indicating that this same pathway occurs in humans as well (Fig. 1).

In the study by Meng et al. (6), cold-stressing animals for 6 d was sufficient to drive changes in nerve density in the WAT. It will be important to determine the minimum and maximum amounts of stress needed to induce sympathetic axonogenesis in the tissue and whether acute or chronic stressors have differential effects on sympathetic nerve density in adipose tissue. Strenuous endurance exercise can induce sympathetic activation (9); however, this type of training is not generally considered suitable for patients with obesity-related diseases. Identifying the minimum amount of sympathetic activation necessary to drive eosinophils into the adipose tissue and facilitate axonal branching will be important to translate these findings into the treatment of obesity.

Additionally, it will be critical to determine whether chronic stress has a different impact on this pathway. Acute stress has been found to bolster immune function (10) and can be protective in ischemia–reperfusion injury models (11). Chronic stress, however, dampens immune function, renders animals more susceptible to ischemia injury (11), and can drive development of metabolic dysfunction. Chronic stress can result in sustained high levels of glucocorticoids (GCs) (12), which have been shown to drive obesity in animal models and in patients with Cushing's syndrome. Furthermore, increased GC levels are associated with metabolic dysfunction, including insulin resistance and hyperlipidemia (13). Interestingly, recent studies have found that GC-induced obesity is not fully explained by either enhanced food intake or changes in BAT function (14). Eosinophils express the GC receptor, and signaling by GC inhibits the production, function, and survival of human eosinophils (15). Treatment of rats with GC resulted in less sympathetic nerve density in BAT (16); however, the impact of GC signaling on WAT innervation is still unknown.

Chronic stress is also associated with higher circulating levels of proinflammatory cytokines, including tumor necrosis factor alpha (TNFa), IL-1, IL-18, and IL-6. This cytokine milieu is associated with type 1 inflammatory responses as opposed to IL-5, which is associated with type 2 responses. It is possible that the inflammation associated with chronic stress or metabolic dysfunction in obesity inhibits the recruitment of eosinophils to adipose tissue, resulting in impaired sympathetic innervation. The decreases in nerve density in adipose tissue during obesity and diabetes and following GC treatment suggest a countermechanism to eliminate sympathetic axons. In the brain, specialized macrophages prune immature axons from neurons to facilitate synaptic circuit remodeling (17). It will be fascinating to determine whether macrophages, eosinophils, or other immune subtypes in the adipose tissue play a similar role in removing sympathetic axons and what signals drive this process. This work by Meng et al. (6) provides a solid foundation to understand how increases in sympathetic innervation are achieved in adipose tissue; future work building upon this foundation will be needed to understand how this process goes awry in different disease states and how this process can be manipulated to treat metabolic disorders and obesity.

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This work has further ramifications beyond the field of obesity research. Neuronal axons are also recruited into other tissues undergoing wound healing and in solid tumors (18). Increased nerve density is associated with poor prognosis in multiple tumor types, including breast (19) and prostate cancer (20). In prostate cancer, sympathetic nerves promote tumor initiation, while cholinergic nerves promote tumor metastasis (21). The sympathetic nervous system also promotes breast cancer growth in animal models. While neurotrophins, including NGF, can be produced directly by tumor cells, the role of immune cells in promoting axonogenesis in tumors is unexplored. Eosinophilia can be found in several types of tumors, particularly hematopoietic, colorectal, lung, cervical, breast, and ovarian cancers. Increased eosinophils can be pro- and antitumorigenic, depending on the tumor type (22). Significantly, other immune cell types also produce neurotrophins, particularly macrophages. These differences may hint at differential roles for sympathetic nerve fibers in different tumor types, different functions of eosinophils, or different cell types driving the recruitment of nerves into the cancer.

Overall, the work of Meng et al. (6) defines the surprising mechanism by which increased sympathetic innervation is achieved in

adipose tissue. This work opens the door to further investigation of how increased innervation is achieved in other tissues as well as how this process is modulated in obesity and metabolic dysfunction to result in diminished sympathetic innervation.

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1 E. T. Chouchani, S. Kajimura, Metabolic adaptation and maladaptation in adipose tissue. *Nat. Metab.* **1**, 189–200 (2019).
2 H. Jiang, X. Ding, Y. Cao, H. Wang, W. Zeng, Dense intra-adipose sympathetic arborizations are essential for cold-induced beiging of mouse white adipose tissue. *Cell Metab.* **26**, 686–692.e3 (2017).
3 A. Giordano *et al.*, Regional-dependent increase of sympathetic innervation in rat white adipose tissue during prolonged fasting. *J. Histochem. Cytochem.* **53**, 679–687 (2005).
4 P. Wang *et al.*, A leptin-BDNF pathway regulating sympathetic innervation of adipose tissue. *Nature* **583**, 839–844 (2020).
5 W. Zeng *et al.*, Sympathetic neuro-adipose connections mediate leptin-driven lipolysis. *Cell* **163**, 84–94 (2015).
6 X. Meng *et al.*, Eosinophils regulate intra-adipose axonal plasticity. *Proc. Natl. Acad. Sci. U.S.A.* **119**, e2112281119 (2022).
7 H. Kobayashi, G. J. Gleich, J. H. Butterfield, H. Kita, Human eosinophils produce neurotrophins and secrete nerve growth factor on immunologic stimuli. *Blood* **99**, 2214–2220 (2002).
8 A. Solomon *et al.*, Nerve growth factor is preformed in and activates human peripheral blood eosinophils. *J. Allergy Clin. Immunol.* **102**, 454–460 (1998).
9 F. Iellamo *et al.*, Conversion from vagal to sympathetic predominance with strenuous training in high-performance world class athletes. *Circulation* **105**, 2719–2724 (2002).
10 F. S. Dhabhar, Enhancing versus suppressive effects of stress on immune function: Implications for immunoprotection versus immunopathology. *Allergy Asthma Clin. Immunol.* **4**, 2–11 (2008).
11 E. D. Eisenmann, B. R. Rorabaugh, P. R. Zoladz, Acute stress decreases but chronic stress increases myocardial sensitivity to ischemic injury in rodents. *Front. Psychiatry* **7**, 71 (2016).
12 J. P. Herman *et al.*, Regulation of the hypothalamic-pituitary-adrenocortical stress response. *Compr. Physiol.* **6**, 603–621 (2016).
13 A. M. Pasieka, A. Rafacho, Impact of glucocorticoid excess on glucose tolerance: Clinical and preclinical evidence. *Metabolites* **6**, 24 (2016).
14 I. H. N. Luijten *et al.*, Glucocorticoid-induced obesity develops independently of UCP1. *Cell Rep.* **27**, 1686–1698.e5 (2019).
15 R. P. Schleimer, B. S. Bochner, The effects of glucocorticoids on human eosinophils. *J. Allergy Clin. Immunol.* **94**, 1202–1213 (1994).
16 F. Mousovich-Neto *et al.*, Brown adipose tissue remodelling induced by corticosterone in male Wistar rats. *Exp. Physiol.* **104**, 514–528 (2019).
17 L. Weinhard *et al.*, Microglia remodel synapses by presynaptic trogocytosis and spine head filopodia induction. *Nat. Commun.* **9**, 1228 (2018).
18 H. Wang *et al.*, Role of the nervous system in cancers: A review. *Cell Death Discov.* **7**, 76 (2021).
19 D. Huang *et al.*, Nerve fibers in breast cancer tissues indicate aggressive tumor progression. *Medicine (Baltimore)* **93**, e172 (2014).
20 I. H. Lee *et al.*, Perineural invasion is a marker for pathologically advanced disease in localized prostate cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **68**, 1059–1064 (2007).
21 C. Magnon *et al.*, Autonomic nerve development contributes to prostate cancer progression. *Science* **341**, 1236361 (2013).
22 M. Samoszuk, Eosinophils and human cancer. *Histol. Histopathol.* **12**, 807–812 (1997).