IMMUNE REGULATION

Brain–fat axis in adaptive immunity

> TNF signals in the hypothalamus initiate lipolysis and early adaptive immune responses in the periphery

Innate immune signals are essential for the initiation of adaptive immune responses and it is known that the brain can respond to innate cytokines, such as tumour necrosis factor (TNF), that are produced in the periphery. However, it is currently unclear whether the brain contributes to the initiation of adaptive immunity. Cai and colleagues now show that hypothalamic responses to TNF convey early signals that promote peripheral adaptive immune responses through the induction of lipolysis in fat tissue.

The authors noted an increase in TNF concentrations in the cerebrospinal fluid of mice as early as 1 day after intravenous injection of *Listeria monocytogenes*. To understand what effect TNF in the central nervous system might have, low doses of TNF were injected daily for 3 days into the hypothalamus of wild-type mice. The authors found that the numbers of activated B cells and T cells, but not macrophages, in the spleen and epididymal fat were increased in TNF-treated mice compared with control mice. Of note, the increase in lymphocyte numbers in the spleen and epididymal fat was comparable to that observed in mice after 3 days of *L. monocytogenes* infection.

Short hairpin RNA-mediated knockdown of TNF receptor 1 (*Tnfr1*) and *Tnfr2* specifically in the mediobasal hypothalamus (an area that has high levels of TNFR1 expression) severely impaired the increase in lymphocyte numbers in the spleen and epididymal fat of *L. monocytogenes*-infected mice. Furthermore, the restoration of TNFR1 expression only in the mediobasal hypothalamus of TNFR1- and TNFR2-deficient mice increased spleen and fat lymphocyte numbers and resulted in fewer viable bacteria in infected mice compared with controls. Thus, TNF signalling in the hypothalamus promotes the induction of adaptive immunity to bacterial infection.

Of note, denervation of the epididymal fat to break the brain–fat axis reduced the effects of hypothalamic TNF on lymphocyte numbers in both the epididymal fat and the spleen, which suggests that the epididymal fat is important in conveying the brain signal to the spleen.

How does TNF in the brain mobilize lymphocytes in the spleen and epididymal fat? Hypothalamic injection of TNF did not modulate the levels of innate immune cytokines in adipose tissue but it did increase the expression of mRNAs encoding lipolytic molecules. Both hypothalamic TNF injection and bacterial infection increased fatty acid concentrations in the blood, suggesting that lipids might be the link between the brain–fat axis and the adaptive immune system. Treatment of mice with the long-chain fatty acid palmitate was shown to increase the number of spleen and epididymal fat lymphocytes. Furthermore, pre-treatment of mice with the fatty acid synthase inhibitor cerulenin attenuated the increase in spleen and fat lymphocyte numbers in response to hypothalamic TNF injection and to *L. monocytogenes* infection. Further analysis showed that hypothalamic TNF also increases leptin concentrations and that this adipokine functions together with fatty acids to induce adaptive immune responses.

Finally, the authors noted that the basal expression of TNF-induced genes was higher in the hypothalamus of obese mice than in that of lean mice, as was the number of lymphocytes in epididymal fat. Unlike lean mice, the expression of these genes did not substantially increase in the hypothalamus of obese mice, nor did the number of lymphocytes in both the epididymal fat and spleen, following hypothalamic TNF injection. This observation may explain the impairment of adaptive immunity that has been described in obesity.

Together, these data show that TNF signals in the hypothalamus initiate lipolysis and early adaptive immune responses in the periphery. This suggests that the brain–fat axis has an important role in rapidly linking innate immune signals to adaptive immune responses.

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ORIGINAL RESEARCH PAPER Kim, M. S. *et al.* Rapid linkage of innate immunological signals to adaptive immunity by the brain-fat axis. *Nature Immunol.* http://dx.doi.org/10.1038/ni.3133 (2015)