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Immunology: Fast and feel good?

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Claims that fasting eases symptoms of autoimmune disease have been met with scepticism. But the idea receives some support from the finding that leptin, a hormone that controls body weight, also regulates autoimmunity.

Malnourished people present a tempting target for pathogens. Measles, for example, is renowned for being a more serious disease in populations that are starving or close to starving. Yet many people with the autoimmune diseases rheumatoid arthritis or multiple sclerosis, whose immune systems attack their joints or brain, claim that the symptoms of their disease can be reduced by fasting or a change in diet[1]. The idea that food can support a robust immune system and help fight infection, and that starvation can lead to a dampened immune response and alleviate symptoms of autoimmune disease, has mostly been taken as folklore, with little or no scientific basis. But in a paper in the Journal of Clinical Investigation, Sanna and colleagues[2] have shown an intimate relationship between autoimmune disease, starvation and leptin — a key regulator of body weight — in mice.

Leptin is a hormone that was shown in 1994 to be mutated in a certain type of obese mouse[3]. It is also produced in humans. Leptin is secreted by adipocytes (fat cells) as well as by other tissues, and the initial studies of its function concentrated on its role in regulating food intake and body weight. Recently, leptin has been implicated more generally in insulin metabolism, nutrient use, reproductive function and the response to stress[4].

Leptin also regulates inflammatory and immune responses and directly affects the immune system, especially T cells[5]. The addition of this hormone to T cells in culture can alter both their growth rate and the pattern of cytokines — soluble proteins that mediate immune function — that they secrete. For instance, leptin has been shown to enhance the activity of T cells that produce pro-inflammatory

cytokines; these same T cells orchestrate many organ-specific autoimmune diseases.

Sanna et al.2 have now studied the role of leptin during the course of the mouse autoimmune disease experimental autoimmune encephalomyelitis (EAE), which serves as a model of human multiple sclerosis. The authors used several methods to look at leptin's effects. They found that increases in leptin levels in the circulation of mice were correlated with the period before and at the start of clinical disease. They also used mice in which the gene for leptin is non-functional to confirm previous reports that these mice do not develop EAE. Furthermore, T cells that can induce EAE after being transferred into normal mice did not do so after being transferred into leptin-deficient mice. Sanna et al. also found that starvation — which reduces leptin levels — inhibited the development of EAE.

This brings us back to the clinical observations that suggested that starvation can regulate symptoms of autoimmune disease. Many controlled trials in humans have shown that fasting and dietary change can ameliorate the symptoms of rheumatoid arthritis, but the explanation put forth — that this is due to a reduction in the levels of anti-food (allergic) antibodies — is difficult to substantiate6, 7. In view of Sanna and colleagues' data, we must also consider whether fasting and changes in diet might be changing leptin levels, thus altering the function of T cells.

The implication of this new work is that leptin drives the activity of pro-inflammatory, self-reactive T cells, and that starvation, which reduces leptin production, changes the pattern of cytokines generated and the disease-inducing potential of the T cells. So, the authors show that instead of producing pro-inflammatory cytokines, T cells from the starved mice generate anti-inflammatory cytokines, which generally inhibit and regulate organ-specific autoimmune diseases. The idea that leptin could also have a significant role in multiple sclerosis is strengthened by studies of the genes expressed in the brains of patients with this disease: leptin and related genes are expressed more than usual8.

In the context of the whole animal, however, there is still much to understand about the potential interactions between fat metabolism and immunity. The importance of these questions to multiple sclerosis is highlighted by another recent study9 of EAE. This work found that drugs of the statin family, which inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase and reduce cholesterol levels, are also beneficial to animals with EAE, again by altering the cytokine profile of self-reactive T cells. Another enzyme — stearoyl coenzyme A desaturase-1, which is involved in fatty-acid synthesis — is thought to contribute to leptin's effects on metabolism10.

Although these enzymes are on different biosynthetic pathways, their genes are

regulated by a common set of gene-transcription factors (adipocyte-determination differentiation-dependent factors, also called sterol-regulatory-element-binding proteins)11 that also regulate the leptin gene12. So the coordinated control of these different metabolic pathways and leptin could be tied, by transcription factors, both to each other and to aspects of immune function.

In a broader context, these results illustrate once again the trade-off between resistance to infection and susceptibility to autoimmunity. This view is supported by genetic evidence that the regions on chromosomes that influence susceptibility to infection overlap with those that influence susceptibility to autoimmune disease13. The demonstration2 that starvation can stop EAE reminds us how profoundly our state of immunity is also contingent on our relationship with the environment. Adequate nutrition supports an immune response poised to repulse pathogens. It may also be the best substrate for the seed of autoimmunity to take root.

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