ocean currents that bring warm water from the tropics northwards. The deceleration leads to a 15% reduction in the simulated strength of this ocean circulation system between 2050 and 2100.

Meanwhile, in the Southern Hemisphere, the increased amount of fresh water released by the Antarctic Ice Sheet traps warm waters of the Southern Ocean beneath the sea surface. The trapped waters enhance the melting of floating ice shelves, leading to even greater ice loss from the Antarctic Ice Sheet. Including such interactions between the ice sheets and other parts of the climate system produces an increase of about 50% in the predicted amount of ice-sheet loss by 2100, as well as a greater variability of global temperatures. These results show that ice sheets should be investigated and modelled as an integral part of the climate.

The studies by Edwards, Golledge and their respective colleagues demonstrate that polar ice sheets will have a crucial role in Earth's climate in the future, and highlight the need to explore the two-way coupling between the ice sheets and other climate components. They also emphasize the limitations on the modelling of these remote ice sheets.

For instance, current numerical models have a coarse spatial resolution that cannot capture all of the outlet glaciers in the Greenland fjords. Moreover, these models cannot accurately simulate the migration of grounding lines — the transitions between grounded ice sheets and floating ice shelves — in Antarctica. As a result, the models rely on simple parameterizations to account for such effects. Further work is needed to continue to improve numerical models and to better understand how ice sheets will affect Earth's climate over the coming decades and centuries. ■

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PHYSIOLOGY

A metabolic role for gut immune cells

The gut is an active site of immune defence against disease-causing microbes. A study in mice shows that a type of immune cell in the gut's wall also helps to regulate sugar and fat metabolism. SEE LETTER P.115

DARIA ESTERHÁZY & DANIEL MUCIDA

The intestine has a large number of immune cells, which help to repair tissues and defend against microbial infection. The one-cell-thick lining of the gut (the intestinal epithelium) is the interface between the core of the body and the intestinal space, which is constantly exposed to food and to gut-resident and invasive microbes. The intestinal epithelium contains a type of immune cell called an intestinal intraepithelial lymphocyte (IEL). He *et al.*[1] show on page 115 that, in addition to their immune function, IELs have a role in the control of the body's metabolism by regulating levels of a hormone that is released after food consumption.

IELs are one of the largest populations of T lymphocytes (T cells) in the body[2], and provide the first line of specific immune defence against microbes in the gut. Dysregulation of IELs causes loss of integrity of the intestinal mucosal barrier (the physical and immune barrier that surrounds the intestinal space), increased susceptibility to infections and inflammatory bowel disease[3]. He *et al.* suggested that IELs might also have a metabolic role, because these cells are abundant in the portion of the intestine where most nutrient absorption occurs, express genes associated with metabolism, constantly move along the gut epithelium even in the absence of infection, and are close to epithelial cells[4].

The involvement of immune cells in the control of metabolism and in the progression of metabolic disease has been studied in other tissues. Most notably, macrophage cells and regulatory T cells influence metabolism in fat tissue and in blood vessels, and the function of these tissues is dysregulated in individuals with the obesity-related collection of metabolic disorders called metabolic syndrome[5].

50 Years Ago

Mumiyo, a waxy substance of unknown origin found on rocks in Asia and Antarctica, was formerly thought to have healing properties, and has recently aroused considerable interest in the Soviet Union as a possible medicine … Writing in *Arbok 1967*, Dr. T. S. Winsnes reports that he has seen snow petrels in the mountains of Dronning Maud Land spitting out a thick pink substance that looks very much like mumiyo … the colour probably caused by the crustaceans which constitute most of the bird's diet. The spittle accumulates — sometimes several kilos of it — around the nest in the form of wax, sometimes hanging down like stalactites. Dr. Winsnes believes that this substance is the mumiyo of the Antarctic, although, of course, he cannot say whether it has a similar origin in Asia.
From *Nature* 8 February 1969

100 Years Ago

Under the title of "The Louse Danger", the British Museum … has issued a third "poster" in the economic series. Attention is directed … to the danger of the clothes (or body) louse as a carrier of relapsing fever, typhus, and trench fever. In order to avoid lice, regular washing of underclothing and bed-linen is advocated. It is further desirable to avoid contact with persons suspected of being verminous; hospital workers … are advised to wear white linen overalls … When eggs of the louse are present in the hair, close clipping or shaving is necessary; in the case of women, washing the hair with an insecticidal solution is advised … Simple instructions for the disinfestation of clothing and bedding are appended, together with information concerning the most useful insecticides.
From *Nature* 6 February 1919

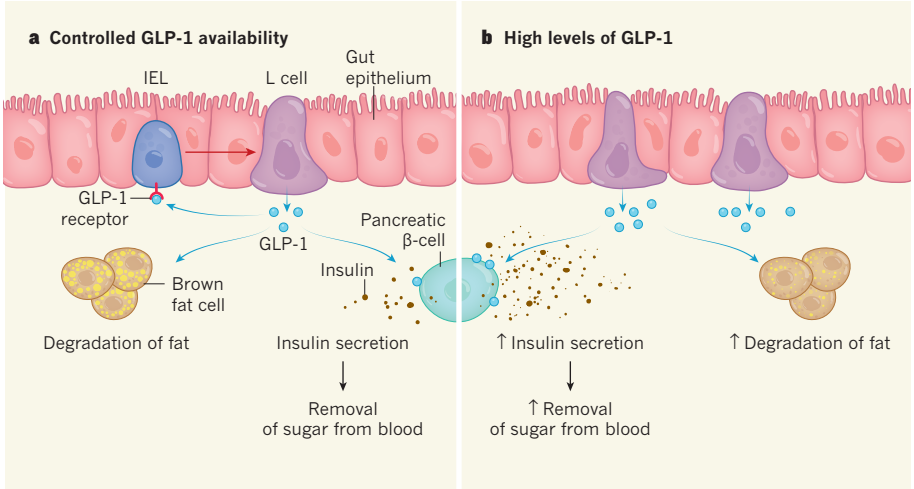

Figure 1 | A metabolic role for intestinal intraepithelial lymphocytes (IELs). He *et al.*[1] show that immune cells called IELs affect levels of a hormone called GLP-1, which is a key regulator of glucose levels in blood after meals. **a,** The authors propose that IELs regulate (red arrow) the differentiation, proliferation or gene-expression program of L cells (the intestinal cells that secrete GLP-1), and also capture some of the available GLP-1 with their GLP-1 receptors. This controls GLP-1 levels, thereby controlling fat degradation by brown fat cells and the removal of sugar (glucose) from the blood by pancreatic β-cells, which secrete insulin. **b**, In the authors' study, mice with low numbers of IELs had increased, abnormal levels of circulating GLP-1 and increased insulin secretion by pancreatic β-cells, which led to decreased levels of sugar in the blood. The metabolism of brown fat tissue, which degrades fat molecules, was also more active in these mice. These findings highlight the dual immunological and metabolic role of IELs.

He *et al.* used genetically engineered mice that lack a protein called integrin β7, which helps to attract T lymphocytes to the intestinal epithelium, where they become IELs. Accordingly, these mice had reduced IEL numbers. They were also metabolically hyperactive compared with wild-type mice: their brown adipose tissue spent more energy 'burning' fat and their pancreas released more insulin after the mice had eaten sugar, lowering the levels of glucose in their blood. The authors observed that integrin-β7-deficient mice that had a diet rich in fat and sugar were protected against features of human metabolic syndrome such as obesity, hypertension, diabetes and atherosclerosis.

Although the absence of integrin β7 is likely to affect several types of cell, when He *et al.* inactivated the gene encoding integrin β7 only in specific immune-cell populations in otherwise wild-type mice, they saw that IEL depletion made a major contribution to the antidiabetic and lipid-lowering effects they had previously observed. These effects resemble those resulting from elevated levels of glucagon-like peptide 1 (GLP-1). This hormone is released from specialized cells in the gut epithelium, called L cells, in response to the presence of sugar and bile acids in the gut, or in response to neuronal stimulation. GLP-1 controls the levels of glucose in the blood directly by inducing insulin release from β-cells in the pancreas and indirectly by stimulating the proliferation of these cells, slows the rate of digestion by slowing gut motility and the emptying of the stomach, and activates the neural signalling pathways associated with satiety[6].

Given that IELs and L cells are found close to each other and that IELs have many copies of the GLP-1 receptor[7], the authors went on to measure circulating GLP-1 levels and L-cell numbers in integrin-β7-deficient mice. They observed that the levels of the hormone and the numbers of cells were elevated compared with those in wild-type mice, which suggests that the metabolic differences between these mice and wild-type mice have a hormonal basis. The authors propose that IELs act as a key rheostat in a circuit, controlling GLP-1 levels in two ways: by regulating the production of new L cells; and by directly capturing released GLP-1 using their GLP-1 receptors, thus acting as a GLP-1 'sink' (Fig. 1). When food is scarce, GLP-1 needs to be suppressed, but in the context of obesity, increased GLP-1 levels are beneficial. In fact, the GLP-1 pathway has already been harnessed therapeutically: long-lived GLP-1 analogues and GLP-1-breakdown inhibitors are part of the clinical treatment of metabolic syndrome[6].

This study opens several questions that will require an interdisciplinary approach to answer. First, although IELs might regulate the levels of circulating GLP-1 through expression of GLP-1 receptors, additional mechanisms are likely to be at play, because inactivation of the GLP-1 receptor in immune cells has no effect on GLP-1 levels and also because the transport of GLP-1 from L cells to blood and lymph is rapid. For example, GLP-1 might act as a molecular cue that attracts IELs, or it might stimulate IELs to secrete additional factors that regulate host metabolism.

Second, the mechanisms by which IELs regulate L-cell numbers and the secretion of GLP-1 from these cells are unclear. IELs might influence the differentiation of intestinal stem cells into L cells, regulate the proliferation of L cells, act on the epithelial cells lining the intestine, or influence L-cell gene expression by mechanisms that are still to be identified.

Third, given their location and numbers, IELs probably respond to various nutritional states and regulate multiple metabolic or hormonal activities in the intestinal epithelium. Future studies might uncover nutritional cues that trigger IELs to regulate GLP-1. Analysis of gene expression in the intestinal epithelium might also reveal additional pathways that are regulated by IELs.

Finally, more-fine-grained analysis of different IEL types might help to clarify whether particular subsets of these cells have specific metabolic or antimicrobial roles, and how they balance these two functions. IELs come in different flavours: natural IELs, which mature in the thymus before migrating to the intestine, and peripherally induced IELs, which are absent at birth and accumulate in the gut with time[3]. Natural and peripherally induced IELs share a core gene-expression program, but they differ in location, in the specific molecules they recognize and react against, and in their immunological functions. It is tempting to speculate that IEL subsets that are particularly abundant in the small intestine have a major role in sensing metabolic cues. Although depleting specific IEL subsets without affecting other T-cell populations in the body is currently challenging, approaches for doing this are needed to complement He and colleagues' observations on the effects of general integrin β7 deficiency.

Despite these unanswered questions, He and colleagues' finding that IELs have a role in the control of whole-body energy balance is a remarkably important observation for a cell type that is normally ignored in mainstream metabolic studies. Further studies will tell us whether and how this finding can be exploited to treat metabolic disorders without compromising the integrity of the gut barrier. ■

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