MEDICINE

The Microbes Made Me Eat It

Susceptibility to obesity is influenced by the interaction between microbes and immune system function in our digestive system.

Darleen A. Sandoval and Randy J. Seeley

We share our bodies with a huge array of microorganisms. Many of these live in the intestine and number in the trillions (*1*). On page 228 in this issue, Vijay-Kumar *et al*. (*2*) show that the interaction between our immune system and these gut microbes plays an important role in the metabolic diseases that plague developed countries, with profound implications for the rise in obesity and what can be done about it.

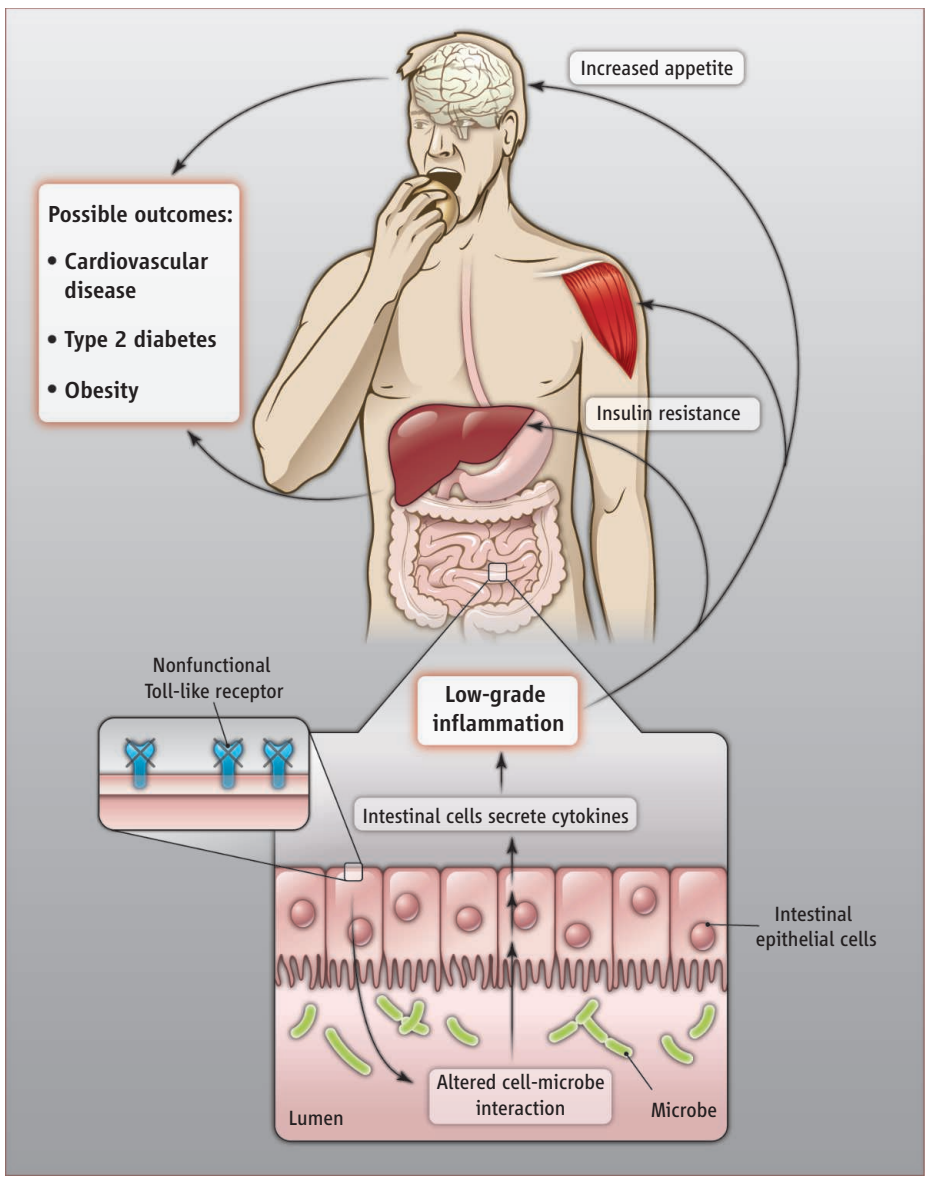
There are few proven hypotheses regarding the cause of obesity, type 2 diabetes, and cardiovascular disease. One possibility is that gut microbes contribute to these conditions—referred to collectively as metabolic syndrome—by regulating immune function. Because of its large surface area and exposure to diverse microbes and the food we eat, the gastrointestinal tract is a unique interface between the external and internal environment. This positions the gastrointestinal tract to play a predominant role in immunity.

Although the human body depends on bacteria in the gut for normal functioning, bacteria in other locations may cause infections that must be targeted by the immune system. One component of this response is Toll-like receptors that are expressed by certain immune cells. These receptors recognize the flagella of bacteria and activate the immune system. Obesity is associated with an increase in immune system activity and this may contribute to a range of other symptoms associated with obesity, including elevated risk for cardiovascular disease and type 2 diabetes (*3*).

Vijay-Kumar *et al*. show that mice lacking Toll-like receptor 5 (expressed by intestinal cells, as well) were obese and had many characteristics of metabolic syndrome, all of which were exacerbated when the mice were put on a high-fat diet. It should not be surprising that manipulation of the immune system might result in such an outcome given the importance of inflammation to the metabolic syndrome. However, by crossing these mice with mouse strains lacking other key components of immune system signaling, the authors found that this phenotype did not change. Metabolic syndrome therefore was not the result of direct interaction between the Toll-like receptor and these other immune system molecules. So if not the immune system, what could account for the resulting metabolic syndrome?

When Vijay-Kumar *et al*. treated the obese mice with antibiotics to kill their microbes, they reversed the metabolic syndrome. Additionally, by transferring bacteria from the gut of obese mice to that of mice that were depleted of gut bacteria, they could recapitulate the metabolic syndrome of the obese mice. Thus, the gut microbiota in the obese mice was both necessary and sufficient for the resulting obesity.

This isn't the first time that researchers have linked gut microbes to our waistlines. Earlier studies (*4*, *5*) found that obese humans and obese mice had different bacteria in their gastrointestinal tracts than lean individuals. They concluded that in obese individuals, the mix of gut microbes could extract a small amount of calories from what would normally be undigested food, and that these calories contributed to weight gain. However, the hypothesis implies that in starvation,



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Microbes and obesity? The absence of Toll-like receptor 5 in mice alters the gut microbiota, causing increased food intake, insulin resistance, and obesity. Is this true for humans?

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when the need to extract calories from food increases, our gut bacteria would actually become less efficient. Moreover, our bodies sense calories, and it is unclear why animals would not adjust to greater caloric extraction by eating less food.

Vijay-Kumar *et al*. paint a different picture of how gut bacteria might contribute to obesity. Rather than delivering additional calories to its host, gut bacteria interact with physiological processes that control multiple aspects of metabolism. Importantly, what regulates this interaction is the immune system, through activity of a Toll-like receptor. Thus, it may be that part of how the human immune system influences metabolic disease is via regulating gut microbes; this, in turn, might regulate other aspects of our immune system, including the production of proinflammatory cytokines (see the figure).

The study by Vijay-Kumar *et al*. falls under a growing set of theories that obesity is the result of infection. Whereas this work focuses on a potential role for bacteria, others have speculated that specific viral infections can lead to increased body weight (*6*). Although the thought of obese individuals as "contagious" adds many negative connotations to a group that already suffers enormous discrimination, the idea that some gut bacteria contribute to susceptibility to obesity means that we may be able to reverse this trend by targeting the key microbes. These insights may allow us to identify new strategies to prevent obesity by manipulating immune system–gut microbiota interactions through drugs, the food we eat, or probiotics.

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MATERIALS SCIENCE

Holding On by a Hard-Shell Thread

The byssal threads that secure mussels onto surfaces have a hard coating created by iron cross-links of proteins rich in L-dopa.

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Mussels anchor to surfaces in turbulent aqueous environments with a remarkable acellular tissue, the byssus, or "beard." The threadlike byssal attachments are strong yet highly extensible, and have a thin cuticle coat that is harder than the core of the thread itself. On page 216 of this issue, Harrington *et al*. (*1*) present results that show how the chemistry of byssal thread cuticle may impart these distinctive mechanical properties.

The major cuticular protein in mussels, called mfp-1 (mussel foot protein 1), contains 10 to 15 mol % of the catecholic amino acid 3,4-dihydroxyphenyl-L-alanine (dopa). The core proteins of the threads are collagen-like and contain very little dopa. The mussel employs a truly elegant approach to byssal thread fabrication (see the figure). In a series of events that are reminiscent of industrial approaches to polymer injection molding, the mussel injects liquid protein solution onto the substrate surface and into a groove along the length of the foot. The protein solidifies in a short period of time. Detachment of the foot reveals the newly formed thread and adhesive plaque. The mussel then repeats this process many times to secure its attachment to the substrate.

The mussel relies on the durability of the byssus for its survival. The byssal threads have very robust mechanical properties, and have been shown to have self-healing capacity (*2*). Harrington *et al*. focused on the mechanochemistry of the byssal thread cuticle. Earlier studies of byssal threads revealed the cuticle to be about five times as stiff as the core and enriched in iron and calcium, but otherwise free of detectable inorganic mineral phases (*3*, *4*). Catechols are known to have a high affinity for transition metals, including iron, and iron ions can bind either two or three dopa molecules to form bis- and tris-complexes, respectively (*5*).

The possibility of iron complexation by dopa, together with evidence for colocalization of mfp-1 and iron in the thread cuticle, has led to speculation of a mechanical role for dopa-iron complexes (*4*). However, direct chemical and spectroscopic evidence for the localization of dopa-iron complexes in byssal thread cuticle has been lacking. Harrington *et al*. filled this gap and established a framework for understanding the possible mechanical function of dopa-iron coordination in the mussel byssal thread cuticle. The authors used in situ confocal Raman spectroscopy on slices of byssal thread tissue to demonstrate the existence of dopa-iron complexes within the thread cuticle. The submicrometer resolution

Making strong attachments. A still image is shown of a mussel attached to a surface. The attachment process is revealed in movie S1. As the foot detaches from the surface, it leaves behind an intact byssal thread and adhesive pad.

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