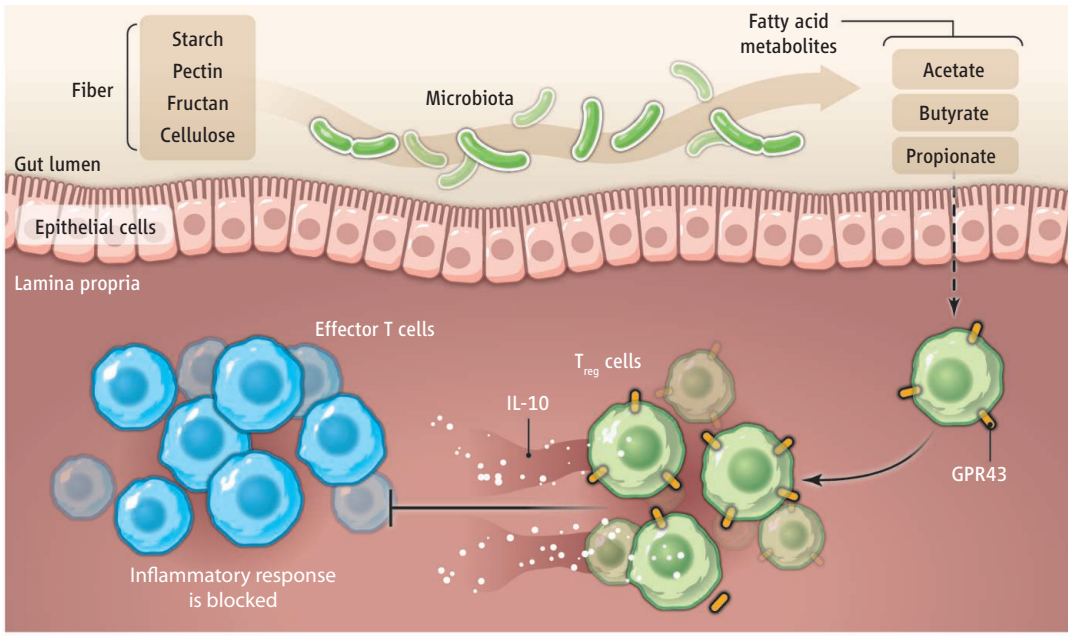
IMMUNOLOGY

Feed Your T_{regs} More Fiber

Microbes that metabolize dietary fiber can generate key fatty acids that enforce regulatory T cells in the gut.

Julia Bollrath and Fiona Powrie

The human intestine harbors up to 10^{11} bacteria per gram of intestinal content, comprising over 500 different species (*1*) that have coevolved with their hosts in a mutually beneficial relationship. These bacterial communities promote human health through effects on nutrition and immune system development and function, changing in distinct ways over time and in different disease states. Precisely how bacteria communicate with their hosts to promote immune function is poorly understood. On page 569 of this issue, Smith *et al*. (*2*) show that common bacterial metabolites—short-chain fatty acids—selectively expand regulatory T (T_{reg}) cells in the large intestine. T_{reg} cells suppress the responses of other immune cells, including those that promote inflammation. This finding provides a new link between bacterial products and a major anti-inflammatory pathway in the gut.



Bacterial metabolites fight intestinal inflammation. Commensal bacteria metabolize fiber and generate short-chain fatty acids. These fatty acids are ligands for GPR43 expressed by T_{reg} cells and stimulate their expansion and immune-suppressive properties such as the production of IL-10, thereby controlling proinflammatory responses in the gut.

Intestinal homeostasis and the maintenance of gut health require an appropriate balance between immune effector and regulatory pathways. T_{reg} cells (those that express the transcription factor Foxp3) are abundant in the intestine and play a nonredundant regulatory role, particularly through their production of the anti-inflammatory cytokines transforming growth factor–β (TGF-β) and interleukin-10 (IL-10) (*3*). Intestinal bacteria can control this balance. For example, segmented filamentous bacteria (*Clostridium* genus) induce the accumulation of effector T cells in the small intestine of mice (*4*), whereas a mixture of clostridia species of the subclusters IV and XIVa prompt the expansion of colonic T_{reg} cells (*5*). Furthermore, *Bacteroides fragilis*, a commensal bacterium common in the human intestine, promotes expression of IL-10 by T_{reg} cells (*6*).

Smith *et al*. observed that feeding germ-free mice three short-chain fatty acids (propionate, acetate, butyrate), individually or in combination, increased the frequency and number of Foxp3 T_{reg} cells in the large intestine to an amount similar to that observed in conventionally reared animals. Different bacterial families in the large intestine can produce short-chain fatty acids as end products of the fermentation of complex carbohydrates such as dietary fiber. The majority of the expanded T_{reg} cell population expressed the transcription factor Helios, which suggests that they acquired Foxp3 expression in the thymus. This is of particular interest because bacterial-driven T_{reg} cell generation in the intestine is thought to occur locally and result in T_{reg} cells that do not express Helios. Propionate also increased the expression of Foxp3 and IL-10, but not TGF-β in colonic T_{reg} cells, indicating that short-chain fatty acids can also selectively enhance T_{reg} cell function.

Propionate showed a superior effect on T_{reg} cell expansion compared to acetate and butyrate, which may be explained by its higher affinity (*7*) for G protein-coupled receptor 43 (GPR43), a receptor for short-chain fatty acids (*8*). GPR43 was thought to be primarily expressed by adipocytes, intestinal epithelial cells, and leukocytes (neutrophils and monocytes). However, Smith *et al*. show that intestinal T_{reg} cells also express GPR43, which is driven by the presence of bacteria. Importantly, the observed effect of short-chain fatty acids on T_{reg} cell expansion was abrogated in mice lacking GPR43. This does not appear to be a nonredundant mechanism as conventionally reared *Gpr43*-null mice did not show any deficiency in their T_{reg} cell frequency under steady-state conditions. Mechanistically, Smith *et al*. show that short-chain fatty acids are natural inhibitors of histone deacetylases (HDACs) 6 and 9, consistent with the promotion of T_{reg} cell function by HDAC inhibition (*9*).

Does GPR43 engagement enhance T_{reg} cell suppressive function? Incubation with short-chain fatty acids indeed increased the suppression of effector T cell proliferation in a GPR43-dependent manner. Similarly, feeding conventionally reared mice either the short-chain fatty acid mix or propionate alone enhanced the ability of intestinal T_{reg}

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cells to ameliorate colitis in a mouse model of inflammatory bowel disease.

Clostridia species belonging to cluster IV and XIVa are a prominent source of acetate, butyrate, and to a lesser extent propionate in the colon (*10*). However, these bacteria increase the development of T_{reg} cells (those that do not express Helios) by inducing epithelial cells to produce TGF-β (*10*). This suggests that there are distinct pathways through which intestinal bacteria can influence intestinal T_{reg} cells. A combination of clostridia species (cluster IV and XIVa) stimulate local differentiation of T_{reg} cells, whereas administration of short-chain fatty acids leads to GPR43-dependent accumulation of thymus-derived T_{reg} cell populations. Further studies are required to determine whether GPR43 signaling in T_{reg} cells boosts proliferation or promotes survival, and to characterize the relative role of this mechanism in sustaining T_{reg} cell activity in the intestine.

How can intestinal bacterial communities be exploited to influence immune responses that benefit the host? One approach is to feed specific "substrates" to the host that would preferentially expand beneficial bacteria—so-called prebiotics. However, the risk of increasing closely related but detrimental species through this approach cannot be ruled out. Thus, while members of the clostridia class are associated with spurring an increase in anti-inflammatory T_{reg} cells (*5*), an expansion of the closely related *Clostridium* cluster XI has been observed in mice sustained on a high-fat diet (*11*). In this case, a shift in the intestinal microbiome resulted in increased amounts of the bacterial metabolite deoxycholic acid, which in turn led to a higher incidence of liver cancer. This illustrates how closely related bacteria can have distinct effects on the host.

A different approach is to isolate beneficial bacterial species and enrich them within the existing bacterial community of the host. The isolation of 17 human clostridia species that can stimulate the expansion of T_{reg} cells in mice (*10*) opens up therapeutic options, but whether feeding these species will result in persistent changes in the preexisting bacterial communities and lasting effects on host immunity remains unclear. Perhaps the most appealing strategy is to identify the bacterial components or metabolites that affect host immunity. This would allow modification of immune cell activity without tampering with microbiota composition. Indeed, Smith *et al*. demonstrate the potential therapeutic value of understanding how bacterial components and metabolites promote human health.

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PHYSICS

Spinning the Doppler Effect

Detection of an object's rotation by exploiting the orbital angular momentum of light may find applications in remote sensing and astronomy.

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The sound from a moving object undergoes a pitch change—the Doppler effect—caused by the acoustic wave frequency increasing as the object approaches and decreasing as it moves away. A similar effect—a blue or red color shift—occurs for light from moving astronomical objects. Waves scattered off a moving object are also subject to a Doppler shift, an effect used in sonar and radar systems to deduce speed. A spinning object may also induce a Doppler effect in backscattered waves if the rotation axis is not pointing directly at the wave source and detector. The spinning object can thus be seen, at any given time, as composed of parts that are moving toward the detector and parts that are receding from it. However, if the rotation axis points toward the detector, this "piecewise" Doppler effect vanishes. This limitation can now be overcome by using "twisted" light. On page 537 of this issue, Lavery *et al*. (*1*) demonstrate that a spinning object with an optically rough surface may induce a Doppler effect in light reflected parallel to the rotation axis, provided that the light carries orbital angular momentum (OAM).

Under suitable conditions, a laser beam can be associated with an electromagnetic energy flow that, while propagating forward, is also continuously turning around the beam axis. Waves of this kind have OAM parallel to the propagation direction (*2*), whose value per photon is given by an (arbitrarily large) integer times the reduced Planck's constant $\hbar$ ($h/2\pi$). Note that OAM should not be confused with the "spin angular momentum" (SAM) that is associated with circular polarization and limited to $\pm\hbar$ per photon. Light waves with nonzero OAM present a helical-shaped wavefront with a well-defined center, where an optical vortex is located (see the figure). Applications of OAM include particle manipulation (*3*), optical nanolithography (*4*), high-bandwidth communication (*5*), and quantum information (*6*).

In the experiments by Lavery *et al*., a collimated laser beam is directed at a spinning disk, and the reflected light is detected and its frequencies analyzed. The frequency analysis is done by looking for intensity "beating" effects that reveal even tiny shifts. Normal laser beams did not show any Doppler shift, as expected. Conversely, when light with nonzero OAM was used (more precisely, with two opposite OAM components), a frequency shift proportional to the disk's angular speed was detected, as expected for a Doppler effect, but also proportional to the optical OAM (see the figure). Because the OAM has no upper bound, the shift can be made arbitrarily large for a given disk speed.

A detailed analysis shows that the frequency shift is actually associated with a variation of OAM in the scattering process and not just with the nonzero input OAM. A perfect, specular reflection does not alter the OAM (apart from a sign change arising from the propagation reversal) and hence induces no Doppler shift. Scattering from an inhomogeneous surface (diffuse reflection) instead generates wave components carrying different values of OAM that undergo different Doppler shifts, acquiring many

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