Fat fights inflammation

A study on page 1023 reveals a potential benefit of much-maligned high fat foods. According to Layer and colleagues, the same hormone that makes you feel full after a fatty meal might also prevent immune cells from mistakenly attacking food proteins as if they were foreign invaders.

Eating—particularly eating fat-rich foods—triggers the production of a hormone called cholecystokinin (CCK) by cells that line the small intestine. CCK binds to its receptor on cells in the gut, pancreas, and central nervous system (CNS), thus stimulating digestive functions, including gut peristalsis and insulin release, and triggering satiation. Layer and his colleagues recently showed that dietary fat also blunts the inflammatory response in a rat model of hemorrhagic shock.

The new study connects CCK to a recently identified antiinflammatory pathway that is controlled by the vagus nerve. This pathway—dubbed the cholinergic antiinflammatory pathway—is mediated by the neurotransmitter acetylcholine, which is released from vagus nerve endings upon stimulation. Acetylcholine binds to nicotinic receptors on macrophages, thus inhibiting the synthesis and release of inflammatory cytokines such as TNF and interleukin (IL)-6.

Layer et al. now show that the antiinflammatory effect of fat consumption in the rat model of hemorrhagic shock requires both CCK and the vagus nerve, as blocking CCK or severing the vagus nerve abolished this effect. With the vagus nerve intact, fat-induced CCK inhibited the production of circulating TNF and IL-6 and reduced gut permeability. Blocking nicotinic receptors also eliminated the antiinflammatory effects of dietary fat, thus solidifying the connection between fat-induced CCK and the cholinergic antiinflammatory pathway.

The authors think that this pathway might be important in suppressing gut inflammation in response to food proteins and normal gut bacteria, which immune cells might otherwise regard as foreign invaders. They also suggest that this pathway could potentially be targeted in patients as a way to reduce inflammatory complications after surgery.

CD103 spurs on suppressors

An integrin expressed by gut dendritic cells (DCs) gives regulatory T (T reg) cells the green light for suppression, according to a study on page 1051. Annacker and colleagues show that DCs expressing the integrin CD103 are required for T reg cells to subdue gut-attacking effector T cells in a mouse model of inflammatory bowel disease (IBD).

Naturally occurring T reg cells help protect against autoimmunity and excessive inflammation by suppressing the activity of effector T cells. This group had previously shown that transferring T reg cells protects against T cell–induced IBD in mice. The suppression of IBD requires the cytokine TGF-β and possibly the high levels of CD103 that are seen in a subset of T reg cells.

Annacker et al. now show, however, that CD103 is not required on the effector T cells for them to induce disease, nor on the T reg cells for them to suppress disease. However, CD103 was not completely expendable. T reg cells could not suppress colitis when transferred into CD103-deficient mice, suggesting that CD103 expression on non–T cells somehow spurs the T reg cells into action.

The relevant CD103-expressing cells were DCs, consistent with the study by Johansson-Lindbom et al. (page 1063) showing that CD103 marks lymph node DCs that originated in the gut. But how these DCs communicate with T reg cells is not clear. Both groups showed that CD103+ DCs, but not CD103− DCs, induced the expression of the gut-homing chemokine receptor CCR9 on effector T cells in vitro. This suggests that CD103+ DCs might similarly induce CCR9 expression on T reg cells, thus endowing them with the ability to migrate to the gut—a possibility not yet tested in vivo.

But the effect of CD103 could also be indirect, suggests senior author Fiona Powrie. CD103 may help trap DCs in the gut by binding to its receptor (E-cadherin) on intestinal epithelial cells, consistent with the recent finding that CD103 is needed to retain pathogenic CD8+ T cells in the gut during graft versus host disease. Although this mechanism remains speculative, retention of DCs in the gut might be a prerequisite for endowing T reg cells with the ability to suppress.
FoxP3 gets a new gig

On page 1141, the one-trick transcription factor FoxP3 reveals a new function. According to Chang and colleagues, FoxP3 does more than just drive regulatory T (T reg) cell development; it also promotes the proliferation of developing thymocytes.

FoxP3 is required for the development of CD4⁺CD25⁺ T reg cells, which subdue the activation of conventional T cells and thus protect against chronic inflammation and autoimmunity. Mice and humans that lack FoxP3 develop a spontaneous, multi-organ autoimmune disease that has been primarily attributed to the lack of T reg cells. But one fact suggests that this explanation may be too simple. Irradiated mice that are reconstituted with FoxP3-deficient bone marrow do not develop disease, suggesting that FoxP3 also functions in non-hematopoietic cells.

Chang and colleagues now show that FoxP3 is not exclusive to T cells, but is also expressed in thymic epithelial cells. In mice lacking FoxP3, developing thymocytes were unable to proliferate normally, resulting in thymic atrophy. The proliferation defect was caused by a lack of FoxP3 in thymic stromal cells, rather than in T cells, as normal thymocytes also failed to proliferate in a FoxP3-deficient thymic environment.

How FoxP3 expression on thymic epithelial cells helps drive thymocyte proliferation is unknown. Also unclear is how the proliferation defect contributes to autoimmune disease, although there is a long-standing but poorly understood link between thymic atrophy and T cell–driven autoimmune disease. JEM

CCR5 saves lives

Although West Nile virus (WNV) infections have made headlines in recent years, little is known about how the virus causes disease or how the immune system fights back. On page 1087, Glass and colleagues show that immune cells must invade the central nervous system to combat the virus, and the chemokine receptor CCR5 is their entry ticket into the brain.

WNV is an RNA virus that attacks the brain and can cause meningitis and encephalitis. Although infections with WNV can be fatal, most cases are mild or asymptomatic, suggesting that the immune system is capable of fighting off the virus. But the details of the anti-WNV immune response remain poorly characterized.

Glass and colleagues now show that WNV infection in mice triggers an influx of T cells, natural killer cells and macrophages into the brain in response to local production of chemokines. The influx of cells, which protected the mice against lethal infection, largely depended on the expression of CCR5 on the responding cells. In CCR5-deficient mice, fewer cells gained access to the brain and the infection was uniformly fatal.

To determine whether CCR5 is equally important for combating WNV infection in humans, the authors are now testing whether people who had severe or fatal infections with WNV were more likely to carry the CCR5 deletion mutation. This mutation is best known for its ability to protect against HIV infection, as CCR5 is a cellular coreceptor for HIV. JEM

New target for T regs

The natural killer (NK) cell is a new target for regulatory T (T reg) cell tyranny, according to a study on page 1075. Ghiringhelli and colleagues show that the antitumor activity of NK cells is snuffed out by T reg cells, allowing tumors to grow unchecked.

NK cells are innate immune cells that help destroy NK cell–sensitive tumors, such as melanomas and gastrointestinal tumors, which express activating ligands for these cells. The activation and antitumor functions of NK cells are triggered by the binding of these ligands to the activating receptor NKG2D on the NK cells. In many cancer patients, NK cell activity is hampered by the shedding of NKG2D ligands from tumor cells or by other unknown mechanisms.

This group recently showed that a drug that activates NK cells in patients with gastrointestinal cancer improved their prognoses. They now report that the patients who did not respond to this therapy had increased numbers of circulating T reg cells, whereas the patients who responded did not. The T reg cells from nonresponding patients prevented NK cells from killing tumor cells in vitro.

In mice, transfer of T reg cells blocked the killing capacity of NK cells. This inhibition depended on the expression of membrane-bound TGF-β on the T reg cells, which triggered the down-regulation of NKG2D on the NK cells. Thus TGF-β–induced inhibition of NK cell activation, which normally helps curtail inflammation and prevent autoimmunity, helps certain tumors avoid being recognized by these killer cells. JEM