MICROBIAL EFFECTS ON DRUG METABOLISM

Gut bacteria harbor enzymes and pump out other molecules that can influence how medications are activated or broken down. One example is the Parkinson’s drug levodopa (L-dopa), for which studies have suggested these interactions help explain differences in efficacy among individuals.

INTESTINE

Researchers found that some gut bacteria produce an enzyme called tyrosine decarboxylase that can convert L-dopa into dopamine as the drug passes through the small intestine, before it can reach the brain. Testing the stool of patients with Parkinson’s, the team discovered that the abundance of the bacterial gene for tyrosine decarboxylase correlated with a need for a higher dose of L-dopa to control their symptoms (Nat Commun, 10:330, 2019).

Another team identified a small-molecule inhibitor that appears to block the enzyme’s action in mice (Science, 364:aead6323, 2019).

BRAIN

After crossing the blood-brain barrier, L-dopa is converted to dopamine by neurons’ own enzymes to treat the symptoms of Parkinson’s disease. Because there is no transporter protein for dopamine, it can’t cross the blood-brain barrier itself, so L-dopa that’s converted to dopamine prematurely in the intestine can’t reach the brain.

REVIVING UP THE IMMUNE SYSTEM

In addition to releasing products that directly act on drugs in the body, resident microbes can affect drugs’ action through the immune system, which is particularly relevant for patients’ responses to immunotherapy. While little is known about the mechanisms by which certain bacterial species seem to boost a patient’s chance of success with these immune-modulating treatments, hints of a causal role have emerged from studies that compared responses in tumor-ridden mice with normal microbiomes to those in rodents whose gut microbes had been depleted by antibiotics.

TNF boost

In one study, gut microbes appeared to prime murine immune cells to secrete tumor necrosis factor (TNF) when the animals were treated with Cpg oligonucleotide immunotherapy—short, synthetic segments of DNA that can help stimulate the immune system to attack cancer cells. TNF in turn induced tumor necrosis (Science, 342:967-70, 2013).

CDB⁺ T cell ASSIST

In another study, mice were treated with tumor-specific CDB⁺ T cells from other mice—a similar procedure to CAR T cell therapy—and gut microbes promoted dendritic cell maturation via the transmembrane protein toll-like receptor 4 (TLR4). The mature dendritic cells then activated the CDB⁺ T cells, inducing them to kill tumor cells (Cell, 177:299-304, 2019).