Once triggered into action, an immune cell overhauls its metabolism in ways that could be exploited for treatment.

By Mitch Leslie

About 12 years ago, Gary Glick and his wife noticed something wrong with their son, Jeremy. He seemed to be lagging behind his twin sister, recalls the immunologist and chemical biologist at the University of Michigan in Ann Arbor. “They were growing in unison, and he sort of stopped.” Jeremy, who was 9 or 10 at the time, also looked sickly and pale and began complaining of nagging pains in his stomach and elsewhere.

Rachel Lipson Glick, a physician, was stumped by their son’s mysterious ailment. So were other doctors. It took about 3 years to rule out myriad cancers, endocrine malfunctions, and other potential causes and to determine that Jeremy had Crohn disease, an inflammation of the digestive tract stoked by misbehaving immune cells.

The diagnosis made life harder for Jeremy, now 22 and a senior at college. To control the symptoms, he injects the antibody drug adalimumab (Humira). He will likely need it, or another immune-inhibiting treatment, for the rest of his life.

By coincidence, one of those alternatives might stem from his father’s work. Gary Glick, like an increasing number of other researchers, is convinced that the immune cells driving conditions such as Crohn disease share a feature that could be their undoing: their metabolism. He has spent the past 2 decades searching for drugs that target metabolic adaptations of immune cells.

Clinical trials by Lycera, a company Glick founded, are now assessing the first of those drugs for psoriasis and ulcerative colitis, an intestinal illness related to Crohn disease.

Drug companies are working to develop other candidates. Researchers are also look-
ing to deploy existing drugs that tamper with metabolism, such as the diabetes treatments metformin and 2-deoxylglucose (2DG). “It’s a very exciting time,” says immunologist Jonathan Powell of Johns Hopkins University’s School of Medicine in Baltimore, Maryland. “Potentially, all immunologic diseases are targets for metabolic therapy.”

Cancer researchers have also tried to disrupt cell metabolism, even testing some of the same drugs immunologists are investigating. But many scientists are convinced the strategy will work better for immune diseases than for tumors because drugs to treat those illnesses need only to suppress a relatively small number of overexuberant cells, not eliminate them. And whereas existing drugs that restrain immune cells, such as adalimumab, can compromise our defenses against pathogens, Glick and other scientists think that drawback won’t affect their strategy. Focusing on the metabolism of overactive immune cells, he says, offers “a way to directly target these cells while sparing immune function.”

IN THE 1920s, the German doctor and chemist Otto Warburg was the first to realize that immune cells have a distinctive way of fueling themselves. To power their activities, cells need to produce the molecule adenosine triphosphate (ATP). They can make it directly through glycolysis, a biochemical pathway that dismembers glucose. Or they can generate ATP through a more involved process called oxidative phosphorylation, which requires energy-laden molecules produced by glycolysis but also enlists other biochemical reactions that break down fatty acids and amino acids such as glutamine (see graphic, p. 1456).

Normal body cells typically rely on oxidative phosphorylation for most of their energy needs, but Warburg discovered that cancer cells rapped up glycolysis. He also noticed that some healthy cells depended on glycolysis: immune cells.

Warburg was on the right track, but researchers now know that when immune cells aren’t fighting pathogens, they set their metabolism to low and produce ATP mainly through oxidative phosphorylation. The arrival of a threat, such as a flu virus reproducing in the lungs, activates the cells, galvanizing them to combat the invader. At that point, “they undergo these massive metabolic changes,” says immunologist Erika Pearce of the Max Planck Institute of Immunobiology and Epigenetics in Freiburg, Germany. The stimulated cells don’t just require more energy, she notes. An activated T cell can divide several times per day, quickly spawning an army of millions of descendants. To sustain that mobilization, the cells also require large amounts of raw materials, such as the precursors of DNA, proteins, and lipids.

How exactly an activated immune cell satisfies its massive demand for energy and molecular material depends on what type of cell it is. Activated helper T cells, which serve as immune commanders, seem to follow Warburg’s paradigm. They guzzle glucose and crank up glycolysis, although they also boost the rate of oxidative phosphorylation, which requires energy-laden molecules produced by glycolysis but also enlists other biochemical reactions that break down fatty acids and amino acids such as glutamine (see graphic, p. 1456).

Immune cells also make different metabolic choices depending on whether they are memory cells, which persist for years and protect us from getting sick from the same pathogen more than once, or shorter-lived effector cells specialized to attack microbes immediately. Memory T cells, for instance, typically favor oxidative phosphorylation and consume fatty acids. Effector T cells, by contrast, turn up glycolysis and are heavy glucose users—a difference reflected in their mitochondria, the organelles that serve as cellular power plants, Pearce and her colleagues reported 2 years ago.

Although memory T cells “have these beautiful, intact, threadlike mitochondria,” she says, effector T cells mince their mitochondria. The organelles are where oxidative phosphorylation takes place, and breaking them up may make that metabolic pathway less efficient and promote glycolysis, the researchers suggest.

Metabolic adaptations permit immune cells to perform their protective roles, but sometimes they lead cells to malfunction. In rheumatoid arthritis, for instance, activated T cells slip into the joints, says immunologist Cornelia Weyand of Stanford University in Palo Alto, California. “They like it there, and they stay and they cause chronic tissue inflammation.”

That behavior reflects a change in metabolism. Like other activated T cells, the T cells implicated in rheumatoid arthritis rely on glycolysis. But they tweak that pathway to make less ATP and more of the molecular precursors needed to support their rapid division. As a result, the T cells run short of reactive oxygen species—key signaling molecules that control their behavior—and go rogue. They speed up their reproduction and specialize into varieties that promote inflammation.

The cells also become better gymnasts, skilled at slithering through narrow spaces into the joints. Weyand and her colleagues found that the abnormal T cells sprouted ruffles on their cell membranes that enabled them to penetrate deeper into tissues. Within the joint, the mobile T cells help stimulate other cells to form a lesion that resembles a nonhealing wound, Weyand says, and that causes pain and further joint deterioration.

“The metabolism of the cell controls its behavior, and its behavior is not good for the patient,” she says.

PEARCE SAYS the prospect of meddling with immune cell metabolism to treat diseases frightens some of her colleagues, who fear crippling the body’s entire defense system or harming other vital cells. “If you give an inhibitor of glycolysis, isn’t that going to kill someone?” they ask her. But immunologist Jeff Rathmell of Vanderbilt University Medical Center in Nashville says that only a small fraction of immune cells—and of body cells in general—boost their use of those pathways and would
be affected by metabolism-altering drugs. “Most cells don’t care.”

Work in animals suggests that targeting immune metabolism is a promising approach. In one 2015 study, immunologist Laurence Morel of the University of Florida in Gainesville and colleagues dosed mice that were genetically modified to develop a lupuslike condition with metformin and 2DG. Metformin curtails oxidative phosphorylation, whereas 2DG squelches glycolysis. Together, the molecules reversed lupus neurological symptoms such as muscle destruction in the animals and reduced multiple sclerosis, in which the immune system attacks nerves’ insulating myelin sheath. The compound prevented myelin destruction in the animals and reduced neurological symptoms such as muscle weakness, the scientists reported in 2014. In another study, Rathmell and colleagues added dichloroacetate, which suppresses glycolysis, to the drinking water of mice that have a condition that mimics multiple sclerosis, in which the immune system attacks nerves’ insulating myelin sheath. The compound prevented myelin destruction in the animals and reduced neurological symptoms such as muscle weakness, the scientists reported in 2014.

Impeding cellular metabolism also could curb the immune system’s attacks on transplanted organs, Powell and colleagues have found. They gave metformin, 2DG, and a third drug that blocks the metabolism of glutamine to mice that had received skin grafts or heart transplants. The skin grafts survived about four times longer in the treated mice than in control animals, which quickly rejected the tissue. Transplanted hearts also worked much longer in mice that received the drug trio, the team reported in 2015 in Cell Reports.

**Alternative energy sources**

Activated immune cells change what they consume and which metabolic pathway they use to break down that fuel to produce energy-carrying ATP. Some types load up on glucose, increasing glycolysis, and they consume more glutamine. Fatty acids remain a staple for other cells, which still depend on oxidative phosphorylation.

![Diagram of metabolic pathways]

Glutamine

Fatty acids

Glucose

Glycolysis

Oxidative phosphorylation

ATP

Raw materials

Cell

Mitochondrion

Adenosine triphosphate

- Increase intake
- Decrease intake

Helper T cell

Cytotoxic T cell

Regulatory T cell

B cell

B or T memory cell

years ago, Argentine researchers reported fewer new brain lesions in 30 patients with multiple sclerosis who took metformin or another drug that short-circuits oxidative phosphorylation. A clinical trial by Chinese researchers is testing whether metformin can quell lupus flares. And so far, such drugs seem safe. “Metformin on its own does very little to impair immunity, for example, but can reduce chronic inflammation,” Rathmell says.

Skeptics note that researchers also have tried to repurpose metformin and 2DG to block metabolism in cancer cells, with inconsistent results. However, Powell and other scientists say they aren’t discouraged. In contrast to cancer cells, “You don’t actually have to kill an [immune] cell to modify its metabolism,” Rathmell says.

These hand-me-down drugs weren’t designed to tweak immune cell metabolism, adds cancer biologist Ralph DeBerardinis of the University of Texas Southwestern Medical Center in Dallas. “We shouldn’t be surprised if they don’t have the potency or specificity to have a significant effect.”

Some scientists think talk of treatments is premature. Inhibiting immune cells’ energy-producing reactions in a chronic disease “is an appealing idea,” says mitochondrial biologist Navdeep Chandel of Northwestern University’s Feinberg School of Medicine in Chicago, Illinois. But he contends that researchers don’t understand immune cell metabolism well enough to know how to intervene safely and effectively.

Yet a study published online this week in *Science* provides more support that inhibiting immune metabolism can quell human diseases. The work centers on a drug, dimethyl fumarate, that has already received approval from the U.S. Food and Drug Administration as a treatment for multiple sclerosis. Although researchers knew that the drug suppresses immune cells, they weren’t sure how. A team led by scientists at Johns Hopkins now reports that the compound cripples an enzyme necessary for glycolysis, bolstering the idea that the pathway can be targeted by drugs.

Glick is confident that he and others are on to something. The compound he discovered dates to research he began in the mid-1990s. “I sort of backed into it,” he says. Glick and his colleagues were looking for compounds that would kill B cells, the antibody-producing cells that help cause the symptoms of lupus. After testing several compounds, they found one that stimulates an enzyme necessary for oxidative phosphorylation.

Lycera is evaluating an improved version of that molecule in people with psoriasis or ulcerative colitis in part because it’s easier to test drugs on those diseases than on lupus, whose symptoms affect more organs and are harder to track. Unlike the adalimumab that Jeremy Glick injects, this drug can be taken in pill form. Lycera plans to announce the results of its two trials later this year.

This month, a new company founded by Gary Glick started clinical trials of an existing antiparasite drug, niclosamide, in patients with ulcerative colitis. Niclosamide, which kills tapeworms by inhibiting oxidative phosphorylation, has a long safety record, Glick notes. “It’s approved for children and pregnant women,” he says.

Glick was searching for compounds that tinker with immune cell metabolism years before his son was diagnosed with Crohn disease, but he says Jeremy’s illness furnished extra motivation. “If he could wake up every morning and take a pill that dad invented, he’d be thrilled,” Glick says.
Putting immune cells on a diet
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