UC SANTA BARBARA

THE Current

August 12, 2024

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An appetizer can stimulate immune cells' appetite, a boon for cancer treatments

The body has a veritable army constantly on guard to keep us safe from microscopic threats from infections to cancer. Chief among this force is the macrophage, a white blood cell that surveils tissues and consumes pathogens, debris, dead cells, and cancer. Macrophages have a delicate task. It's crucial that they ignore healthy cells while on patrol, otherwise they could trigger an autoimmune response while performing their duties.

Researchers at UC Santa Barbara sought to understand how these immune cells choose what and when to eat. A paper published in Developmental Cell describes how the team programmed macrophages to respond to light in order to investigate how encounters with cancer cells change the macrophages' appetite. "We discovered that giving macrophages an appetizer makes them hungrier for their next meal," said senior author Meghan Morrissey, an assistant professor in the Department of Molecular, Cellular, and Developmental Biology.

The results present a new way to increase the effectiveness of cancer immunotherapies that harness macrophages to combat the disease. It also offers a more complex account of trained immunity, a kind of memory exhibited in the innate immune system that scientists have only recently recognized.

Using light to control the cellular appetite

While monitoring the body, macrophages scout for cells and debris tagged with the antibody IgG by other immune cells. These function as “eat me” signals to the macrophages, which detect them via Fc receptors (FcR) embedded in their cell membrane. Fc receptors are mobile, and begin to cluster once activated by IgG. Once this reaches a certain threshold, the macrophage engulfs the target.

Lead author Annalise Bond, a doctoral student in Morrissey’s lab, developed another way to cluster the FcR that doesn’t require IgG. With help from UCSB professor Max Willson, she designed a synthetic protein containing part of the FcR receptor fused to cryptochrome 2 (CRY2). This protein clusters together when activated by blue light, enabling Bond to precisely control the system and trigger the FcR at will.

The trick worked marvelously. Bond was able to use light to coax the macrophages to consume silica beads coated with a lipid membrane to mimic cancer cells. All without any IgG. Now they could give the macrophages a “light snack” to see how it affected their eating habits later on.

Pavlov’s macrophages

Bond stimulated engineered macrophages with light, then made the cells wait for different periods of time. She then presented them with the mock cancer cells, this time displaying that IgG “eat me” antibody.

The light-activated group ate much more after their simulated snack than the control group, which lacked light-activated FcR. “I’ve described it as Hungry Hungry Hippos,” Bond said, “because they’re just gobbling up everything that’s there.” Activating FcR with subthreshold levels of the IgG antibody on cancer cells also primed the macrophages for their next meal.

However, with too much stimulation, the effect disappeared. “If the macrophages got so much IgG that they actually eat, then it wasn’t an appetizer,” Morrissey explained. “It was more like a meal. So they weren’t hungry anymore.”

The authors aren’t positive why macrophages behave this way, but they have a hypothesis. As a macrophage scouts around healthy tissue, its top priority is to avoid

triggering autoimmunity. So the macrophage sets a pretty high activation threshold. Now consider a macrophage that begins to encounter IgG antibodies. “Once you see a hint that something’s wrong, now your top priority is clearing the infection, and you’d be willing to damage the tissue a little bit if you had to,” Morrissey said.

What’s going on?

The macrophages’ appetite peaked around an hour after the initial trigger, before dipping and then rising again for a sustained period after four hours. Bond was curious what mechanisms underly this pattern. “One hour is way too fast for the cell to make new proteins,” Morrissey said, so something else must be going on.

Indeed, the macrophages retained their short-term priming when Bond blocked protein synthesis, suggesting that something else controlled this response. However, disabling protein synthesis eliminated the cells’ long-term enhanced appetite, indicating that this behavior relies on changes to gene expression and protein synthesis.

With more testing, Bond discovered that subthreshold activation of FcR triggered changes to how the receptors move around the cell membrane. It increases the receptors’ mobility, enabling them to aggregate more easily when exposed to IgG within about an hour. At the same time, the cell begins upregulating different genes and producing new proteins, explaining the longer term effects.

“This short-term mechanism is really interesting because it’s a totally different type of immune memory than what’s been seen before,” Morrissey said.

Hungry macrophages eat more cancer

Macrophages find antibodies like IgG irresistible; they’ll eat pretty much anything tagged with them, even the glass beads Bond used in her experiments. As a result, monoclonal antibodies have become a popular treatment for various diseases. In fact, antibodies are currently used in many different cancer therapies. Bond was able to increase the efficacy of a common antibody (Rituximab) that is used to treat lymphoma.

Bond and Morrissey’s results suggest that multiple, small doses of antibody therapy will be more effective than a single large dose, since previous doses can prime the cells for the next treatment. Indeed, oncologists found this to be true through trial and error.

There are also other macrophage therapies that might benefit from pretreatment: exposing engineered macrophages used in certain therapies to IgG before introducing them to the patient so they are primed to consume more cancer cells.

A memory spectrum

For a long time, biologists and doctors thought only the adaptive branch of the immune system had any sort of immunological memory. But a more nuanced picture has begun to emerge.

This experiment showed that even parts of the immune system that aren’t commonly thought of as having memory might respond to prompts. And it suggests that immunological memory is a spectrum, with some cells reacting to the here and now; others remembering infections for decades; and some, like macrophages, falling in between.

The work also presents a more complex portrayal of macrophages, suggesting that they’re more sophisticated decision makers than scientists had thought. “Macrophages need to think about the situation they’re in,” Morrissey said. “Are they in healthy tissue and need to avoid autoimmunity, or are they fighting an infection and need to go out guns blazing?”

Diving further into the details

Macrophages actually have two versions of the Fc receptor: One promotes their appetite while the other inhibits it. And both are triggered by IgG. Macrophages have more of the activating version, so that one eventually wins out. But it’s not clear why the cell has both, rather than just a smaller number of activating FcR.

It’s a mystery Bond is working to solve. “Now that I have this tool kit to explore macrophage appetite, I am really interested in understanding how the inhibitory FcR functions,” she said. The technique she developed enables her to selectively trigger

just one FcR, so she might just be able isolate the role the inhibitory FcR plays in her future work.

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