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Recently discovered cell is unexpected player in psoriasis

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When the FDA assesses a drug, it looks closely at its safety and its effectiveness, but it doesn't require a precise understanding of how the drug works. A new study by Rockefeller University scientists shows that a strikingly successful psoriasis drug, etanercept, may not act on the immune cells that scientists had originally believed. In fact, their findings indicate that the disease itself may be partially driven by these recently discovered cells.

T helper or "Th" cells play a vital role in coordinating immune response. Until now, one of these types of helper cells, called Th1, was believed to be a major contributor to psoriasis because it produces a molecule called interferon gamma, which is strongly associated with the disease.

But by looking at the reactions of immune cells to etanercept, James Krueger — head of the Laboratory of Investigative Dermatology and D. Martin Carter Professor in Clinical Investigation — and his colleagues found that a newly discovered helper cell, Th17, may play a major role in the disease.

Most studies of psoriasis drugs to date have begun looking at patients' disease profiles four weeks after the treatment starts. But by that point, says biomedical fellow and first author Lisa Zaba, "all the action is over." Instead, she decided to look not just at a patient's latent response to etanercept treatment but also at what happens during the first few weeks. "We really wanted to discern patterns of action, so we could determine what's happening first, what's happening second," she says.

“That way, we can go back to the immune system and figure out which cells are partially responsible.”

By watching 20 different patients’ immune reactions to etanercept at four different time points — at the end of one week, two weeks, four weeks and 12 weeks — an interesting pattern began to emerge. At the end of week one, the drug had already decreased the activity of Th17 cells. It wasn’t until the 12th week, however, that interferon gamma levels decreased, indicating that the Th1 cells had been downregulated. “That raises the logical question,” Zaba says. “If this is supposed to be a Th1 disease, why are patients getting better before their Th1 activity goes down?”

When Zaba and her colleagues tried to answer this question, they discovered that the problem likely goes far beyond Th1 cells. In fact, Zaba says, “the dendritic cell is possibly more central to this disease.” Dendritic cells, which are responsible for directing immune response and which have receptors on their surface that etanercept prevents from activating, can’t mature and activate Th cells when the drug is present.

The more scientists understand about how psoriasis works, the better equipped they are to make therapies that treat it. By understanding the immune reaction in more detail, researchers will be able to create a drug more specific than etanercept, and one that can be even more effective.

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