Rare hybrid cell key to regulating the immune system

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Dr. Andrew Mellor, co-director of the Immunotherapy Discovery Institute at the Medical College of Georgia, and M.D.-Ph.D. student Burles A. Johnson III have learned of a rare hybrid immune cell that functions as an on/off switch for the immune system. Credit: Phil Jones, MCG campus photographer

A cell small in number but powerful in its ability to switch the immune system on or off is a unique hybrid of two well-known immune cell types, Medical College of Georgia researchers report.

"This is actually the first cell we know of that has this type of

appearance in nature," Dr. Andrew Mellor, molecular geneticist and immunologist who co-directs MCG's Immunotherapy Discovery Institute, said of the cell that looks like a dendritic cell and a B cell but isn't really either.

The discovery of this rare hybrid could have implications for the efficacy of new therapies that manipulate these two cell types to treat diseases such as cancer and rheumatoid arthritis.

When MCG scientists first reported the human equivalent of this cell in *Science* in 2002, they called it a subset of the dendritic cell that clusters in high exposure areas such as the gut but also roams the body, looking for invaders like a virus or cancer. Dendritic cells show their find to T cells, telling them to ignore or attack by bringing trash-eating macrophages, natural killer cells and the like into the fight.

What seemed most unique about the subset is its ability to express indoleamine 2,3 dioxygenase, or IDO, to turn off T cells. IDO is an enzyme used by fetuses and tumors alike to escape the immune response.

The new studies show that is only part of the cells' distinctiveness. The cells also have the identifying markings of B cells, known for their ability to make antibodies against invaders. In fact, they found the IDO-presenting cells came from the same precursor cell as B cells. But, when the scientists looked at mice missing B cells, they still found the IDO-producing cells. Hence, the cell didn't need to produce antibodies to turn off T cells.

In reality, IDO-expressing cells have properties of both cells, said Burles A. Johnson III, an MCG M.D.-Ph.D. student and first author of the paper published online this week in PNAS. "It looks like a B cell and it's not. It looks like a dendritic cell and it is and it isn't," Johnson said.

While their studies are in mice, the cells also are in humans, showing up in some unfortunate places such as the drainage system for tumors, melanoma or even HIV where they likely help the diseases survive.

They also may be showing up in new dendritic cell therapies designed to strengthen the immune response to cancer. If the therapies happen to include some IDO-expressing cells, those could end up helping the cancer, said Mellor, the paper's corresponding author. "All you need is a few of these cells in your dendritic cell vaccine and you don't get stimulation any more, you get suppression," Mellor said.

Their confusing face could also cause hybrids to be lost in B cell-depleting therapies designed to lessen the immune system's attack on joints in rheumatoid arthritis. "These therapies may also deplete IDO-expressing cells and decrease therapy effectiveness because you are eliminating cells that are there to help you," Johnson said.

"This gives us new insight into why these therapies might not be working as well as we think they might," Mellor added. Long-term goals include figuring out how to manipulate the hybrid's activity to benefit patients.

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