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The B side of stroke

By Lev Osherovich, Senior Writer

Oregon researchers have found that B_{reg} cells in the periphery can limit stroke-induced brain inflammation in mice.[1] The findings add to a growing list of indications, including cancer, rheumatoid arthritis and multiple sclerosis, in which academics have shown that B_{reg} cells can have protective effects. The key to turning these rare cells into therapy will be finding ways to culture B_{reg} cells *in vitro* or expanding their number *in vivo*.

Previously, T_{reg} cells were thought to control brain inflammation.[2] The new study, by an **Oregon Health & Science University** team, calls that hypothesis into question and suggests the key players are actually B_{reg} cells.

"People now think that there's a big immunological component to stroke"
—Halina Offner, Oregon Health & Science University

B_{reg} cells "are a very small proportion of B cells, less than 1%," said Thomas Tedder, professor of immunology at **Duke University**. Tedder, whose lab focuses on B_{reg} cells, said the cells' normal role is to limit the inflammatory effects of conventional B cells during the early stages of an immune response, before a T cell response has time to develop.

"People are now starting to move into this area but are just getting started," he said. "I've talked to about 20 different companies in the past year" about B_{reg} cell basics.

Peripheral interest

A team led by Halina Offner, professor of neurology, anesthesiology and perioperative medicine at Oregon Health & Science University, as well as other groups, had previously seen signs of B_{reg} cell involvement in autoimmunity-associated neural inflammation.

The Oregon team set out to see if B_{reg} cells have effects on other inflammatory brain conditions, looking first at stroke.

Because it is not yet possible to selectively eliminate B_{reg} cells *in vivo*, the group first tested whether B cells in general affected stroke-associated brain damage. The team induced ischemic stroke in mice unable to make either conventional B cells or B_{reg} cells.

Mice lacking B cells had larger brain infarcts and worse neurological functioning after transient brain ischemia than wild-type mice, suggesting B cells blunt the severity of brain damage in stroke.

This result was surprising because B cells, unlike many immune cells, do not infiltrate stroke-damaged regions of the brain. The team found that B cell–deficient mice had higher numbers of other proinflammatory cells in damaged regions of their brains than wild-type mice—but transplanted B cells, which reversed this increase in inflammation, did not migrate into the brain.

"When we inject GFP-labeled B cells into these mice, we see these cells only in the periphery. They don't go to the central nervous system," said Offner.

Thus, Offner suspected the B cells were exerting their effects on stroke from the periphery, in part via IL-10, an anti-inflammatory cytokine produced by B_{reg} cells.

They thus looked at whether the specific absence of B_{reg} cells led to the worsening of stroke-induced brain damage. To test this idea, Offner transplanted B cells from either wild-type or Il-10 knockout mice into mice lacking B cells altogether.

Transfusion of wild-type B cells improved stroke outcomes, whereas transfusion of Il-10-deficient B cells had no effect. That finding suggests IL-10 from B_{reg} cells is required for dampening brain inflammation.

Lastly, the team found that levels of circulating Il-10 and the number of Il-10-producing B cells rose after ischemia, suggesting that these cells become activated during stroke.

Results were published in *The Journal of Neuroscience*.

T vs. B

Offner's findings raise the possibility that the immunological component of stroke could be modulated with therapies that increase the peripheral activity of B_{reg} cells.

"People now think that there's a big immunological component to stroke," said Offner, but most work has focused on local inflammatory events in the brain rather than peripheral regulation of that inflammation.

According to a 2009 report by German researchers, the response to stroke-induced brain inflammation may also involve T_{reg} cells.[2]

It is thus possible that both types of regulatory immune cells are working at different time points to dampen post-stroke inflammation, with B_{reg} cells acting earlier than T_{reg} cells, as was seen in a recent study of B_{reg} cells in rheumatoid arthritis.[3]

The big unknown is whether increasing the number or activity of B_{reg} cells will have a therapeutic effect. Offner is now devising a cell surface marker screening strategy to obtain large quantities of B_{reg} cells to test this idea.

Meanwhile, Duke's Tedder is developing *in vivo* methods to increase B_{reg} cell activity, such as activating B_{reg} cells in an antigen-specific manner.

Although other teams have recently reported success in culturing T_{reg} cells,[4–6] Tedder said working with B_{reg} cells in cell culture is particularly challenging.

B_{reg} cells "are functionally very different than T_{reg} cells," said Tedder. "You can't expand them as readily *in vitro*, and B_{reg} cells only transiently produce IL-10 before differentiating into conventional antibody-producing B cells."

Tedder said B_{reg} cells, like innate immune cells, can be activated by toll-like receptor (TLR) agonists. At least 20 companies are

developing agents that target TLRs for a wide range of indications.

Tedder and Offner agree that simply treating stroke patients with IL-10 is unlikely to work, as that cytokine is thought to be only one of many anti-inflammatory factors mobilized by B_{reg} cells.

Offner did not patent her findings.

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COMPANIES AND INSTITUTIONS MENTIONED

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