Proliferation cues 'natural killer' cells for job change

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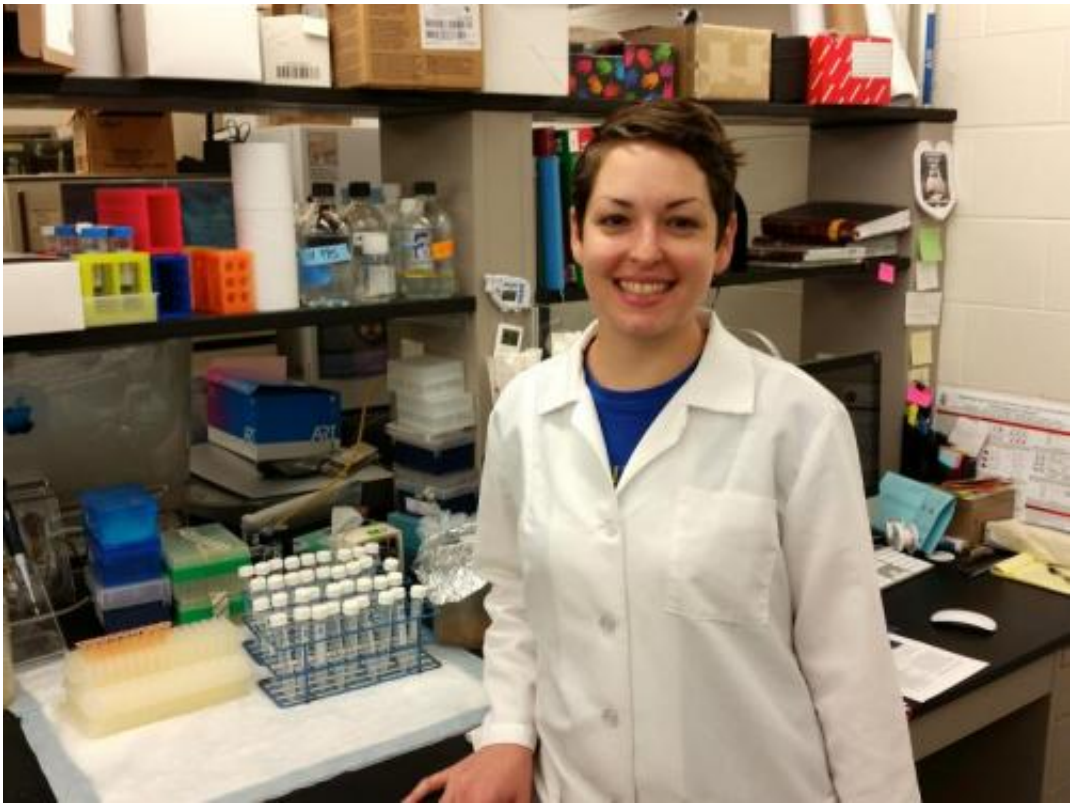

Working with colleagues including Professor Christine Biron, graduate student Margarite Tarrio helped discover that when 'natural killer' cells proliferate after infection, their role changes from from marshaling the immune response to regulating it. Credit: David Orenstein/Brown University

The immune system maintains a rich abundance of "natural killer" cells to confront microbial invaders, but as the body gains the upper hand in

various infections it sometimes starts to produce even more of the cells. For three decades, scientists haven't understood what purpose that serves. In a new paper, Brown University researchers show one: proliferation helps change the NK cells' function from stimulating the immune response to calming it down, lest it get out of hand.

In a series of experiments now published online in the *Journal of Immunology*, the researchers show that the process of proliferation unlocks expression of the gene in NK cells for producing Interleukin-10(IL-10), a protein that moderates other immune system cells.

"It's really important for regulating potentially dangerous CD8 T cell responses," said Margarite Tarrio, co-lead author of the paper and a graduate student in the lab of Brown immunology Professor Christine Biron. "If you get CD8 T cells that are hyperactivated they can cause a tremendous amount of damage."

Ever since Biron and colleagues published the first observations of NK cell proliferation in 1982, she has sought to figure out why it happens. Knowing the answer is important both as a matter of basic immunology and because NK cells, as crucial members of the body's first line of infection defense, are often the subjects of efforts to harness the immune system in protection against infections and cancer.

"The work provides another important role for lymphocyte proliferation, to set up the conditions needed for changing function," Biron said. "It is likely to be part of the mechanism for changing the functions of other immune cells, and the insight may help in designing vaccines."

Shown down to the gene

An association between NK cells and IL-10 production doesn't

necessarily emerge in all infections, but it does come up in some pretty important ones. Scientists have observed it in human cases of hepatitis C, for example.

In the new study, the researchers used a different virus, known as MCMV in mice, as part of their investigation of NK proliferation. The human version, CMV, can cause birth defects if it's active in a woman who is pregnant.

The first step was to confirm that in mice infected with MCMV, NK cells were indeed pumping out the IL-10. The researchers noticed that in highly infected mice, NK cells produced IL-10 about 3.5 days into the infection – days later than when they'd produce IFN-gamma, a protein that helps to mount, rather than defuse, the immune system response.

In lab cultures, they found that only cells that were about 3.5 days post infection would produce IL-10. A subsequent experiment showed that exposure to a virus wasn't necessary, per se, but several rounds of replication and proliferation (over about 3 days) enabled the IL-10 production.

"Taken together, these studies show that the NK cell IL-10 response is associated with extensive proliferation, either under in vitro conditions independent of infection, or in vivo during infection," wrote the authors, including co-lead author and former Brown postdoctoral researcher Seung-Hwan Lee, who is now at the University of Ottawa.

Having shown that IL-10 production was associated with NK cell proliferation, Tarrio, Biron and colleagues sought even more evidence: The mechanism in the NK cells that triggers the switch to IL-10 production.

They found it by comparing the genome-wide conformation of DNA in

NK cells before and after proliferation in infected mice. They found that in NK cells that hadn't undergone the proliferation process, the gene for IL-10 was tightly wrapped up and inaccessible for expression. Post-proliferation cells had IL-10 genes that were more open and accessible for expression.

"When we got those results everybody was really excited about it, because pulling out epigenetic changes from a cell population during an infection in vivo is really pretty remarkable," Tarrio said.

New investigations

Because the epigenetic study looked at the broader genome of NK cell DNA, not just at the IL-10 gene, Tarrio added, the researchers can now go back to the data to look for other proliferation-induced changes. That could tell them whether proliferation perhaps alters other important functions in NK cells.

"It's entirely likely there are other changes going on and it could be for other purposes," Tarrio said. "This is one answer to why NK cells proliferate."

With her first grad school paper now published, Tarrio is continuing the research with Biron. The next question in her thesis work will be how long post-infection proliferation and any associated functional changes persist in the NK cells.

Provided by Brown University