Finding about classic suppressor of immunity points toward new therapies for bad infections

January 7 2014

Dr. Tracy L. McGaha is an immunologist at Medical College of Georgia at Georgia Regents University and GRU Cancer Center. Credit: Phil Jones

A well-documented suppressor of immunity that's used by fetuses and tumors alike, just may be able to change its spots, researchers report.

In the face of a significant bacterial infection, for example, indoleomine 2,3-dioxegenase, or IDO, also appears capable of helping key immune cells called macrophages produce inflammation to destroy the invader,

said Dr. Tracy L. McGaha, immunologist at the Medical College of Georgia at Georgia Regents University and GRU Cancer Center.

The surprising finding points toward new therapeutic targets when inflammation goes overboard, known as a cytokine storm, as with the overwhelming and highly lethal infection septicemia.

"It's always described as a one-way street, but it appears IDO has a dual role," said McGaha, corresponding author of the study in the journal *Molecular and Cellular Biology*. "It promotes inflammation when it needs to and, where there is no need for classic inflammation, it can immediately switch to a suppressant mechanism," McGaha said.

IDO's upregulation in macrophages helps these immune cells make important decisions about whether to ignore or attack. "It just depends on the environment the cell finds itself in," McGaha said. He and others also are showing that macrophages, well-documented garbage consumers in the body, have this larger role as well as a driver of the immune response.

While studying more about IDO's role in modulating macrophages response to cell debris, McGaha and his colleagues found that when they added a piece of a bacterial cell wall to prompt an inflammatory reaction, they found an increased number of IDO-expressing macrophages in the mix, which seemed counterintutitive considering IDO's role as a suppressor, McGaha said.

That's how they learned IDO actually does both. IDO basically works by degrading the essential amino acid tryptophan, producing a stress response in the now-starving cell that prompts an increase in the stress response kinase GCN2, which essentially shuts down protein production and cell activity. Unless there is another stressor, which is what happened when the researchers added the bacterial cell wall.

In this infection model, high levels of GCN2 appear instead to nudge macrophages to make more pro-inflammatory mediators, resulting in rampant inflammation in the mice. In this environment, gene activity goes up to the point that the previously sluggish protein production is revived. "The overall affect is you get more inflammation," McGaha said.

And that's where potential new therapies for selectively blocking inflammation surfaced. When they knocked out GCN2, severe inflammation decreased and survival increased in animal models of septicemia. McGaha hopes the laboratory findings will eventually translate to hospital intensive care units.

"Macrophages can do a lot of things and only one of them is make inflammatory products, like cytokines, in response to infection," McGaha said. "They also are involved in wound healing and tissue reconstitution maitenance. So if a macrophage comes into an area that has a lot of mechanical damage, say from trauma, you don't want to make proinflammatory things because that will hurt the ability of the tissue to heal itself."

The good news is that drugs that block GCN2 already are under development to fight cancer and agonists exist that could bolster a positive immune response, such as increasing the potency of a vaccine, McGaha said. "If we can manipulate GCN2's activity in various contexts, we can help finetune the immune response in the direction we want."

Next steps including looking at how GCN2 manipulates immunity, particularly its impact on protein production.

MCG's Drs. Andrew Mellor and David Munn were the first to report that the fetus expresses IDO to help avoid rejection by the mother's immune system. Subsequent studies have shown tumors also use IDO for

protection and clinical trials are studying the tumor-fighting potential of an IDO inhibitor. On the flip side, there is evidence that increasing IDO expression can protect transplanted organs and counter autoimmune disease. Mellor and Munn are co-authors on the new study, which was supported in part by the National Institutes of Health and Wellcome Trust.

Provided by Medical College of Georgia