Discovery reveals how protective immune cells protect themselves

January 25 2016

Researchers at St. Jude Children's Research Hospital have discovered the mechanism by which immune cells called regulatory T cells keep themselves intact and functional during their demanding task of holding the immune system in check. Such T cells are key to preventing the immune system from attacking the body in autoimmune disease.

The researchers said their findings suggest that drugs influencing this protective mechanism could be used to alert the immune system to fight cancers.

Led by corresponding author Hongbo Chi, Ph.D., a member of the St. Jude Department of Immunology, the research appeared on the *Nature Immunology* website today as an advance publication.

The researchers discovered that once regulatory T cells are activated to begin their work, they are protected by a kind of cellular "cleanup" process called autophagy. This natural destructive biological mechanism targets and degrades molecules that are no longer needed, essentially ridding the cell of molecular garbage. Until these studies, no one knew how regulatory T cells maintained themselves when activated.

"Regulatory T cells are very specialized cells that require activation to perform their function in curtailing undesirable immune responses," Chi said. "But this activation is a double-edged sword, in that this very activation can destabilize them. They need to modulate this activation, or they will lose their stability and many of them will die. That could

damage immune function."

In their experiments, the researchers performed imaging studies in activated regulatory T cells that demonstrated autophagy was, indeed, functional in the cells. Next, in mouse studies, the scientists deleted key genes, called Atg7 or Atg5, whose function was necessary for autophagy in regulatory T cells. The scientists found that the mice showed key characteristics of regulatory T cell malfunction, including inflammatory and autoimmune disorders. The mice also more readily cleared tumors from their bodies, due to activated immune systems.

Chi said that eliminating autophagy also affected the fate of such regulatory T cells. "Once those T cells lack autophagy activity, they tend to undergo excessive cell death," he said. "But even for the remaining surviving cells, they tend to be overly activated and lose their identity, because they start to behave like non-regulatory T cells. That is why loss of autophagy in regulatory T cells produces a two-fold effect on both survival and stability."

Detailed analysis also revealed how the elimination of autophagy affected the basic energy-producing metabolic pathways of the T cells, compromising their function.

Chi said the new understanding of autophagy's role in regulatory T cells could enable a two-fold approach to immune therapy for cancers. The authors noted: "From this perspective, by strengthening tumor-associated immune responses, targeting [regulatory T cell] autophagy could act in synergy with strategies that block autophagy in tumor cells for added benefits in cancer therapy."

In the current studies, the researchers used a transplanted colon cancer cell line. In further studies, they plan to explore the role of autophagy in immune reactions toward other tumor cell types, to determine whether

such therapies might be effective in a broad range of cancers.

The researchers will also aim at better understanding the detailed biochemical mechanisms regulating how autophagy connects to the cell's metabolic pathways.

Provided by St. Jude Children's Research Hospital