Immune cell subset in mouse model of disease promotes healing and reduce inflammation

16 October 2014, by Steve Tokar

A scientific team led by UC San Francisco researchers found that regulatory T cells (T_{regs}), a specialized subset of immune cells, suppress inflammation and muscle injury in a mouse model of Duchenne muscular dystrophy (DMD).

The scientists said that T_{regs} have potential as therapeutic agents for DMD, an inherited disease that strikes children – almost always boys – and leads to progressive muscle degeneration and early death.

They published their findings online October 15, 2014, in *Science Translational Medicine*.

The researchers discovered that T_{regs}, which dampen immune responses, are found in the muscles of mice and humans with genetic mutations that lead to the development of muscular dystrophy, but not in the muscles of healthy wild-type mice or healthy humans.

The finding indicates that the T_{regs} appear in muscle in response to the muscle injury, said lead investigator S. Armando Villalta, PhD, a postdoctoral fellow at the UCSF Diabetes Center.

"When we remove T_{regs} from the muscles of the genetically engineered mice, the disease gets worse," said Villalta. "When we boost the cells in mice, we reduce inflammation and muscle injury."

According to Villalta, the healing effect is due in large part to interleukin-10 (IL-10), an anti-inflammatory protein produced by T_{regs} and other immune-regulating cells. "IL-10 is what we see in these mice, and it is seen in the muscles of people with DMD as well," said Villalta.

Jeffrey A. Bluestone, PhD, the A.W. and Mary Margaret Clausen Distinguished Professor in Endocrinology and Metabolism, the director of the Hormone Research Institute at UCSF, and UCSF executive vice chancellor and provost, led the research.

Bluestone predicted that in human therapy for DMD, the real value of T_{regs} will most likely not be as a stand-alone treatment, but in combination with gene therapy.

DMD is caused by an inherited defect in the gene that expresses dystrophin, a protein essential to muscle integrity. Clinical trials of gene therapies for DMD are underway. However, the therapy itself is known to cause inflammation, Bluestone said, a response to the virus that is used to introduce the healthy dystrophin gene into patients with the disease. Inflammation might also even arise in response to the production of new dystrophin protein made from the healthy gene, he said.

"This is where T_{regs} could potentially be of tremendous help," Bluestone said. He observed that the cells could potentially have three simultaneous therapeutic effects: "They could reduce generalized inflammation caused by the disease, reduce inflammation caused by gene therapy, and lastly, produce factors that would promote healing and regeneration of muscle itself."

Bluestone cautioned that such combination therapy is "clinically, always difficult to do, and difficult to get approved for human trials." In addition, he said, the mouse model of DMD used by the scientists is not as severe as the human disease.

For years researchers have been developing the therapeutic potential of T_{regs} to combat autoimmune responses, and T_{regs} already are in clinical trials at UCSF to treat type 1 diabetes and organ-graft rejection. However, there have been no human

trials so far of T_{regs} in non-autoimmune diseases such as DMD, Bluestone said.

Provided by University of California, San Francisco