Not all cytokine-producing cells start out the same way, study finds

May 13 2013

(Medical Xpress)—Cytokines are molecules produced by immune cells that induce the migration of other cells to sites of infection or injury, promote the production of anti-microbial agents, and signal the production of inflammatory mediators. These events are important for fighting infections. However, sometimes this process goes unchecked, resulting in unwanted inflammation that can damage tissues and organs.

Interleukin 17, or IL17, is a well-studied cytokine that regulates immune function at mucosal surfaces in the body but is dysregulated in many diseases, such as multiple sclerosis, rheumatoid arthritis, and psoriasis.

Not all IL17-producing cells are the same, and the rules regarding how particular cell types are instructed to produce this important mediator differ. Research published this week in *Nature Immunology*, from the Perelman School of Medicine at the University of Pennsylvania by Gary Koretzky, MD, PhD, the Francis C. Wood professor of Medicine and Investigator in the Abramson Family Cancer Research Institute; Martha Jordan, PhD, research assistant professor in Pathology and Laboratory Medicine, Jiyeon Kim, an MD-PhD student in the Koretzky lab, and other members of the Perelman School community including Morris Birnbaum, MD, PhD from the Department of Medicine and scientists in the laboratory of Celeste Simon, PhD, from the Abramson Family Cancer Research Institute and the Department of Cell and Developmental Biology, sheds light on the intricacies of those instructions.

T-helper cells that are present in peripheral tissues are known to be a prominent source of IL17. These cells interact with microbial organisms, in particular in the gastrointestinal tract, and are instructed or "induced" to produce and secrete IL17. These inducible, T-helper, IL17-producing cells are found predominantly at mucosal sites and are important for maintaining the health of these tissues.

"Natural" IL17-producing cells, on the other hand, do not have to interact with microorganisms to become capable of making this important cytokine. What these natural IL17-producing T cells do and how they are instructed to produce IL17 has become a research focus for Jordan and Koretzky.

"Although we know much less about natural IL17-producing cells, previous work from our laboratory demonstrated that these cells obtain their ability to produce this cytokine as they develop in the thymus," says Koretzky. "The current study in Nature Immunology compares the signals used by inducible versus natural IL-17 cells that are necessary for cytokine production, testing the hypothesis that they are distinct populations of cells. This may one day help us to develop tools to manipulate one cell population while leaving the other untouched."

The team found evidence that the inducible versus natural cells do, in fact, have very different characteristics. Although the kinase Akt plays a critical role in regulating cytokine production by both cell types, how these cell types use Akt differs. For example, mTORC1, a protein complex activated by Akt, is critical for the generation of inducible IL17-producing cells in the gut; however, natural IL17 cells develop independently of mTORC1. This finding suggests that the trigger for the development of inducible versus natural IL17-producing cells is different. To probe this finding further, Koretzky and Jordan focused attention on different forms of Akt.

Previous work by many laboratories defined different subtypes of Akt, and emerging data suggest that these forms may have differential functions in various tissues.

This finding was extended to inducible and natural IL17-producing T cells in the current *Nature Immunology* publication, as the team found that one particular form of Akt—Akt2—is necessary for optimal inducible cell development but dispensable for natural IL17-producing cells. The findings show how a previously unknown role of Akt and its partner molecules shapes the maturation of IL17-producing cells.

Understanding the rules that govern IL17 cell development and function will suggest ways to specifically modulate one population or the other, which may be important during IL17-mediated immune responses, especially when that response spins out of control.

More information: www.nature.com/ni/journal/vaop … nt/full/ni.2607.html

Provided by University of Pennsylvania School of Medicine