Research sheds light on how immune system's 'first responders' target infection

February 27 2012

University of Texas Medical Branch at Galveston researchers have discovered previously unsuspected aspects of the guidance system used by the body's first line of defense against infection.

The new work focuses on the regulation of immune response by two forms of the signaling molecule IL-8, as well as IL-8's interaction with cell-surface molecules called glycosaminoglycans (or GAGs for short).

Infected or injured tissues release IL-8 to attract bacteria- and virus-killing white blood cells known as neutrophils, a process known as "recruitment." As IL-8 proteins disperse from the infection site, they anchor themselves to GAGs to provide "signposts" that help neutrophils find their target.

"Neutrophils are killing machines but they're also blind, so they shoot at anything and everything — to fight infection effectively and minimize collateral tissue damage, they have to be precisely directed and activated," said UTMB associate professor Krishna Rajarathnam, lead author of a paper on the study in the *Journal of Leukocyte Biology*. "This process of spatial and temporal control is quite complex, but we've gained a fundamental insight into a very basic mechanism."

That mechanism is based on IL-8's existence as both a single unit (a monomer) and a pair (a dimer). In nature, during the course of onset and resolution of infection, IL-8 could exist as a monomer, dimer, or both.

To study how this process affects immune response, Rajarathnam and his colleagues created two forms of IL-8 not found in nature: one made of monomers unable to join into dimers, and the other of dimers unable to split into monomers. They then carried out a series of mouse experiments with monomers, dimers and "wild-type" (normal) IL-8 in which they found that differing concentrations of IL-8 monomer and dimer clearly influenced the strength of neutrophil recruitment.

In addition, drawing on earlier work, they determined that these effects varied depending on the location of the infection — leading them to the conclusion that IL-8 monomers and dimers interact differently with GAGs in different body tissues.

"Our previous experiments involved IL-8 in the lung, and in this study we looked at what happened if we injected IL-8 in the peritoneum, the abdominal wall," Rajarathnam said. "In the lung, the neutrophil activity we saw for wild-type IL-8 was between the monomer alone or the dimer alone, but in the peritoneum the wild type actually produced greater activity. It was synergistic, meaning that in the wild type the monomer and the dimer interact cooperatively to facilitate neutrophil recruitment."

Such unpredictable results are to be expected when investigating a phenomenon as complex as immune response, according to Rajarathnam.

"I believe we have discovered a crucial and fundamental mechanism that regulates neutrophil function," Rajarathnam said. "Our future goal is to characterize the distinct activities of monomer and dimer to see if we can 'control' runaway inflammation and related neutrophil-induced tissue damage in diseases such as sepsis."

Other authors of the paper include graduate student Pavani Gangavarapu, assistant professor Lavanaya Rajagopalan, instructor

Deepthi Kolli, assistant professor Antonieta Guerrero-Plata and Dr. Roberto Garofalo.

"This was a truly translational project, bringing together researchers from both basic and clinical sciences to study the molecular mechanisms underlying disease," Rajarathnam said.

Provided by University of Texas Medical Branch at Galveston