UT SOUTHWESTERN MEDICAL CENTER NEWS

Media Contact: Deborah Wormser
214-648-3404
deborah.wormser@utsouthwestern.edu

UT Southwestern researchers identify new source of powerful immunity protein

DALLAS – July 10, 2013 – Researchers at UT Southwestern Medical Center report the identification of a new cellular source for an important disease-fighting protein used in the body's earliest response to infection.

The protein interferon-gamma (IFN-γ) keeps viruses from replicating and stimulates the immune system to produce other disease-fighting agents. Neutrophils, the newly identified cellular source of the protein, are the major component of the pus that forms around injured tissue.

The researchers also report that the neutrophils appear to produce IFN-γ through a new cellular pathway independent of Toll-like receptors (TLRs): the body's early warning system for invasion by pathogens. This finding indicates that mammals might possess a second early-alert system – the sort of built-in redundancy engineers would envy, said Dr. Felix Yarovinsky, assistant professor of immunology and senior author of the study published online in the *Proceedings of the National Academy of Sciences* in June.

"We believe our mouse study provides strong evidence that neutrophils, white blood cells created in the bone marrow, produce significant amounts of IFN-γ in response to disease," Dr. Yarovinsky said. "The finding of a new and essential cellular source for IFN-γ challenges a long-held belief in the field and is significant because neutrophils are the most common kind of white blood cell."

Two pathogens were used in this study: the parasite *Toxoplasma gondii* – which can cause brain damage in humans and other mammals that have compromised immune systems – and a type of bacterium that causes gastroenteritis, *Salmonella typhimurium*.

Innate immunity is the body's first line of defense against pathogens, including those that it has never before encountered. Adaptive immunity is the secondary system that battles pathogens to which the body has previously been exposed and to which it has developed antibodies.

Textbooks list natural killer (NK) cells and T cells as the body's significant sources of IFN-γ. Although large numbers of neutrophils have long been observed to congregate at the site of a new infection, they were commonly thought to be first responders or foot soldiers rather than generals in the battle against disease, as this study indicates they are, Dr. Yarovinsky explained.

About 20 years ago, there were clinical reports in humans and animals suggesting that neutrophils might produce IFN-γ, but the idea was largely ignored by the scientific community until the

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last decade, he said.

Since then, studies at UT Southwestern and elsewhere have found that mice lacking NK and T cells, and therefore expected to be unable to produce IFN-γ, somehow continued to withstand infections better than mice genetically unable to make any IFN-γ. These observations suggested the possibility of an unknown source of the protein, he explained.

In a series of experiments, the UT Southwestern researchers identified neutrophils as the major source of IFN-γ in mice lacking NK and T cells. "Based on what we know about neutrophils, their large numbers and rapid deployment to the site of infection should provide an important means of very early, robust, and rapid elimination of disease-causing agents," the researchers wrote. Although neutrophil-derived IFN-γ alone is insufficient to achieve complete host protection, the protein significantly extended the survival of mice in this study, Dr. Yarovinsky said.

In related news, the Burroughs Wellcome Fund in June announced that Dr. Yarovinsky had been selected for its 2013 Investigators in the Pathogenesis of Infectious Disease Award to further investigate mechanisms of host defense against various infectious diseases mediated by IFN-γ produced by neutrophils. The award will provide $500,000 over five years to pursue this line of research.

Others involved include first author Carolyn Sturge, a graduate student of immunology; former research assistant Alicia Benson; research assistant II Megan Raetz; graduate student Cara L. Wilhelm; Dr. Julie Mirpuri, assistant professor of pediatrics; and Cancer Immunobiology Center Director Dr. Ellen Vitetta, professor of immunology and of microbiology.

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About UT Southwestern Medical Center

UT Southwestern, one of the premier academic medical centers in the nation, integrates pioneering biomedical research with exceptional clinical care and education. The institution's faculty includes many distinguished members, including five who have been awarded Nobel Prizes since 1985. Numbering more than 2,700, the faculty is responsible for groundbreaking medical advances and is committed to translating science-driven research quickly to new clinical treatments. UT Southwestern physicians provide medical care in 40 specialties to nearly 90,000 hospitalized patients and oversee more than 1.9 million outpatient visits a year.

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