

## UCSD Medical Researchers Show Protein's Role In Stopping Bacterial-induced Inflammation

September 19, 2005 |

In findings that could have implications for autoimmune disorders and drug-resistant bacterial infections, researchers at the University of California, San Diego (UCSD) School of Medicine have identified a key protein involved in the appropriate shut-down of inflammation following an immune response to invading pathogens.

Published in the April 28, 2005 issue of the journal *Nature*, the study in mice and lab cultures of immune cells called macrophages showed that a protein called I-kappa-B kinase alpha (IKKa) is responsible for terminating an inflammatory response before it can damage cells and organs.

Senior author Michael Karin, Ph.D., UCSD professor of pharmacology, explained that IKKa is part of a sophisticated two-punch system that maintains a proper inflammatory response. While it is well known that IKKa's sister protein, IKK beta (IKKb), initiates the inflammatory response, little was known about the mechanism for stopping the response before it injures tissue, such as the damage that occurs in chronic bacterial and parasitic infections like tuberculosis and leprosy, or in autoimmune disorders like rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus (SLE).

Karin's team, which was the first to identify the IKK protein complex in 1996, determined in this new investigation that both IKKa and IKKb are activated at the same time following a microbial infection. While IKKb initiates the inflammatory response by causing the degradation of inhibitory proteins called IkbBs, IKKa interacts with two additional proteins – RelA and C-Rel – which move into the nucleus of the cell after the IkbBs are degraded. After being "tagged" by IKKa in the cytoplasm of the cell, RelA and c-Rel bind to genes that mediate the inflammatory response. But their life is limited – the IKKa-mediated "tag" ensures that RelA and c-Rel will bind to their target genes for only a short duration. Once RelA and c-Rel are removed from their target genes, the inflammatory response is terminated.

"This is very important for a proper inflammatory response in infection and immunity," Karin said. "The inflammatory response involves the production of potentially toxic mediators, so it is important that inflammation be allowed to do its work rapidly, but only transiently."

The new findings also have implications for disorders such as flesh-eating staph infections and drug-resistant bacterial infections that are difficult to treat. The researchers note that in these cases, it might be possible to develop an inhibitor of IKKa that boosts the inflammatory response to better fight these infections. However, such an inhibitor should have a short half-life, so that its potential devastating effect can be properly terminated.

The Karin lab, which has made several of the past discoveries involving IKKb's pro-inflammatory role, has also studied IKKa over the years, but they have identified roles unrelated to the primary inflammatory response. For example, in 2001, the investigators determined that IKKa was essential for formation of the skin's outer layer.\* In a follow-up study, the team found clues that IKKa may be more involved in the immune response than they previously thought, but its role still appeared limited.\*\* The current study is the first, however, to specifically show the novel mechanisms used by the protein to control the duration of an inflammatory response.

The study was funded by the National Institutes of Health. The co-first authors were Toby Lawrence, Ph.D., and Magali Bebien, Ph.D., post-doctoral fellows in the Laboratory of Gene Regulation and Signal Transduction, UCSD Department of Pharmacology. Currently, Lawrence is an assistant professor and member of the Faculty of Medicine, Imperial College London. Additional authors were George Liu, Ph.D., UCSD Division of Pediatric Infectious Diseases, UCSD School of Medicine; and Victor Nizet, M.D., associate professor of pediatrics, UCSD School of Medicine.

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\* UCSD Researchers Discover Protein Essential for Formation of Skin's Outer Layer

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\*\* UCSD Researchers Discover New Role For Immune-Response Enzyme

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