Discovery of a New Signaling Mechanism May Lead to Novel Anti-Inflammatory Therapy

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A team of researchers at the University of California, San Diego School of Medicine has uncovered a new signaling mechanism used to activate protein kinases that are critical for the body's inflammatory response. Their work will be published in the July 18 online edition of *Science (Science Express)*.

"In addition to helping explain the basic mechanisms of transmembrane receptor signaling, these results may identify a potential therapy for interfering with inflammation," said Michael Karin, Ph.D., professor of pharmacology and pathology in UC San Diego's Laboratory of Gene Regulation and Signal Transduction.

The tumor necrosis factor (TNF) receptor (TNFR) family codes for a large number of cell surface receptors of great biomedical importance, and its signaling mechanisms have been the subject of intense investigation during the past decade. Specific inhibitors of TNF receptor 1 (TNFR1) activation are being used in the treatment of rheumatoid arthritis, psoriasis and inflammatory bowel disease, and receptor activator of NF-kB (RANK) inhibitors were recently found to be effective in the treatment of osteoporosis and other bone loss diseases.

Now Atsushi Matsuzawa, Ph.D., and Ping-Hui Tseng, Ph.D., postdoctoral fellows in the Karin laboratory, describe how engagement of CD40, a member of the TNFR family, results in assembly of multiprotein signaling complexes at the receptor. However, according to the researchers – and contrary to previous expectations – signaling cascades that lead to activation of Jun Kinases (JNK) and p38 MAP Kinases (MAPK) are not initiated until these complexes dissociate from the receptor.

The authors found that complex translocation from the cell surface receptor to the cytoplasm, which is required for JNK and p38 activation, depends on degradation of a signaling protein called TRAF3. This process can be inhibited by a class of compounds known as Smac mimics.

"As Smac mimic compounds do not interfere with the activation of NF-kB-dependent innate immunity but do prevent the induction of JNK- and p38- dependent inflammatory mediators, they

may serve as the prototypes for new anti-inflammatory therapy," said Karin, who also noted that current drugs that work by interfering with TNFR signaling exceed $5 billion a year in revenue.

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