

Researchers Determine There Is An Innate Immunity

An enzyme involved in DNA repair has been shown by researchers at the University of California San Diego (UCSD) School of Medicine to also play a critical role in innate immunity, the bodys first response against invading bacteria, viruses and toxins.

Published in the Dec. 8, 2000 issue of the journal *Cell*, the research was headed by Eyal Raz, M.D., UCSD associate professor of medicine, who notes that the enzyme, called DNA-dependent protein kinase (DNA-PK), now has been shown to be an essential element that protects the body from both internal and external dangers.

DNA-PK provides a link between genome defense (the DNA repair machinery) and host defense (innate immunity), he says. Now that we know the enzymes dual role, someday we may be able to use stimulants of the immune response to activate the bodys DNA repair in cases where it is required.

The potential applications include treatments for DNA instability caused by radiation induced injuries or mutations caused by the side effects of cytotoxic medications used to treat cancer situations that can lead to increased incidences of secondary malignancies, he adds.

DNA-PK was identified in the activation of innate immunity, the body's first-line defense against invading pathogens. Innate immunity identifies infectious agents by their pattern, or structure, and within minutes mounts a broad, rapid response with macrophages and natural killer cells. A second form of immune response, adaptive (or acquired) immunity, takes several days to gear up its attack. Adaptive immunity recognizes previous contact with a specific microbe and directs its defense against that specific invader with T-cells and B-cells.

In recent years, scientists have identified part of the cascade of events within the body that leads to the innate immune response. When bacterial DNA is released from invading bacteria which enter the host, it stimulates an enzyme complex called IKK, which activates a transcription factor (or molecular switch) called NF-kB, leading to activation of macrophages which attack the invading bacteria. What was not known was the molecular link, or additional molecules involved in the process between the bacterial invasion and the NF-kB activation.

The UCSD team speculated that the intracellular enzyme DNA-PK might be involved in the process. DNA-PK is located in both the nucleus of the cell and in the cytoplasm, the cellular area between the cell membrane and nucleus. It was known that DNA-PKs role in the nucleus was to repair DNA double-stranded breaks created by radiation (x-rays, gamma rays, etc.) or by intrinsic cellular processes. However, the cytoplasmic functions of DNA-PK were unclear.

Over a five-year period, the UCSD team studied normal mice and mice bred without DNA-PK. In order to stimulate the immune response in the mice, the researchers used bacterial DNA and a synthetic oligonucleotide (ODN), a short segment of the bacterial DNA which has immunostimulatory (ISS) properties. Called ISS-ODN, the synthetic DNA segment was developed several years ago by Raz and his UCSD colleagues. Both natural bacterial DNA and the synthetic ISS-ODN lead to the activation of NF-kB in the normal mice, but not in the DNA-PK deficient mice. Additional tests using chemical inhibiting agents also verified the role of DNA-PK in the innate immune response to bacterial DNA or ISS-ODN.

In their *Cell* paper, the researchers also discuss the location of the molecular pathway that includes DNA-PK. They note that bacterial DNA and ISS-ODN activate DNA-PK within the cell, rather than on the cell surface.

Additional authors of the *Cell* paper are Wen-Ming Chu, Xing Gong, Kenji Takabayashi and Augusto Lois, who, along with Raz, are members of the UCSD Department of Medicine and the UCSD Sam and Rose Stein Institute for Research on Aging; Michael Karin, Zhi-Wei Li and Yi Chen, Laboratory of Signal Transduction and Gene Regulation, UCSD Department of Pharmacology; Hong-Hai Ouyang and Gloria C. Li, Departments of Radiation Oncology and Medical Physics, Memorial Sloan-Kettering Cancer Center, New York; and David J. Chen, Life Science Division, Lawrence Berkeley National Laboratory, Berkeley, CA.