2 genes are important key to regulating immune response

December 29 2007

A research team at Weill Cornell Medical College in New York City has identified two genes that may be crucial to the production of an immune system cytokine called interleukin-10 (IL-10).

The discovery fills in an important "missing link" in a biochemical pathway that's long been tied to disorders ranging from lupus and Type 1 diabetes, to cancer and AIDS.

"IL-10 production has to be kept in a delicate balance for health," explains study senior researcher Dr. Xiaojing Ma, Professor of Immunology and Microbiology in the Departments of Microbiology and Immunology and Pediatrics at Weill Cornell. "Too much IL-10 can leave the body more vulnerable to killers such as viruses and cancer, and to certain antibody-driven autoimmune diseases such as lupus, while too little can lead to run-away inflammatory pathology. Therefore, a better understanding of IL-10 regulation moves us closer to understanding these illnesses and -- potentially -- how to better treat them," he says.

The findings are reported in this month's issue of *Immunity* (vol. 27).

Dr. Jianguo Liu, of Weill Cornell, and Dr. Elaine Y. Chung, formerly of Weill Cornell and now a post-doc at the University of Pennsylvania, were co-lead researchers on the study.

Every second, millions of the body's cells undergo naturally programmed cell death -- a process called apoptosis. In healthy individuals, these

dying or dead cells are spotted and then quickly ingested and removed by immune system "scavenger" cells such as macrophages.

However, to prevent this type of clean-up from triggering a wider immune response, macrophages express the IL-10 cytokine in the presence of apoptotic cells.

IL-10 suppresses the activity of immune system T-cells that might otherwise run amuck, Dr. Ma explains.

"That can be a good thing, of course," he says. "But on the other hand, when immune system T-cell activity is weakened too much, that can help encourage AIDS in those infected with HIV. Also, excessive T-cell suppression can keep the immune system from destroying rogue cancer cells in people battling malignancy."

All of this means that "anything that we can learn about IL-10 production -- and related T-cell suppression -- is a boon to medical research," Dr. Ma explains.

Prior studies had already shown that CD36 -- a protein receptor lying on the surface of the macrophage -- was important for the recognition of apoptotic cells by macrophages. In this work, the researchers observed that CD36 also helped to trigger IL-10 production whenever apoptotic cells were around.

The team then asked a deeper question: "What signals lead to IL-10 production from CD36 present at the cell surface?"

To find out, the Weill Cornell group first exposed macrophages to apoptotic (dying) cells. They then used sensitive assays to look for key biochemical changes occurring downstream of CD36 activation.

"We found proteins in the cell nucleus that were binding to a site we knew was critical for the production of IL-10 as macrophages encountered apoptotic cells," Dr. Ma says. In subsequent biochemical experiments, the team identified the two genes responsible for the transcription (gene-directed production) of these proteins.

These genes -- pre-B transcription factor 1(Pbx-1) and Pbx-regulating protein 1 (Prep-1) -- are best known to scientists as partners for their role in embryonic development and several forms of leukemia, with Pbx playing a major part in hematopoeisis, the production of new and myriad blood cell types.

"In that sense, their presence as immune system transcription factors came as a big surprise to us," Dr. Ma says. "In fact, we still haven't figured out exactly how Pbx-1 and Prep-1 are involved in regulating IL-10 transcription. I really hope this study opens up new avenues for immunologists to find out whether there's a brand new biochemical pathway to be discovered."

The findings could also reveal exciting new information as to how aberrant IL-10 expression contributes to disease.

"Because IL-10 expression (and related T-cell suppression) are so important to the etiology of so many illnesses, discoveries like ours could point to molecular pathways that may become important new targets for drug discovery going forward," Dr. Ma explains. "It's these types of breakthroughs in the lab that -- step by step -- will end up bringing real hope to patients down the line."

Source: New York- Presbyterian Hospital