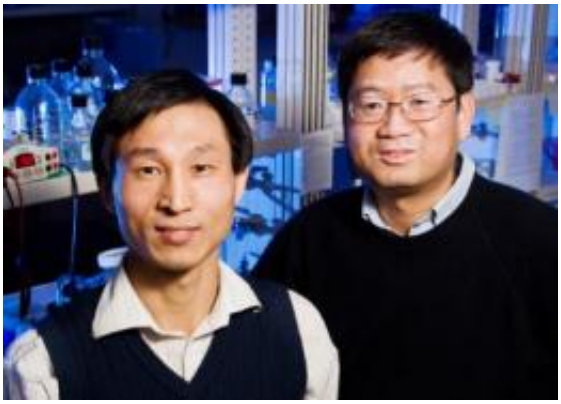
Researchers discover a new pathway that regulates inflammation

March 11 2009



University of Illinois biochemistry professor Lin-Feng Chen, right, and his colleagues, including postdoctoral researcher Xiaodong Yang, identified a novel pathway that controls the activity of a key protein involved in inflammation. Photo by L. Brian Stauffer, U. of I. News Bureau.

Inflammation, the body's earliest response to damage or infection, can aid the healing process and trigger an immune response against invading pathogens. But inflammation gone awry can also undermine health, as in diseases such as rheumatoid arthritis or asthma.

Researchers at the University of Illinois have identified a novel pathway that controls the activity of a key protein involved in inflammation. Their findings could have important implications for the treatment of diseases or conditions linked to chronic inflammation.

At the heart of the cell's inflammatory response is a protein complex called NF-kappa B. In the new study, biochemistry professor Lin-Feng Chen and his colleagues deciphered a molecular code that controls its function. Their results appear in the *European Molecular Biology Organization (EMBO) Journal*.

The NF-kappa B protein complex consists of two subunits that can bind to DNA and regulate the expression of particular genes. The complex acts like a molecular switch that can be turned on when the cell is under attack and then off when the attack has been cleared. Upon activation, it rapidly moves into the nucleus and sets in motion an army of proteins that cause inflammation. Often referred to as the master regulator of the immune system, NF-kappa B belongs to a large family of proteins called transcription factors that control which genes are turned on or off.

"Inflammation is like a chemical storm during which many special chemicals that signal the immune system are released at the site of infection," Chen said.

"NF-kappa B, the protein which is central to the inflammatory response, has to be tightly controlled; otherwise things could go crazy within the body."

Normally, a second protein inactivates NF-kappa B by directly binding to it. But when the cell is under stress (for example, during infection), this inhibitory protein is dismantled. NF-kappa B, now relieved of inhibition, rushes into the nucleus and activates gene expression. Once it finishes its job, NF-kappa B stimulates the production of its inhibitory partner and is itself inhibited again.

Recent studies found that NF-Kappa B also was being degraded in the nucleus, indicating an alternate means by which NF-kappa B activity is regulated in the cell.

"Every step of NF-kappa B activation is tightly controlled," Chen said. He and his colleagues hunted for the signals that could control its degradation and inactivation.

Chen's earlier work gave him important clues about how protein activity can be modified when small chemical groups are added to the protein after it is assembled. This process, called post-translational modification, tags the proteins. Like the sign on the front of a bus declaring its destination, the tags direct proteins to different fates.

"One of the goals of our lab is to study how post-translational modifications affect NF-kappa B activity under normal and diseased conditions," Chen said.

To identify whether a particular molecular tag, called a methyl group, could be added to NF-kappa B to regulate its activity, Xiao-Dong Yang, a postdoctoral researcher in Chen's lab and lead author on the new study, performed a simple experiment. He mixed the NF-kappa B protein with a protein whose function is to add a methyl group to certain other proteins. He discovered that a subunit of NF-kappa B was, in fact, being labeled with a methyl group.

Adding a methyl group increases the weight of the protein by a very small amount. In collaboration with chemistry professor Neil Kelleher, the researchers used an ultrasensitive molecular scale, called mass spectrometry, and identified two amino acids in the protein that had been modified with the methyl group.

In a series of experiments, Chen and his colleagues found that the presence of the methyl group signaled that NF-kappa B was to be degraded in the nucleus. This showed, for the first time, how NF-kappa B could be degraded and regulated independent of its inhibitor protein.

Chen said that understanding the role of different post-translational tags on NF-kappa B could lead to the discovery of a "transcription factor code" or "NF-kappa B code," similar to the "histone code." Like the genetic code, which spells out the sequence of amino acids in a protein, the transcription factor code stores information about how various post-translational modifications signal different biological fates.

"In some cancers and inflammatory diseases NF-kappa B is permanently active. The turn-off mechanism has been inactivated," Chen said. He hopes that the discovery of this pathway could lead to the development of new drugs to influence the methylation - and hence the activity - of this transcription factor and the inflammatory response.

Source: University of Illinois at Urbana-Champaign (news : web)