UCSD Study of Nuclear Receptors Could Change Anti-Inflammatory Treatments

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Several nuclear receptor proteins appear to overlap in their ability to exert anti-inflammatory effects, according to new research by scientists at the University of California, San Diego (UCSD). Nuclear receptors are important drug targets for a number of diseases, for example, glucocorticoid receptors for asthma and arthritis. But use of drugs targeting these receptors is sometimes limited by unwelcome side effects. The new findings may suggest a way to overcome this obstacle.

In a paper being published in the September 9 issue of the journal Cell, Christopher Glass, M.D., Ph.D., professor of cellular and molecular medicine at the UCSD School of Medicine, and his colleagues show that three nuclear receptor proteins – glucocorticoid, PPAR gamma and LXR – can work together to repress the cellular responses to certain kinds of pro-inflammatory molecular signaling. These nuclear receptors are important in "turning off" inflammatory responses to bacteria or viruses and allowing the cells to return to a normal state.

"Basically, we are looking at a 'tuning system' to maintain a proper level of immunity, but without an inappropriate inflammatory response that would contribute to a chronic disease state," Glass said.

The researchers have also, for the first time, identified on a genome-wide level how these proteins work to influence the body's inflammatory response. By identifying the molecular mechanism by which each receptor inhibits particular genes involved in anti-viral responses, more powerful drugs could be developed to fight immune diseases such as arteriosclerosis and arthritis, with fewer side effects.

"We now have a molecular understanding of why inflammatory responses caused by certain infections are sensitive to glucocorticoid drugs for example, while others are resistant," said Glass. "These observations further explain how drugs used to inhibit one type of inflammation could basically cripple the immune system to respond to specific viral infections and make that disease much worse."

Glass's studies of nuclear receptors have focused on their regulation of gene expression in the macrophage, a basic cell that recognizes structures or patterns on pathogens that aren't present in normal cells. The macrophage is responsible for producing and responding to hormone-like molecules that control inflammation – important for the understanding of immune diseases such as arteriosclerosis, psoriasis and rheumatoid arthritis that are triggered by autoimmune responses. While macrophages and other immune cells are essential against infectious organisms, they can also promote chronic inflammatory diseases.

When the macrophage thinks it sees an infection, it "turns on" or expresses hundreds of genes, enabling the macrophage to communicate with other cells and combat infection. In some diseases, however, certain protein complexes become modified and begin to look like the proteins associated with bacteria or viruses. The macrophage misinterprets this pattern on a modified protein, which causes it to initiate an inflammatory response. In this work, the UCSD team looked at a number of pathogen-associated molecule patterns used to stimulate the macrophage, with the long-term goal of finding a way to manage inflammation without compromising the immune system.

While it had been shown in past studies that the macrophage responded to certain drugs, it was never studied on a genomic-wide level how receptors actually did the job of inhibiting the macrophage's inflammatory responses. The patterns reported in the paper suggest that each of the receptors plays a slightly different role in how the macrophage mounts an inflammatory response, working in different but overlapping ways.

The findings also have potential clinical significance in showing how two or three nuclear receptors activated at the same time very dramatically shut down inflammatory responses. This suggests that the drug that works with one particular receptor, but with negative side effects, could be given at a lower dose along with different drugs targeting the other receptors. For example, one class of potent corticoid drugs used to treat severe asthma has many negative side effects, including high blood pressure, diabetes and obesity.

"What is of particular interest in this study," said Glass, "is that adding two drugs together could have a much more substantial interaction while using much less of each drug. This could result in much better therapeutic results with fewer side effects. The observation that these proteins can function together opens up new avenues of clinical investigation into the treatment of diseases."

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