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Discovery Points to New Way to Control Atherosclerosis

Howard Hughes Medical Institute researchers have discovered a genetic switch that can drastically reduce fatty deposits in the coronary arteries of mice.

According to the researchers, the switch is a regulator of the inflammatory process. It affects immune cells called macrophages, which are the primary culprits in creating the artery-clogging plaques. The scientists believe that the switch, a protein called PPAR-delta, could be an attractive target for drugs aimed at controlling inflammation in a variety of diseases, including cancer, neurodegenerative diseases, inflammatory joint and bowel diseases and immune disorders.

The researchers, led by Howard Hughes Medical Institute investigator [Ronald Evans](#), reported their findings in the September 12, 2003, issue of the journal *ScienceExpress*, the online counterpart of the journal *Science*. Evans and colleagues at the Salk Institute for Biological Studies collaborated on the studies with researchers at Brigham & Women's Hospital and Stanford University.

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- Ronald M. Evans

PPARs are a family of proteins, called nuclear receptors, which control the activity of networks of genes in cells. Although Evans and his colleagues had discovered PPAR-delta about 12 years ago, most researchers had been focusing on its close relative, PPAR-gamma.

"Most of the field had gravitated toward studying PPAR-gamma because it is the target of anti-diabetic drugs, which is a five-billion-dollar-a-year industry," said Evans. "We decided to put the spotlight on PPAR-delta because we wanted to understand how it works."

Evans and his colleagues launched an effort five years ago to produce mice in which the PPAR-delta gene had been specifically eliminated in the macrophages of mice. They chose the macrophage as their target because PPAR-gamma was known to control accumulation of fatty lipids in macrophages, a major step in the formation of atherosclerotic lesions.

In their experiments, the researchers fed both normal and PPAR-delta-deficient mice a fatty diet and compared the formation of atherosclerotic plaques in both strains of mice.

“In earlier studies, we'd found that knocking out PPAR-gamma made the lesions progress much more rapidly,” said Evans. “However, to our complete surprise, we found the opposite result with PPAR-delta knockouts. The lesions almost failed to develop at all, so these mice had very clean arteries. It's as if you have two brothers from the same family, and you expect some similarity, but they turn out to be very different from one another.”

The researchers' experiments indicated that, unlike PPAR-gamma, which regulated lipid accumulation, PPAR-delta seemed to control the inflammatory pathway in macrophages.

Evans and his colleagues next tested whether the pro-inflammatory genes in the PPAR delta-deficient mice had been activated.

“These genes are of two types,” explained Evans. “One set of genes is involved in attracting macrophages to lesions, and the other set controls the signals that one macrophage sends to another to attract it to an inflammatory site. We found that this second signaling system was completely compromised in the PPAR-delta-knockout mice. So, the macrophages don't know there's a problem, and the ones that do get into the lesion aren't very efficient; so inflammation is greatly reduced.”

Further studies revealed a previously unknown and highly unconventional mechanism by which PPAR-delta controls inflammatory signaling, said Evans. Rather than simply switching on inflammation-signaling genes, the PPAR-delta protein normally sequesters an inflammatory repressor protein called BCL-6, allowing inflammatory signaling to proceed. Thus, when PPAR-delta is knocked out, blocked by drugs, or affected by a chemical trigger called a “ligand,” BCL-6 is freed to repress inflammation.

The discovery of this new type of regulatory mechanism could provide researchers with a model that will be useful in deciphering other molecular signaling systems that operate in a similar way, said Evans.

Evans emphasized that the discovery of PPAR-delta's powerful effect in controlling inflammation in macrophages suggests that it could become a major target for drugs to treat atherosclerosis, as well as other diseases.

“These findings are clinically significant because inflammation itself is a major stimulator of coronary artery diseases—as we see in this study—but also of cancer, neurodegenerative diseases, inflammatory joint disease, inflammatory bowel disease, and many disorders in which the immune system goes awry.

“So, the discovery of a new pathway to suppress inflammation has far-reaching implications, in part, because it can now be studied in detail and secondly because it can be controlled by an orally active drug,” Evans said.

To extend their understanding of PPAR-delta and its clinical potential, Evans and his colleagues are now exploring the protein's role in an array of other cells, including fat cells and muscle cells.