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Macrophage protein has major role in inflammation

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Researchers at the University of California, San Diego School of Medicine have discovered that a multi-tasking protein called FoxO1 has another important but previously unknown function: It directly interacts with macrophages, promoting an inflammatory response that can lead to insulin resistance and diabetes. Contrarily, it also generates a negative feedback loop that can limit damage from excessive inflammation.

The findings by Jerrold M. Olefsky, MD, Associate Dean for Scientific Affairs and professor of Medicine, and colleagues are published in the November 2 issue of *The EMBO Journal*.

FoxO1 belongs to a group of well-known transcriptions factors crucial to determining the fate of cells. Earlier research has shown that FoxO1 helps govern the expression of genes involved in diabetes, cancer and aging. One unusual aspect of FoxO1 is that exposure to insulin causes cells to exclude the protein from their nuclei, inactivating it.

Olefsky and colleagues conducted a massive sequencing survey to find all of the places in the human genome where FoxO1 binds to and influences genes. They detected about 10,000 sites, but one group immediately attracted their attention: the inflammatory pathway in the macrophage – a type of white blood cell that ingests foreign invaders and is a major player in the immune response system.

The scientists discovered that FoxO1 independently binds to the promoter region of the gene for Toll-like receptor4 (TLR4), a protein on

macrophages' surface that acts to bind to and recognize microbial-derived molecules. "TLRs are the gateway to inflammatory signaling in the macrophage. They start the inflammation response," said Olefsky. "Discovering that FoxO1 regulates them is a pretty critical finding."

Specifically, Olefsky said FoxO1 behaves like a priming agent. "It gets the macrophage armed and ready." That in itself is not necessarily a problem. Indeed, it's probably part of FoxO1's normal function. But in people suffering from obesity or type 2 diabetes, FoxO1 can exacerbate an already existing problem of chronic inflammation. It can make already overabundant macrophages even more responsive, essentially pouring gasoline on an inflammatory fire.

The initiation of an inflammatory response by FoxO1 also begins the process of ending it – at least in healthy systems. "FoxO1 primes macrophages to respond exuberantly to inflammation, but obviously you don't want that to go on very long," said Olefsky. "So the macrophage pumps out inflammatory cytokines that go off to do their thing, but these cytokines also come back and work on the macrophage, inducing FoxO1 to leave the nucleus and deactivate. It's a pretty robust response, though usually you need more than one of these negative feedback loops to control a process."

The discovery of FoxO1's role adds another important element to a fuller understanding of how the inflammatory process and the immune system work, Olefsky said. It helps explain how obesity and type 2 diabetes, which result in reduced insulin signaling, can lead to enhanced inflammation.

Practical applications for the new findings are less clear. FoxO1 is not a typical target for therapeutic drugs. Drug manufacturers would have to devise a novel method to interfere with FoxO1. "A small molecule might do it," said Olefsky. "That's possible, but right now that's an unknown."

Provided by University of California - San Diego