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Researchers discover new drug target for inflammatory disease

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UC Davis researchers have defined a cellular process that promotes inflammation and, at the same time, found an important starting point for identifying and testing new drugs for diseases such as sepsis, rheumatoid arthritis, cardiovascular disease and some cancers.

The scientists discovered that a protein called sPLA2-IIA binds to two integrins labeled alpha-V-beta-3 and alpha-4-beta-1, causing them to rapidly multiply and boosting an immune system response already gone awry due to disease.

"We have known for a while that this protein is elevated with inflammation," said Yoshikazu Takada, UC Davis professor of dermatology and lead author of the study, which appears in the September 19 issue of *The Journal of Biological Chemistry*. "Our outcome shows with much more precision how the protein actually works to advance inflammation. The potential impact of the finding on our ability to block inflammation and stop the disease process in its tracks is enormous."

Protein sPLA2-IIA has been a major drug discovery target for years, but efforts to counteract the protein have yielded mixed results. Takada explains that this is due to the fact that its intercellular relationships in humans were not well-known. Scientists have previously identified receptors for the protein in mice cells. However, Takada and his team are the first to find that the protein binds to completely different receptors — the two integrins — in human cells.

Integrins are the "networkers" of the immune system, playing key roles in the attachment of cells to other cells. Integrins are also important to signal transduction, the process by which a cell transforms from one kind of signal or stimulus into another.

"We need to know the mechanisms of inflammation to be able to disrupt it," said Takada. "Now that we know more about how this protein interacts with these integrins, researchers can be much more successful in screening potential drugs that can block the binding process and hopefully the immune response it kicks into overdrive as well."

In the current study, Takada and team evaluated the possibility of integrin binding by sPLA2-IIA using a computer program that predicts how small molecules bind to receptors. They then performed laboratory experiments using human cells to confirm the resulting predictions.

The researchers conducted additional experiments using human leukemia and lymphoma cell lines, because they are known to express integrins, in order to measure changes in the inflammatory response due to sPLA2-IIA-integrin binding. They found an increase in the number of monocytes, which are important first-line defenders for the immune system responsible for attacking foreign substances in the body. At elevated levels, monocytes indicate an overresponsive immune system.

The involvement of integrins to the inflammatory process is of particular interest to study co-author Kit Lam, chief of hematology and oncology with UC Davis Cancer Center.

"These two and other integrins are found on cancer cells," Lam explained. "And inflammation certainly plays a role in the onset, progression and maintenance of certain cancers. This outcome could have a huge impact on our work in finding medications that halt or at least reduce the impact of inflammation on this disease."

Takada and his colleagues will next be working to screen for molecules that block the binding of sPLA2-IIA to integrins and show that this blockage is enough to shut down an unwanted inflammatory response.

"We cannot ignore integrins anymore," Takada said. "More basic research is needed to understand how integrin-binding results in pro-inflammatory signals. We have to continue to better understand the integrin signaling process if we are to find more potential drug targets for the treatment of inflammation."

Source: University of California - Davis