Unexpected new mechanism behind rheumatoid arthritis

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A team of researchers at the University of Gothenburg, Sweden, has identified an enzyme that protects against inflammation and joint destruction. Made when the researchers blocked production of the enzyme GGTase-I in transgenic mice, this unexpected discovery could lead to the identification of new mechanisms that control the development of inflammatory disorders, as well as new medicines.

The article has been published in the Journal of Clinical Investigation (JCI). GGTase-I is found in all cells but is particularly important for the function of so-called CAAX proteins in inflammatory cells. GGTase-I attaches a cholesterol-like fatty acid on the CAAX proteins.

Researchers previously believed that this fatty acid played an important role in activating the proteins and could contribute to the functioning of inflammatory cells. There are now medicines that include substances that suppress the activity of GGTase-I with the aim of stopping the CAAX proteins from working. These substances are already being clinically tested on cancer patients, and researchers have also wondered whether they could be used to alleviate inflammatory disorders such as rheumatoid arthritis.

However, treatment with substances that inhibit GGTase-I has often been non-specific, making it difficult for researchers to assess the real potential of GGTase-I as a drug target.

"We therefore developed genetic strategies in transgenic mice to switch

off the gene that codes for GGTase-I," says PhD student Omar Khan who is heading up the study along with professor Martin Bergö and co-worker docent/consultant Maria Bokarewa from the Institute of Medicine. "This allowed us to investigate whether a complete blockade of GGTase-I can inhibit the development of inflammatory disorders and whether there are any side-effects."

However, the results were quite the opposite of what the researchers were expecting. Instead of inhibiting inflammation, the deficiency of GGTase-I in macrophages (a common type of inflammatory cell) led to the mice developing chronic inflammation with cartilage and bone erosion in the joints, very similar to rheumatoid arthritis in humans.

"We had to reassess the role that GGTase-I plays in the function of CAAX proteins, and found that one group of CAAX proteins could not only function quite normally in macrophages that didn't have any GGTase-I, but even increased in number and activity. This led to hyper-activation of the macrophages, which produced large quantities of inflammatory substances and, in turn, led to arthritis in the mice."

GGTase-I acts on over 50 different CAAX proteins. The study shows that just one of these proteins – RAC1 – appears to be behind the disorder. This means that one function of GGTase-I is to suppress the activity of RAC1 and protect mice from developing arthritis. The results suggest that medicines that inhibit GGTase-I might actually induce arthritis instead of providing a cure. This will be important information for the ongoing clinical trials with GGTase-I inhibitors in cancer patients.

"The study has also resulted in an effective and simple genetic mouse model for arthritis that can be used to study the effect of new medicines and identify the mechanisms involved in the development of the disorder," says Khan. "The next step is to try to decide whether and how

GGTase-I and RAC1 are implicated in arthritis in humans."

CAAX PROTEINS

CAAX proteins are a collection of proteins in the cells that have the amino acid sequence C-A-A-X at one end. This sequence is a signal for the protein to attract a number of enzymes, including GGTase-I, which switches on a cholesterol-like fatty acid on the CAAX proteins. This enables the protein to bind to membranes in the cells, for example the inside of the membrane that surrounds the cell. CAAX proteins include RAS (a well-known cancer protein) and the RAC and RHO proteins, which are important for many different cell functions.

Provided by University of Gothenburg