Preventing cell death as novel therapeutic strategy for rheumatoid arthritis

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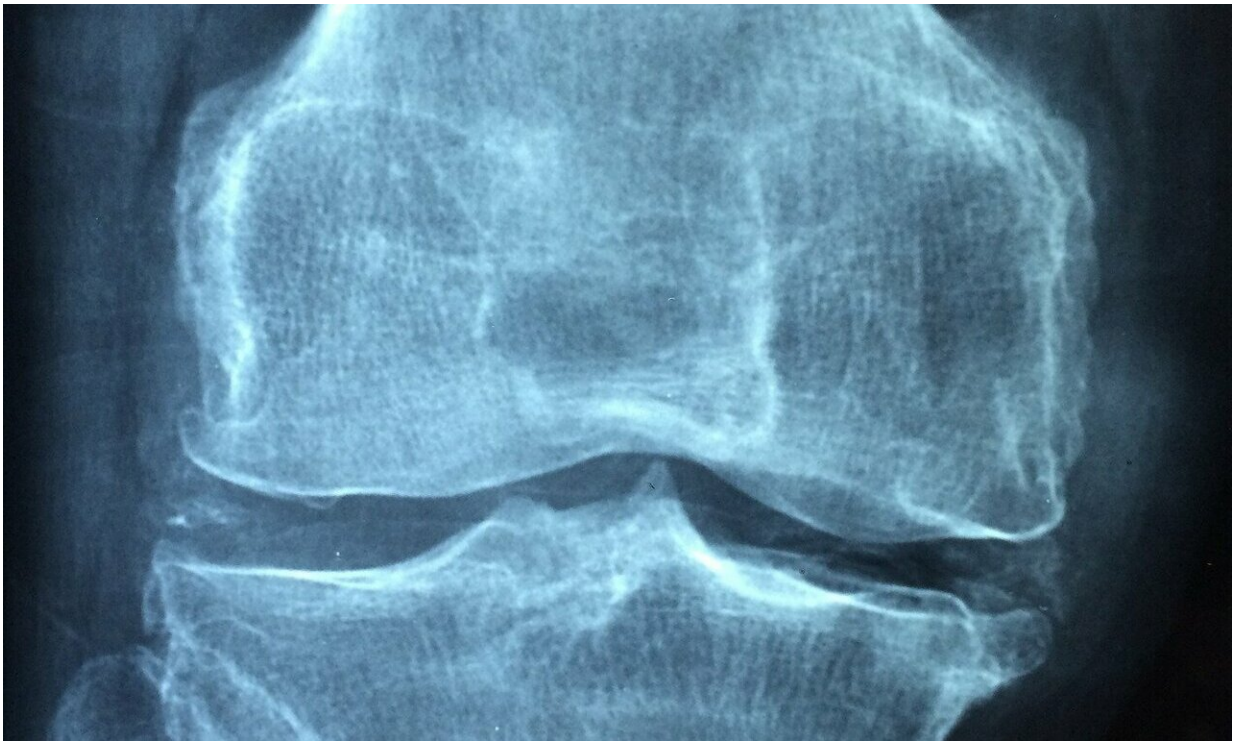

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A collaborative study has identified a new molecular mechanism causing rheumatoid arthritis. The researchers found that death of macrophages, an immune cell type, can trigger the disease. Moreover, they discovered how the protein A20 prevents macrophage death and protects against arthritis. These findings open up new possibilities for the treatment of

this debilitating disease.

Understanding arthritis

Rheumatoid arthritis (RA) is a chronic and progressive inflammatory disease that affects the joints, causing a painful swelling that eventually results in bone erosion and joint deformity. It affects 1 to 2 percent of the population, is very painful and severely affects the patients' quality of life. There is no cure for RA, but the disease progression in most patients can be slowed down with anti-inflammatory drugs. The underlying molecular mechanisms that cause the disease have remained largely unclear. Understanding these mechanisms is very important and may help in developing new therapies to treat patients suffering from RA.

Cell death and inflammation

The collaboration involved Prof. Manolis Pasparakis and Dr. Apostolos Polykratis (University of Cologne), Dr. Marietta Armaka (BSRC "Alexander Fleming," Athens), Dr. Yoshitaka Shirasaki and Dr. Yoshifumi Yamaguchi (University of Tokyo), and Prof. Geert van Loo and Arne Martens (VIB-UGent). The study builds further upon earlier research at the VIB-UGent Center for Inflammation Research that demonstrated that the protein A20 suppressed arthritis by preventing inflammation. Now, the researchers show that the inflammatory response is caused by the fact that a fraction of specialized immune cells , macrophages, die by a specific inflammation-promoting type of cell death called necroptosis. The researchers were able to prevent the development of RA by blocking necroptosis.

Prof. Geert van Loo (VIB-UGent) says, "We could also identify why these macrophages are dying, and could demonstrate the importance of a

specific part in the protein A20 for the prevention of cell death and RA development."

Dr. Marietta Armaka says, "We revealed how the particular type of macrophage demise shapes the activation of synovial fibroblasts, a key cell type that orchestrates the destruction of cartilage and bone tissue in RA."

New therapies

This study confirms the crucial importance of A20 in the control of inflammation, but now also shows that preventing cell death is a critical anti-inflammatory function of A20 to protect against arthritis.

Prof. Manolis Pasparakis says, "From a therapeutic perspective, this is a very important finding, since it suggests that drugs inhibiting cell death could be effective in the treatment of RA, at least in a subset of patients where macrophage death could provide the underlying trigger."

Several pharmaceutical companies are developing new drugs to inhibit cell death, which will hopefully help to treat patients suffering from inflammatory diseases, including rheumatoid arthritis.

The study is published in *Nature Cell Biology*.

More information: A20 prevents inflammasome-dependent arthritis by inhibiting macrophage necroptosis through its ZnF7 ubiquitin-binding domain, *Nature Cell Biology* (2019). DOI: 10.1038/s41556-019-0324-3 , www.nature.com/articles/s41556-019-0324-3

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