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Defect in A20 gene expression causes rheumatoid arthritis

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Researchers from VIB (Flanders Institute for Biotechnology) and Ghent University have shown that a defective gene can contribute to the onset of rheumatoid arthritis, an often-crippling inflammation of the joints that afflicts about 1% of the world's population. Until now, the underlying molecular mechanism of the disease was largely unclear. In the study, published in *Nature Genetics*, the researchers demonstrate that a cell-specific defect in the expression of the A20 gene (TNFAIP3) can contribute to the development of rheumatoid arthritis in mice, thereby identifying A20 as a possible target for the generation of new drugs.

Rheumatoid arthritis (RA) is a chronic progressive joint disease that starts with the inflammation of the synovial membrane and soft tissues around the joints, but often spreads to cartilage and bones. The disease is very painful for the patient. Although the cause of rheumatoid arthritis remains unknown, autoimmunity plays a crucial role. Currently, the progression of the disease can be slowed down, but RA cannot be cured.

A20 is an intracellular negative regulator of the NF-kB transcription factor, which plays a key role in the generation of the inflammatory response. Excessive activation of NF-kB can lead to a whole range of inflammatory diseases, including arthritis. The research group of Rudi Beyaert investigates the molecular mechanisms that control NF-kB activation and earlier in vitro research already indicated a key role for A20. Moreover, genome-wide association studies in humans recently suggested that defects in A20 could contribute to several autoimmune diseases, including RA.

VIB researchers led by Geert van Loo and Rudi Beyaert at Ghent University have developed mice with myeloid cells incapable of producing A20. In collaboration with Dirk Elewaut, rheumatologist at Ghent University Hospital (Ghent University), who co-supervised the research, they found that these mice had elevated levels of pro-inflammatory cytokines in their blood and joints, and spontaneously developed RA with severe inflammation and osteoporosis. Interestingly, the arthritis in this mouse model was not dependent on TNF, a cytokine that normally plays an essential role in many inflammatory diseases including RA. On the other hand, they were able to demonstrate a role for IL-6 and Toll-like receptor 4 (TLR4).

The study confirms the crucial role of A20 in the control of inflammatory responses and shows that a defect in A20 in myeloid cells can give rise to RA that is not responsive to anti-TNF treatment. From a therapeutic perspective, this is a very important finding, since anti-TNF therapy fails in 30% of RA patients. The A20-deficient mice are therefore an interesting new mouse model for the study of new therapeutics for RA.

In collaboration with Bart Lambrecht (Ghent University Hospital, Ghent University), the VIB researchers recently demonstrated that mice lacking A20 in dendritic cells, a specific myeloid cell type, also develop an autoimmune pathology that in this case shows more similarities with systemic lupus erythematosus, which is characterized by acute and chronic inflammation of various tissues of the human body (Kool et al., Immunity 2011).

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