New point of focus found for the treatment of rheumatoid arthritis and other autoimmune diseases

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Scientists affiliated with VIB and UGent have discovered a mechanism used by the protein A20 to combat inflammation. This could be a very important point of focus in the search for a treatment for autoimmune diseases such as Rheumatoid Arthritis, in which the patient suffers from chronic, uncontrolled inflammation.

Rudi Beyaert (VIB –UGent): We hope that our research can eventually contribute to the development of new therapies against Rheumatoid Arthritis and other auto-immune conditions."

Friday 12 October is "World Arthritis Day".

A20, a protein involved in Rheumatoid Arthritis (RA) and other autoimmune conditions

RA is a chronic progressive joint condition that starts with an inflammation of the joint membrane and affects the soft tissues around the joints. In Belgium, the number of RA patients is estimated at 100,000. The actual cause is unknown, but there is evidence that the immune system is disrupted, which causes the body to attack its own tissues and creates inflammation in various joints.

Rudi Beyaert and his research team previously identified the molecule A20 as an important point of focus for the development of new

medicines against RA and other autoimmune diseases. A20 appears to exert an anti-inflammatory effect in white blood cells.

Unraveling the details of an interaction

For the development of new medicines, it is important to fully understand the anti-inflammatory effect of A20. Previous research has demonstrated that A20 interferes with specific "signaling pathways" in our cells that stimulate the activity of a DNA binding molecule (NF-κB). NF-κB plays a key role in many immunological processes and excessive activation of NF-κB can result in a whole range of "inflammatory diseases", including arthritis. However, it is still largely unknown how A20 interferes with the activity of NF-κB.

Kelly Verhelst and other scientists in the team of Rudi Beyaert have now mapped the specific interaction between A20 and the NF-κB "signaling pathway". They demonstrated that a small particle (ZF7) at the end of the A20 protein binds to certain small molecules (ubiquitin chains), which are attached to specific NF-κB signaling proteins in the cell. This makes it impossible for these proteins to communicate with other proteins, thereby disrupting the signal that would normally result in inflammation.

Research impact

This is very interesting from a scientific point of view, because the VIB scientists have identified a new mechanism that brings us one step closer to the possible development of a new medicine. After all, we now know which part of A20 has an anti-inflammatory effect and how exactly this works. Rudi Beyaert: "Now that we know the importance of this small fragment (ZF7) of A20 for the anti-inflammatory effect, we can also use it as a point of focus for the development of medicines against various

auto-immune diseases. This is one step closer, but we still have a long way to go."

More information: The research was published in the leading journal *The EMBO Journal* (Verhelst et al., A20 inhibits LUBAC-mediated NF-κB activation by binding linear polyubiquitin chains via its zinc finger 7, www.ncbi.nlm.nih.gov/pubmed/23032186)

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