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Scientists shed light on a key molecular mechanism of autoimmune and inflammatory diseases

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An international team of researchers led by prof. Savvas Savvides (VIB-UGent Center for Inflammation Research) has unraveled a crucial aspect of the molecular basis of autoimmune and inflammatory diseases such as psoriasis, rheumatoid arthritis and Crohn's disease. Focusing on the immunomodulatory cytokine IL-23 they discovered that its pro-inflammatory activity, which underlies a wide range of inflammatory diseases, critically depends on structural activation of the cytokine by its receptor, IL-23R. The results of the study are published in the leading journal *Immunity*.

The prevalence of psoriasis, rheumatoid arthritis, inflammatory bowel diseases, and multiple sclerosis, has been rapidly expanding over the last few decades. For instance, an estimated 125 million people worldwide are affected by psoriasis and another 100 million by rheumatoid arthritis, while the presence of inflammatory bowel diseases (Crohn's disease and ulcerative colitis) in ethnic populations and previously unaffected geographical regions is growing at alarming rates. The cytokine IL-23 – a specific type of immunomodulatory protein – plays a crucial role in these diseases. Consequently, IL-23 has become the focus of therapeutic strategies against such diseases.

Reversed roles: when receptor activates cytokine

Since the first description of IL-23 about a decade and a half ago, the

structural and molecular basis for the mechanisms underlying the pro-inflammatory activity of IL-23 remained unclear. Prof. Savvides and his team have now shed light on the unique way that IL-23 interacts with at least one of its receptors. In general, cytokines activate receptors. But surprisingly, in the current study, the opposite appeared to be true.

Prof. Savvas Savvides (VIB-UGent): "We were surprised to find that both IL-23 and its receptor change drastically to create an intimate cytokine-receptor interface. In this interface, the receptor uses a functional hotspot on IL-23, enabling it to recruit an essential co-receptor for pro-inflammatory signaling. The binding site of the co-receptor on IL-23 also emerged as an unexpected finding. What we have now discovered about the pro-inflammatory complex mediated by IL-23 appears to be a new paradigm in the field."

Continued combined expertise

The researchers relied on integrative structural biology, combining methods to describe protein structures in atomic detail with complementary biochemical, biophysical, cellular and in vivo studies.

Prof. Savvides (VIB-UGent): "These initial research milestones from our program on IL-23 will be the cornerstone for further research in our own labs and elsewhere. After all, many questions still remain unanswered. For instance: how does IL-23 bind with other possible co-receptors? Furthermore, our insights are expected to fuel the development of new therapeutic strategies against IL-23."

More information: Yehudi Bloch et al. Structural Activation of Pro-inflammatory Human Cytokine IL-23 by Cognate IL-23 Receptor Enables Recruitment of the Shared Receptor IL-12Rβ1, *Immunity* (2017). DOI: 10.1016/j.immuni.2017.12.008

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