Researchers unfold the mechanisms underlying blood disorders

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A Finnish research team together with researchers from New York, USA, has uncovered a protein structure that regulates cell signalling and the formation of blood cells.

The team's results, published in *Nature Structural & Molecular Biology*, the most prestigious journal in the field, shed light on the mechanisms at play in haematological disorders and provide new opportunities for the design of disease-specific treatment. The work was carried out with funding from the Academy of Finland, the Cancer Society of Finland, National Institutes of Health and the Sigrid Jusélius Foundation.

Blood cell formation and activity is regulated by cytokines, small cell-signalling protein molecules, through a signal pathway mediated by Janus kinases (JAKs), a family of enzymes. Previous studies have shown that mutations in JAKs can cause severe haematological disorders as well as immunological diseases. These mutations are concentrated in the pseudokinase domain.

Leading laboratories and pharmaceutical companies around the world have long aimed at defining the structure of the pseudokinase domain of JAKs, as it has been found to be a veritable hotspot for pathogenic mutations causing haematological disorders. Led by Professor Olli Silvennoinen, the Finnish research team has now successfully determined the three-dimensional atomic-level structure of both the normal and the pathogenic pseudokinase domain.

Professor Silvennoinen's team is the first to describe the structure of the pseudokinase domain of JAKs, laying bare the domain's enzymatic mechanisms at the atomic level. The team also managed to determine the structural change, caused by the JAK2 V617F mutation, which gives rise to common myeloproliferative diseases (MPDs), such as polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF). PV and ET are blood disorders characterised by an overproduction of red blood cells or platelets, whereas MF is a disorder that causes scar tissue to accumulate in the bone marrow. The team's research results can be put to good use in developing new, targeted therapeutics for these disorders.

The study now published in Nature Structural & Molecular Biology builds on the long-standing expertise of Professor Silvennoinen's team in Janus kinases. In the early 1990s, while working in the US, Silvennoinen successfully cloned the JAK2 gene and demonstrated its activity in the signalling pathways of erythropoietin and interferon. In Finland, the Silvennoinen's work focused on the pseudokinase domain, determining and characterising its regulatory function.

The present study was carried out in close collaboration with New York University and Columbia University.

More information: Rajintha M. Bandaranayake, Daniela Ungureanu, Yibing Shan, David E. Shaw, Olli Silvennoinen and Stevan R. Hubbard: "Crystal structures of the Jak2 pseudokinase domain and the pathogenic mutant V617F". *Nature Structural & Molecular Biology*.

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