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Cell signaling discovery provides new hope for blood disorders

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Walter and Eliza Hall Institute scientists have revealed new details about how cell signalling is controlled in the immune system, identifying in the process potential new therapeutic targets for treating severe blood disorders.

Dr Jeff Babon and Professor Nick Nicola, from the institute's Structural Biology and Cancer and Haematology divisions respectively, study interactions between internal cell signalling proteins called JAKs (Janus kinases) and SOCS (Suppressors of Cytokine Signalling).

Dr Babon said the proteins were essential for blood system maintenance and immune responses.

"JAK proteins are activated in response to blood cell hormones called cytokines and instruct immune cells to respond to infection and inflammation," Dr Babon said. "SOCS proteins were discovered at the institute in the early 2000s, and provide a necessary 'negative feedback' response that stops JAKs becoming overactive, which can lead to disease."

Dr Babon said mutations in one particular protein, JAK2, are strongly associated with the development of myeloproliferative diseases.

"When JAK2 is mutated, it tells cells to continually multiply. An excessive amount of blood cells of one type are produced, and the bone marrow is overrun, leading to problems with production of other cell

types, and eventually bone marrow failure," Dr Babon said.

Myeloproliferative diseases, such as polycythemia vera and essential thrombocytopenia, are serious blood disorders in which an excessive number of blood cells accumulate in the bone marrow. They can be very severe and sometimes fatal, and may progress to acute leukaemias.

In a study published today in the journal *Immunity*, Dr Babon and Professor Nicola, with colleagues Dr James Murphy and Dr Nadia Kershaw, report on a key discovery about how the proteins JAK2 and SOCS3 interact. They hope the discovery will lead to new strategies for treating myeloproliferative diseases.

"SOCS3 is a key inhibitor of JAK2 proteins in blood and immune cells, but we didn't know exactly how the two proteins interacted to suppress JAK2 function," Dr Babon said. "We wanted to identify which site the SOCS3 protein bound to on the JAK2 protein to inhibit its action, and were surprised to find that SOCS3 binds to a unique site on JAK2 and directly inhibits the protein, rather than outcompeting other molecules."

Dr Babon said the finding could inspire a new class of therapeutic agents for treating myeloproliferative diseases.

"The SOCS3 binding site is a previously unknown part of the JAK2 protein which could be exploited as a drug target, with greater specificity than other drugs that are currently in clinical trials for inhibiting JAK2," he said.

Provided by Walter and Eliza Hall Institute