THE WALTER AND ELIZA HALL INSTITUTE OF MEDICAL RESEARCH

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Discovery points to more effective ways of regulating cell signalling

A discovery made at The Walter and Eliza Hall Institute provides new insights into enhancing the function of the protein SOCS3, which regulates the response of cells to external stimuli.

SOCS3 (Suppressors of Cytokine Signalling) controls the responses of cells to cytokines (growth factors). It is important that cytokine signalling is properly regulated within the human body. If SOCS3 permits cytokine signalling to be too "loud", then the excess of growth signals can cause crippling inflammatory diseases such as Rheumatoid Arthritis or diseases where cells multiply uncontrollably – cancer.

Conversely, if cytokine signalling is overly repressed by SOCS3, then bone marrow is deprived of sufficient white blood cells required to rejuvenate the damaged immune system following chemotherapy. An unfortunate side effect of chemotherapy is damage caused to the bone marrow that produces the white blood cells of the immune system. This leaves cancer patients prey to opportunistic infections that can delay and adversely affect their recovery.

A cytokine called G-CSF (developed in previous years at WEHI) is in clinical use worldwide to stimulate the restoration of bone marrow and the reinvigoration of the immune system in chemotherapy patients. The success of G-CSF (or Granulocyte Colony Stimulating Factor) depends on the complementary proper functioning of SOCS3.

A research team at WEHI has determined the three-dimensional structure of SOCS3. This discovery about the structure may enable the design of selective inhibitors of SOCS3 that might be useful in extending the activity of G-CSF in restoring white blood cells.

The structure also showed that SOCS3 contains a region that could be engineered out, improving the stability of SOCS3. This newly engineered version of SOCS3 also has the potential to enhance its repressive functions, which may allow inflammatory diseases to be treated more effectively.

The research team was led by Jeff Babon and Ray Norton and included Shenggen Yao, David DeSouza, Lisa Mielke, Naomi Sprigg, Tracy Willson, Doug Hilton, Nick Nicola, Manuel Baca and Sandra Nicholson.

The research is published in the 20 April 2006 issue of the prestigious international journal, *Molecular Cell.*

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