Key protein regulating inflammation may prove relevant to controlling sepsis

May 14 2009

Scientists at Singapore's Institute of Molecular and Cell Biology (IMCB), under the Agency for Science, Technology and Research (A*STAR), have identified the protein, WIP1, as the molecular "brake" that curbs severe inflammation in the body.

The findings may prove relevant to developing more effective treatments against sepsis, the severe inflammatory condition caused by bacterial infection that afflicts many patients in intensive care units (ICU).

In their paper, "WIP1 phosphatase is a negative regulator of NFκB signaling," published in the May 2009 issue of *Nature Cell Biology* (NCB), the IMCB scientists described their results showing the importance of WIP1 as an effective suppressor of inflammation and explained how the body was able to cope with an excess of inflammation brought on by the hyperactivation of the NFκB protein complex, is a signaling molecule that plays a key role in triggering inflammation.

"We have shown that WIP1 plays a critical role in suppressing the activity of NFκB and keeping NFκB levels within a safe range," said IMCB principal investigator Vinay Tergaonkar, Ph.D., who headed the research team. "In doing so, WIP1 minimizes the extent of inflammatory response that could lead to septic shock and subsequent death of patients."

Dr. Tergaonkar and his colleagues compared the inflammatory response in mice lacking in WIP1 and in a control group of mice with normal

WIP1 levels. The inflammatory response was higher in the WIP1 deficient animals. Correspondingly, the inflammatory response in mice with high WIP1 levels was suppressed.

In separate research, a second group of scientists led by Dr. Tergaonkar found further evidence linking chronic inflammation to the development of cancers such as that of the stomach and liver.

Dr. Tergaonkar and his colleagues discovered that the kinase enzyme IκB kinase 2 (IKK2), which is known for causing inflammation through the activation of NFκB, is also responsible for "ordering" the destruction of the tumour suppressor protein p53.

This discovery, published in the February 2009 issue of the *Proceedings of the National Academy of Sciences* (PNAS) and entitled, "Phosphorylation of p53 by IκB kinase 2 promotes its degradation by β-TrCP," provides fresh insight about how cells that have become inflamed due to exposure to high IKK2 activity, can become more susceptible to tumour development.

"Our recent discoveries have provided an explanation on the beneficial and harmful effects of inflammation that have baffled scientists for years," added Dr Tergaonkar. "While the natural inflammatory response serves to help the body clear infection, excessive inflammation, on the other hand, promotes cellular changes that lead to the uncontrolled growth of cells that characterizes cancer and enables its spread. These new insights involving NFκB, WIP1 and IKK2 are fostering new anti-inflammatory therapeutic approaches to human ailments ranging from inflammation (like sepsis) to cancer."

Shen Han-Ming, Ph.D., an expert in cancer cell biology at the National University of Singapore's Yong Loo Lin School of Medicine, said, "Taken together, the work in Dr Tergaonkar's lab has significantly

advanced our understanding of the regulatory mechanisms of NFκB and expanded the functional scope of NFκB. More important, such findings offer new opportunities for modulation of the NFκB signaling pathway and for exploring new therapeutic strategies in various human diseases such as cancer and sepsis."

More information:

• "WIP1 phosphatase is a negative regulator of NF-κB signalling", Nature Cell Biology, May 2009, 11(5), 659 - 666.
Authors: Chew J, Biswas S, Shreeram S, Humaidi M, Wong ET, Dhillion MK, Teo H, Hazra A, Fang CC, López-Collazo E, Bulavin DV and Tergaonkar VB.

• "Phosphorylation of p53 by IκB kinase 2 promotes its degradation by β-TrCP," *Proceedings of the National Academy of Sciences (PNAS)*, Feb 2009, 106(8), 2629-2634. Authors: Xia Y, Padre RC, De Mendoza TH, Bottero V, Tergaonkar VB, Verma IM.

Source: Agency for Science, Technology and Research (A*STAR), Singapore