



Institute of
Molecular and
Cell Biology

PRESS RELEASE
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DISCOVERY OF KEY PROTEIN THAT REGULATES INFLAMMATION SPELLS NEW HOPE FOR ICU PATIENTS

Sepsis – the leading cause of death in non-coronary ICU patients – may now be brought under control

1. Sepsis, the severe inflammatory condition caused by bacterial infection, which commonly afflicts patients in intensive care units (ICU), may soon be less life-threatening. Scientists from the 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” to curb severe inflammation in the body.

2. In their landmark paper published in the May 2009 print issue of *Nature Cell Biology (NCB)* and entitled, “WIP1 phosphatase is a negative regulator of NFκB signalling”, the group of scientists led by IMCB principal investigator, Dr Vinay Tergaonkar, highlighted 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 NFκB¹. “We have shown that WIP1 plays a critical role in suppressing the activity of NFκB and keeping NFκB levels within a safe range. In doing so, WIP1 minimises the extent of inflammatory response that could lead to septic shock and subsequent death of patients,” said Dr Tergaonkar.

3. In their experiments to measure the level of inflammatory response in laboratory mice, Dr Tergaonkar in collaboration with IMCB’s Dr Dmitry Bulavin, discovered that the inflammatory response in mice lacking in WIP1 was higher than that of the control group of mice with normal WIP1 levels. Correspondingly, the

¹ The NFκB protein complex is a well-established signalling molecule which plays a key role in triggering inflammation.

scientists also found that the inflammatory response in mice with high WIP1 levels was suppressed.

Discovery that chronic inflammation may lead to cancer

4. In a separate research, another group of scientists also 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 I κ B kinase 2 (IKK2), which is known for causing inflammation through the activation of NF κ B, is also responsible for “ordering” the destruction of the tumour suppressor protein p53. This discovery, published in the February 2009 print issue of the *Proceedings of the National Academy of Sciences (PNAS)* and entitled, “Phosphorylation of p53 by I κ B kinase 2 promotes its degradation by β -TrCP”, provides fresh insight into how cells, which have become inflamed due to exposure to high IKK2 activity, can become more susceptible to tumour development. (The diagram of the molecular interactions is presented at the [Annex](#).)

5. “Our recent discoveries have provided an explanation on the beneficial and harmful effects of inflammation that have baffled scientists for years. 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 NF κ B, WIP1 and IKK2 are fostering new anti-inflammatory therapeutic approaches to human ailments ranging from inflammation (like sepsis) to cancer²,” added Dr Tergaonkar.

6. Said Prof Shen Han-Ming, an expert in cancer cell biology at the Yong Loo Lin School of Medicine at the National University of Singapore, “I would like to congratulate Dr Tergaonkar's group for their excellent work on nuclear transcriptional factor NF κ B. Taken together, the above-described work in Dr Tergaonkar's lab has significantly advanced our understanding of the regulatory mechanisms of NF κ B and expanded the functional scope of NF κ B. More importantly, such findings offer new

² Dey A, Tergaonkar V, Lane DP. *Nature Reviews Drug Discovery* (2008), 7(12):1031. Sethi G, and Tergaonkar V. *Trends in Pharmacological Sciences* (2009), in press.

opportunities for modulation of the NFκB signalling pathway³ and for exploring new therapeutic strategies in various human diseases such as cancer and sepsis.”

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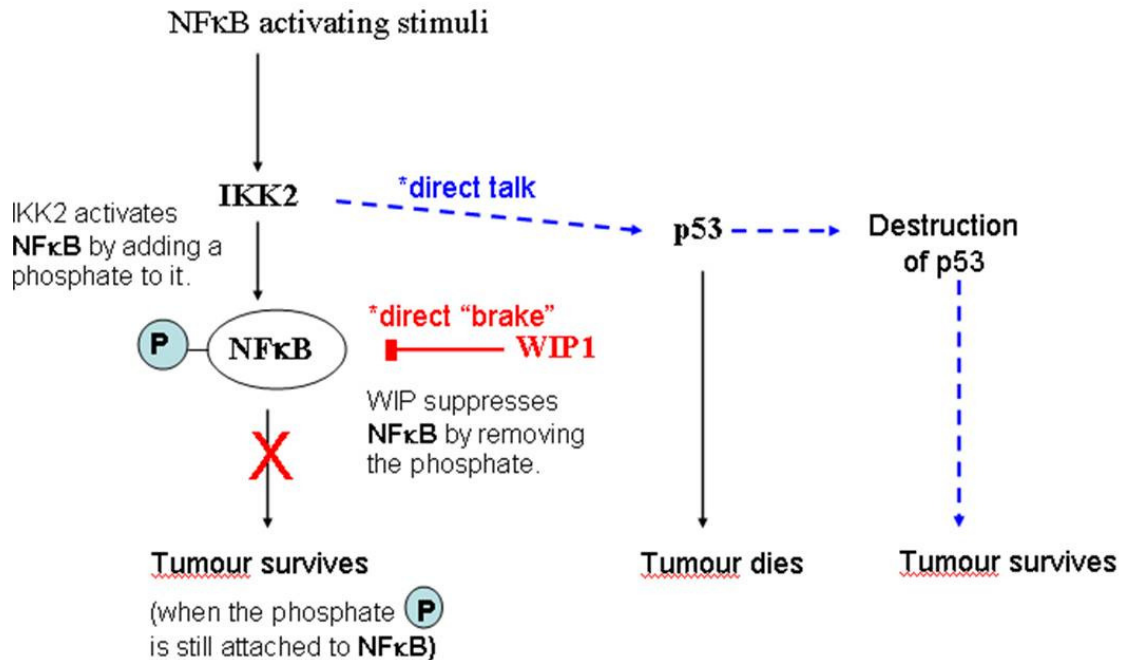
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³ Many previous studies, at IMCB and other labs, have identified NFκB (nuclear factor-kappa B) as a key factor in both health and disease. Several anti-inflammatory drugs on the market also target NFκB.

Annex:

Figure 1, Molecular interplay between the body's inflammatory pathway and tumour suppressor mechanism



* The functions denoted by an asterisk (*) indicate the recent discoveries made by Dr Tergaonkar and his colleagues. They found that IKK2, which was already involved in inflammation, had another role in ordering the destruction of tumour suppressor protein p53. They also found that WIP1 acts as a direct "brake" on NFκB to suppress NFκB activity and keep levels of NFκB within the safe range.

The research findings described in the press release can be found in the following articles:

1. "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*.

2. "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.

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About the Institute of Molecular and Cell Biology (IMCB)

The Institute of Molecular and Cell Biology (IMCB) is a member of Singapore's Agency for Science, Technology and Research (A*STAR) and is funded through A*STAR's Biomedical Research Council (BMRC). It is a world-class research institute that focuses its activities on six major fields: Cell Biology, Developmental Biology, Structural Biology, Infectious Diseases, Cancer Biology and Translational Research, with core strengths in cell cycling, cell signalling, cell death, cell motility and protein trafficking. Its recent achievements include leading an international consortium that successfully sequenced the entire pufferfish (Fugu) genome. The IMCB was awarded the Nikkei Prize 2000 for Technological Innovation in recognition of its growth into a leading international research centre and its collaboration with industry and research institutes worldwide. Established in 1987, the Institute currently has 35 independent research groups with more than 400 staff members. For more information about IMCB, please visit www.imcb.a-star.edu.sg.

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