Ending the perfect storm: Protein key to beating flu pandemics

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Dr. Lukasz Kedzierski, Dr. Sandra Nicholson and colleagues have found the protein SOCS4 plays an important role in regulating the immune system's response to the flu. Credit: Walter and Eliza Hall Institute

A protein called SOCS4 has been shown to act as a handbrake on the immune system's runaway reaction to flu infection, providing a possible means of minimising the impact of flu pandemics.

Scientists from Melbourne's Walter and Eliza Hall Institute have found

that without SOCS4 the immune response to influenza infection is slowed and there is a vast increase in the number of damaging inflammatory molecules in the lungs. This flood of inflammatory molecules, known as a 'cytokine storm', is thought to contribute to flu-related deaths in humans.

Dr Lukasz Kedzierski, Dr Sandra Nicholson and colleagues from the institute, in collaboration with Associate Professor Katherine Kedzierska and colleagues from The University of Melbourne, made the discovery, which was published today in the journal *PLOS Pathogens*.

Suppressors of cytokine signalling (SOCS) molecules control the flow of chemical messages inside cells and were discovered by institute researchers in the 1990s. Immune cells release signalling molecules called cytokines to trigger an immune response that protects the body from infection. If too many cytokines are released, SOCS proteins suppress the activity of the cytokines to prevent unwanted inflammation and tissue damage.

Dr Kedzierski said removing SOCS4 upset the normal immune response to influenza infection. "We showed that, following influenza infection, the immune system did not respond as quickly as expected, and initially sent key immune cells to the wrong location in the body," he said. "In addition, inflammatory cytokines began to accumulate in the lungs, leading to a cytokine storm that causes significant damage to the tissue."

A cytokine storm could result in increased severity of symptoms and, in many instances, to multiple organ failure and death, Dr Kedzierski said. "A cytokine storm is like an uncontrolled chain reaction, and the cytokines that normally stimulate the immune response continue to trigger other immune cells to produce more cytokines. Our research suggests that SOCS4 keeps this response under control, preventing a cytokine storm in the lungs that can lead to a build up of fluid that

restricts breathing and can ultimately result in death."

Cytokine storms are believed to be the primary cause of death in young and otherwise healthy people who are infected with influenza, particularly pandemic flu strains.

"Many of the estimated 50 million deaths caused by the 1918 flu epidemic are believed to have been caused by these cytokine storms," Dr Kedzierski said. "Cytokine storms in patients' lungs are also thought to be responsible for many of the 500,000 influenza-related deaths that occur around the world each year."

Dr Nicholson, laboratory head in the institute's Inflammation division, said the role of SOCS4 in the body was previously unknown. "When other SOCS proteins are removed from laboratory models, their function and the effect of their loss becomes immediately apparent," she said. "However, the SOCS4-deficient model appeared to be completely normal. It was only when we looked at the response to infection that we found the immune system was significantly affected by the loss of SOCS4."

Dr Nicholson said drugs that enhanced or mimicked SOCS4 action could be a useful way of treating pandemic or more aggressive flu strains, as well as other infections.

"Knowing the target and function of SOCS4 may lead to us being able to control inflammation in severe cases of the flu or to the development of new, preventive therapies," she said. "Our research so far is very promising and we have some strong leads to pursue in finding out exactly how this molecule works."

More information: Kedzierski L, Linossi EM, Kolesnik TB, Day EB, Bird NL, et al. (2014) Suppressor of Cytokine Signaling 4 (SOCS4)

Protects against Severe Cytokine Storm and Enhances Viral Clearance during Influenza Infection. *PLoS Pathog* 10(5): e1004134. doi:10.1371/journal.ppat.1004134 .
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