New strategies against bird flu

April 17 2008

The Spanish flu outbreak of 1918 killed between 30 and 50 million people. In the infected patients, the ultimate cause of death was acute respiratory distress syndrome (ARDS). This fatal condition is a massive reaction of the body during which the lung becomes severely damaged. ARDS can be induced by various bacterial and viral infections, but also by chemical agents. These could be toxic gases that are inhaled or gastric acid when aspirated. Once ARDS has developed, survival rates drop dramatically. Among patients infected with H5N1 bird flu, about 50 percent die of ARDS.

An international team of scientists has been addressing the underlying disease mechanisms for the past five years. The team involved researchers from leading institutions in Vienna, Stockholm, Cologne, Beijing, Hongkong, and Toronto as well as the US-army at Fort Detrick. The international effort was coordinated by Josef Penninger and Yumiko Imai of the Institute of Molecular Biotechnology (IMBA) of the Austrian Academy of Sciences.

A first breakthrough came in 2005 when IMBA-scientists identified ACE2 as the essential receptor for SARS virus infections and showed that ACE2 can protect from acute lung failure in disease models (Imai et al. Nature 2005; Kuba et al. Nature Medicine 2005). Based on these data, ACE2 is now under therapeutic development.

In a paper published by Cell this week, the authors describe an essential key injury pathway that is operational in multiple lung injuries and directly links oxidative stress to innate immunity. They also report for

the first time a common molecular disease pathway explaining how diverse non-infectious and infectious agents such as anthrax, lung plague, SARS, and H5N1 avian influenza may cause severe and often lethal lung failure with similar pathologies.

To identify these pathways, the researchers studied numerous tissue samples from deceased humans and animals. Victims of bird flu and SARS were examined in Hongkong, and the US-army provided samples from animals infected with Anthrax and lung plague. Common to all ARDS samples was the massive amount of oxidation products found within the cells. Based on these findings, the scientists showed that oxidative stress is the common trigger that ultimately leads to lung failure.

To elucidate the entire pathway, Yumiko Imai of IMBA developed several mouse models. She was now able to show that a molecule called TLR4 (Toll-like receptor 4) is responsible for initiating the critical signalling pathway. TLR4 is displayed at the surface of certain lung cells called macrophages, important players of the body's immune system. Once activated, TLR4 initiates an entire chain reaction which ends with the fatal failure of the lungs. Surprisingly, mice challenged with inactivated H5N1 avian influenza virus also dveloped the full reaction. On the other hand, mutant mice in which the function of TLR4 was genetically impaired were protected from lung failure in repsonse to the inactivated virus.

Based on these findings, the researchers can now outline a common molecular disease pathway: Microbial or chemical lung pathogens trigger the oxidative stress machinery. Oxidation products are intrepreted as danger-signals by the receptor TLR4. Subsequently, the body's innate immune system is activated. This defense machinery in turn leads to a chain of reactions with severe and often fatal lung damage as a consequence.

For Yumiko Imai, a Postdoc in Josef Penninger's team and pediatrician by training, these results are highly satisfying. Her motivation to study ARDS is based on personal experience in over 10 years at a pediatric intensive care unit. „I have seen so many children die from acute lung failure and felt utterly helpless", Imai says. „ Since we found a common injury pathway, our hopes are high that we may be able to develop a new and innovative strategy for tackling severe lung infections."

Source: Research Institute of Molecular Pathology