(Okayama, 8 August) Boosting levels of a protein that controls the shape and activity of a crucial group of white blood cells improves survival and recovery chances during sepsis.

Blood poisoning following an infection or injury is known as sepsis, and is a major cause of death across the world. Sepsis occurs when the body's immune system goes into overdrive, resulting in damage to its own tissues and organs through insufficient blood supply. However, the exact molecular mechanisms underpinning sepsis and its progression are unclear.

Now, Professor Masahiro Nishibori and co-workers at Okayama University, Shujitsu University and Kinki University, Japan, have shown that a naturally-occurring protein called histidine-rich glycoprotein (HRG) plays a significant role in the prevention of sepsis. They found that HRG controls the shape and activity of white blood cells called neutrophils, enabling them to flow freely and respond correctly in the fight against sepsis.

Nishibori's team aimed to verify the role of HRG – a protein produced and secreted by the liver - because HRG levels decrease rapidly in patients when sepsis takes hold. HRG is known to be involved in the regulation of immune responses, as well as prompting antibacterial and antifungal activity. The team induced sepsis in one group of mice, keeping a healthy group as controls. They purified HRG from human blood plasma, and treated some of the septic mice with a dose of the protein.

The researchers found that the HRG mice quickly regained locomotor activity, and began to recover from sepsis. Further investigations showed that the mice exhibited far less inflammation in the lungs than their non-treated counterparts. Neutrophils in the HRG mice were smooth and spherical in shape, allowing them to flow freely through microcapillaries and veins. The septic mice, however, had deformed neutrophils with irregular shapes. This in turn triggered unwanted activity because the deformed neutrophils became attached to other cells, creating cell clusters that limited blood flow.

“The decrease in plasma HRG constitutes the fundamental pathway for septic pathogenesis,” state the authors in their paper published in eBioMedicine (2016). “Supplementary therapy with HRG may provide a novel strategy for the treatment of septic patients.”

Background

Sepsis

Sepsis is caused by the body’s own response to an infection or an infected injury. Essentially, the immune system goes into overdrive and ends up damaging major organs and tissues by limiting the blood supply. Scientists theorised that sepsis must have its origins in the disruption of healthy cells in the blood, but the precise mechanisms are not yet clear.

The work by Nishibori and his team clarifies the role of histidine-rich glycoprotein (HRG) in tackling sepsis. While it is not yet clear why HRG expression falls as sepsis sets in, this study shows that the loss of HRG in blood plasma is a key factor in sepsis. The decrease in HRG appears to trigger abnormal, deformed white blood cells (neutrophils), which clump together with other cells in the vasculature system and limit blood flow.

In this study, mice given a boost of human HRG during sepsis began to show rapid signs of improvement and increased chances of survival. The neutrophils in the treated mice regained the smooth and spherical shape needed to pass freely through capillaries and the veins, and the blood supply was reinstated.

Future work

Further investigations are needed into the upstream signalling processes involved in HRG action in both healthy and septic patients. Additional studies will also determine if doses of HRG could prove a valuable method of treatment for patients with sepsis.

Novel Understanding of Sepsis Physiology and a Proposal of New Treatment Strategy

Decrease in plasma HRG in septic condition triggers the deformation of circulating neutrophils and the tight attachment of these cells to vascular endothelial cells, associated with ROS production and endothelial cell injury . This in turn facilitates the NETosis, platelet aggregation and coagulation, leading to immunothrombosis and multiple organ failure.

Reference

Hidenori Wake, Shuji Mori, Keyue Liu, Yuta Morioka, Kiyoshi Teshigawara, Masakiyo Sakaguchi, Kosuke Kuroda, Yuan Gao, Hideo Takahashi, Aiji Ohtsuka, Tadashi Yoshino, Hiroshi Morimatsu, Masahiro Nishibori. Histidine-Rich Glycoprotein Prevents Septic Lethality through Regulation of Immunothrombosis and Inflammation. *EBioMedicine*, 2016 Jun 4.

DOI : http://dx.doi.org/10.1016/j.ebiom.2016.06.003

http://www.ebiomedicine.com/article/S2352-3964(16)30247-X/abstract