'Blueprint' for blocking MMP may unlock new treatments for deadly blood infection

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Researchers studying the life threatening infectious disease sepsis have discovered how the infection can lead to a fatal inflammatory response through blood vessel cells. The research, which is published in *EMBO Molecular Medicine*, focuses on blocking crucial Matrix Metalloprotease enzymes (MMP) which activate the response.

Sepsis, and the associated systemic inflammatory response syndrome (SIRS), is a deadly condition caused by an infection of the blood which leads to whole-body inflammation. The condition is a major cause of death in intensive care wards worldwide and is most common in elderly and critically ill patients, as well as patients who are immunocompromised.

"Sepsis is a deadly disease, yet the underlying mechanisms which allow it to change body functions remains poorly understood and this has blocked the advancement of potential treatments," said lead author Athan Kuliopulos, from Tufts Medical Center and Tufts University School of Medicine, Boston. "One such mechanism is the inability of the body to regulate the inflammatory-coagulation response to the infection, which can seriously damage the patient."

The team focused their research on Matrix Metalloprotease-1 (MMP-1) which plays a key role in the immune systems response to invading pathogens and infectious diseases, but can cause uncontrolled tissue damage, which threatens the life of patients.

The study revealed how human sepsis patients have been found to have elevated levels of proMMP-1 and active MMP-1 in blood plasma which predicted both early and late death at 7 and 28 days after diagnosis.

By studying infected mice the team examined how MMP-1 was released from endothelial cells, the thin layer of cells which cover the interior surface of blood vessels. The team found that the blocking of MMP-1 activity suppressed endothelial barrier disruption, helped prevent lung failure, and improved survival in mice.

"We made the discovery that MMP-1, and its mouse equivalent MMP-1a, activates protease-activated receptors which contribute to the pro-inflammatory response of the body to sepsis through endothelial cells," said Kuliopulos. "By blocking the mouse MMP-1 we significantly improved the survival of the mice thus demonstrating a dependence on MMP-1."

The findings reveal MMP-1 to be an important early activator and suggest that therapeutics which target MMPs may prove beneficial in the treatment of sepsis.

"Sepsis remains a common, difficult to manage and stubbornly persistent syndrome when caring for critically ill patients," said Kuliopulos. "This discovery that MMP-1 acts as an activator provides us with a blueprint to investigate entirely new types of treatment for sepsis patients."

More information: Tressel. S, Kaneider. N, Kasuda. S, Foley. C, Koukos. G, Austin. K, Agarwal. A, Covic. L, Opal. S, Kuliopulos. A, “A matrix metalloprotease-PAR1 system regulates vascular integrity, systemic inflammation and death in sepsis”, EMBO Molecular Medicine, Wiley-Blackwell, May 2011, DOI: 10.1002/emmm.201100145

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