Researchers characterize the gene responsible for immune cell death and inflammation during sepsis

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Sepsis is caused by the immune system going into over-drive in response to infection. It leads to extreme inflammation that can cause blood clots and block oxygen from reaching vital organs, resulting in tissue death and multiple organ failure.

Researchers from La Trobe University in Melbourne, Australia have identified and characterized the gene responsible for immune cell death and inflammation during sepsis.

Their significant findings, published today in *Nature Immunology*, reveal the removal of protein receptor TREML4 in cell based and in-vivo experiments leads to almost absolute protection from sepsis, sepsis-induced pneumonia and blood-born Candida infection commonly associated with invasive medical procedures.

Lead researcher Dr. Christina Nedeva, from the La Trobe Institute for Molecular Science, said sepsis is characterized by two deadly stages.

"The initial inflammatory phase, or septic shock, is followed by a prolonged immunosuppression phase, which commonly leads to pneumonia. While the shock accounts for about 15 percent of sepsis-related deaths, the immunosuppression phase accounts for 85 percent," Dr. Nedeva said.

"Excitingly, we've discovered the TREML4 gene regulates both of these phases."

Lead supervisor of the study, La Trobe Associate Professor Hamsa Puthalakath, said current therapies aimed at controlling inflammation such as the use of steroids, help reduce the time that sepsis patients spend in intensive care units, but do not reduce the overall deaths.

"Steroids reduce inflammation, but they also wipe out the immune system, preventing our body from fighting both mild and serious infections," Associate Professor Puthalakath said.

"The removal of TREML4 can be described as the 'Goldilocks' approach, in that it leaves the body with some inflammation, but the immune system remains uncompromised and is healthy enough to fight off infection."

The researchers have already identified the human equivalents of the TREML4 receptor.

"There have been more than 100 clinical trials for sepsis-related therapies in the last 25 years, none of which have proved successful," Associate Professor Puthalakath said.

"La Trobe is on the forefront of potentially life-saving research. We hope to secure new funding for the next stage of our study, which will focus on the development of therapeutic antibodies against the TREML4 receptor."

Sepsis is commonly described as a silent disease because it's often misdiagnosed as the flu. Symptoms include, but are not limited to:

- A high pulse.
- Labored breathing.
- Lethargy or confusion.
- A high or even low temperature.

Each year, Australia records more than 17,000 new cases of sepsis and more than 6,000 deaths. The worldwide death toll is believed to be about 11 million annually. Some who survive will need to have limbs amputated and be left with lifelong disability.

More information: Christina Nedeva et al. TREML4 receptor regulates inflammation and innate immune cell death during polymicrobial sepsis, *Nature Immunology* (2020). DOI: 10.1038/s41590-020-0789-z

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