Monocytes switch roles during sepsis

January 27 2016

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During the course of the deadly disease sepsis, monocytes—a type of white blood cell that helps the body stave off bacteria and viruses—undergo a profound change, A*STAR researchers show. This discovery will help scientists find effective strategies for treating the disease.

Sepsis is the one of the biggest killers of patients in intensive care units

(ICUs). In the United States alone, it is responsible for more than 250,000 deaths each year, and the cost of treating it exceeded US$20 billion in 2011. Yet progress in fighting the disease has been painfully slow, with many seemingly promising therapies leading to disappointment.

One thing that makes sepsis so difficult to control is its ability to morph between two diametrically opposite responses: it initially stimulates the immune system, which it later suppresses. The initial overt inflammatory phase can generally be treated by antibiotics, but the subsequent immunosuppressive phase often proves fatal, as patients with lowered immunity succumb to secondary infections.

"Very often ICU patients get reinfected with hospital-borne bugs and can't survive because their immunity has been compromised" explains Subhra Biswas of the A*STAR Singapore Immunology Network. "Epidemiological studies indicate this as one of the the main causes of mortality."

Biswas and his co-workers have performed a comprehensive study that explored the transcriptomic, functional and mechanistic aspects of the role of monocytes—a neglected area of human sepsis.

By comparing monocytes from patients during sepsis with those after they had recovered, the team discovered that blood monocytes are 'reprogrammed' during the course of sepsis. Specifically, they change from being inflammatory to immunosuppressive, while still retaining their tissue remodeling and antimicrobial abilities. The researchers also pinpointed the culprit for this change—a transcription factor known as hypoxia-inducible factor-1α (HIF1α).

The findings have important implications for treatment strategies. "We have to target sepsis according to the phase the patients are in," says

Biswas. "If they are in the overt inflammatory phase and you give an anti inflammatory drug, it should reduce inflammation. But if they are in the immunosuppressive phase and you give anti inflammatory drugs, it will tremendously increase the risk of secondary infection. Instead you have to boost the immune system."

Existing drugs might be effective against sepsis. "Interestingly, there are drugs targeting HIF1α in clinical trials for cancer," says Biswas. "So there is the option of re-purposing drugs that target this pathway."

The team is currently developing interventions that can be combined with emerging immunotherapies.

More information: Irina N. Shalova et al. Human Monocytes Undergo Functional Re-programming during Sepsis Mediated by Hypoxia-Inducible Factor-1α, *Immunity* (2015). DOI: 10.1016/j.immuni.2015.02.001

Provided by Agency for Science, Technology and Research (A*STAR), Singapore