Inappropriate activation of an immune signaling pathway during infection leaves the body vulnerable to sepsis

26 September 2012

Some bacterial infections will give rise to immune failure in the form of sepsis, a condition that poses an especially serious mortality risk for hospital patients. Credit: iStockphoto.com/francisblack

The inflammatory response is a double-edged sword—it enables the body to mount a vigorous defense against infection, but can also inflict serious physiological damage if allowed to rampage uncontrolled. Patients experience the worst of both worlds when an infection gives way to sepsis. They undergo an initial strong inflammatory response that subsequently gives way to immunosuppression, wherein immune cells no longer respond to toxic molecules produced by bacteria.

"Sepsis is a major cause of mortality in intensive care units worldwide," says Subhra Biswas of the A*STAR Singapore Immunology Network, "but no reliable biomarkers or specific drug therapies are available." This may soon change, thanks to new insights from Biswas and his co-workers. They have revealed how a specific population of immune cells known as monocytes could exacerbate this condition.

"It is believed that these cells play a role in regulating both the inflammatory and immunosuppressive features of sepsis," explains Biswas. However, there is a variety of monocyte subtypes, each of which manifests a different collection of cell surface proteins that might activate distinct downstream signaling pathways. For this study, Biswas and his co-workers focused on a receptor protein called CD16, which is predominantly expressed on a particular subtype of monocytes. In the blood of patients with sepsis, they found increased numbers of CD16-expressing monocytes.

In many infections, sepsis is mediated largely by signaling pathways activated by the Toll-like receptor 4 (TLR4) protein. Biswas and co-workers learned that CD16 activation regulates the effects of TLR4 signaling in monocytes in a manner that may enable sepsis to progress. They observed that stimulation of both CD16 and TLR4 in monocytes led to the increased expression of a number of genes that contribute to inflammation. However, CD16-mediated signals also led to the expression of molecules that inhibit signaling pathways responsible for the initial inflammatory stage of sepsis. "These results indicate the possibility that this pathway acts as a 'switch' to tip the function of monocytes over the course of inflammation," says Biswas.

Although CD16 monocytes seem to be important contributors to sepsis, Biswas points out that their role needs to be further clarified before considering their use as a focus for therapy. "Targeting these cells at the wrong phase of sepsis could lead to problems for patients," he says. Accordingly, he and his team will continue to chart the role of monocytes throughout sepsis in order to understand how progression might be thwarted.

More information: Shalova, I. N., Kajiji, T., Lim,

J. Y., Gómez-Piña, V., Fernández-Ruíz, I., et al. CD16 regulates TRIF-dependent TLR4 response in human monocytes and their subsets. The *Journal of Immunology* 188, 3584–3593 (2012). www.jimmunol.org/content/early … /16/jimmunol.1100244

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