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Scientists identify cell death pathway involved in lethal sepsis

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Sepsis, a form of systemic inflammation, is the leading cause of death in critically ill patients. Sepsis is linked with massive cell death; however, the specific mechanisms involved in the lethality of sepsis are unclear. Now, a new study published by Cell Press in the December 23rd issue of the journal *Immunity* finds that inhibition of a specific cell death pathway called "necroptosis" protected mice from lethal inflammation. The research may lead to new therapeutic interventions for fatal inflammatory conditions that are notoriously hard to control.

Systemic inflammatory response syndrome (SIRS) is a body-wide inflammatory response that can be caused by an infection, such as in the condition sepsis, or by some sort of physical trauma, such as a severe burn. Sepsis and SIRS are thought to be caused by the cytokine tumor necrosis factor (TNF). However, although research has shown that TNF functions in inflammation, cell death, and survival, the specific mechanisms linking TNF with SIRS are not well understood.

"Engagement of TNF receptor 1 activates two diametrically opposed pathways: survival/inflammation and cell death," explains senior study author, Dr. Peter Vandenabeele, from Ghent University and Flanders Institute for Biotechnology (VIB) in Belgium. "An additional switch decides, depending on the cellular context, between apoptosis and necroptosis, two different cell death pathways. In our study, we explored the involvement of both of these cell death pathways in SIRS."

Dr. Vandenabeele and colleagues found that while disruption of

molecules required for apoptosis had no impact on lethal SIRS, inhibition or genetic deletion of RIPK molecules, which are required for necroptosis, provided complete protection against SIRS lethality. Basically, inhibition of one type of cell death did not protect mice from lethal inflammation while disruption of a different cell death pathway improved survival. The researchers went on to confirm their findings in a clinically relevant setting by demonstrating that RIPK deficiency provided protection in a mouse model of peritonitis.

Taken together, the results demonstrate a crucial role for RIPK in sepsis-mediated lethality and uncover potential therapeutic targets for treatment of SIRS and sepsis. "Selectively targeting the necroptosis process may be more advantageous than globally blocking TNF because it leaves space for the important anti-infectious functions of TNF," concludes Dr. Vandenabeele. "New insight into the precise regulatory pathways associated with necroptosis and the molecular interactions involved in the RIPK pathways will provide additional targets for intervention in these high mortality pathological conditions, which have previously been classified as uncontrollable."

More information: Online paper: DOI:10.1016/j.immuni.2011.09.020

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