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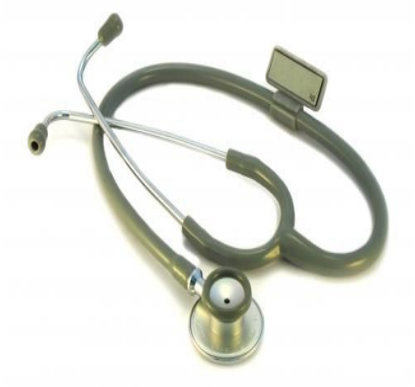
The 'Death Switch' in Sepsis Also Promotes Survival



Researchers from Rhode Island Hospital have identified a protein that plays a dual role in the liver during sepsis. The protein, known as RIP1, acts both as a "death switch" and as a pro-survival mechanism. The ability to identify the triggers for these functions may play a key role in treating sepsis in the future. The study is published online in advance of print in the journal Shock.

Sepsis is a serious condition in which the body is fighting a severe infection that has traveled through the bloodstream and is associated with a high mortality rate. Very few advances have been made to date on the biological mechanisms that cause septic morbidity and mortality. One focus, however, is Receptor Interacting Protein 1 (RIP1). This adaptor protein has been shown to have a signaling function for cells when it reacts with other receptors, and serves to switch an apoptotic cell death (a highly regulated form of death/cell suicide) to a necrotic death (a more disorderly death).

Alfred Ayala, Ph.D., a senior researcher in the division of surgical research within the department of surgery at Rhode Island Hospital and a professor at The Warren Alpert Medical School of Brown University, is the senior author of the study. Ayala says, "We initially hypothesised that RIP1 was involved in the alteration of the apoptotic death pathway to result in a kind of 'programmed necrosis' in the liver. What we actually found was an alternative role for RIP1 in the pathobiology of sepsis in the liver -- one that also promotes cellular survival."Sam McNeal, the lead author on the study and a graduate student at the Alpert Medical School and Rhode Island Hospital, says, "In our animal models, we discovered that survival decreased when we suppressed RIP1. Our findings imply that RIP1's capacity to contribute to the onset of programmed cell death is not its central role in the septic animal and it appears to be necessary for survival of septic injury."

RIP1 is a multifunctional adaptor protein that has three domains: kinase, intermediate and death. The findings from this study indicate that the kinase domain of this protein is more involved in cell function than was previously thought. McNeal explains that this finding is important because knowledge of how the kinase domain is regulated may uncover new therapeutic targets that can be used to mitigate the effects of cellular/organ damage caused by trauma, shock, sepsis or other related conditions.McNeal says, "The function of RIP1 is much more nuanced than we originally thought. We believe it plays a key role in cell function during sepsis, and if the pro-survival trigger can be identified, it could have major implications on how sepsis is treated in the future."

Other researchers in the study with Ayala and McNeal include Mark LeGolvan, D.O., of the department of pathology and Chun-Shiang Chung, Ph.D., of the department of surgery at Rhode Island Hospital and Alpert Medical School. The study was funded through a grant from the National Institute of General Medical Sciences (NIGMS), part of the National Institutes of Health.

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