Preventing the immune system from going haywire during sepsis

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Septic shock is the most severe outcome associated with pathogen infection in the bloodstream. It is a life-threatening condition invariably leading to multiple organ dysfunctions. Currently, septic shock is one of the most frequent causes of death in intensive care units worldwide.

However, it is already known that sepsis-induced multiple organ dysfunction is not a direct effect of the pathogen invasion itself but rather an overreaction of the host immune system against the infection. Many strategies aiming at holding back the extreme response of the immune system have been developed but little progress has been made.

A group of researchers from Santa Catarina, Rio Grande do Sul and São Paulo, in Brazil, have shown that blocking the receptor of bombesin/gastrin-releasing peptide (GRP), a peptide involved with the activation of neutrophil and macrophage immune cells, improves survival in sepsis animal models. Working with RC-3095, an antagonist of the GRP receptor developed by Nobel Laureate Dr Andrew Schally, the group showed that this molecule attenuates the release of the host's exacerbating immune response elements, and reveals a new inflammatory pathway and potential target for new drugs. The study was part of a research effort to investigate additional functions and potential clinical applications for the GRP receptor, initiated by Drs Gilberto Schwartsmann and Rafael Roesler at the Federal University of Rio Grande do Sul.

Led by Drs Felipe Dal-Pizzol and Fabricia Petronilho at the

Universidade do Extremo Sul Catarinense, in Brazil, the group has recently teamed up with Drs Andrew Schally and Norman L. Block at the University of Miami Miller School of Medicine to investigate the potential link between GRP and TLR-4, a receptor found in neutrophils and macrophages. TLR-4 is one of the molecules responsible for spreading the word that the body has been invaded by microbes and that something must be done quickly.

In a paper entitled "Gastrin-releasing peptide receptor antagonism induces protection from lethal sepsis: involvement of toll-like receptor 4 signaling" and published in *Molecular Medicine*, the group shows that RC-3095 reduces the levels of circulating TLR-4 and other immune elements associated with an extreme inflammatory response. Additionally, the group has found that patients with septic shock have greater amounts of GRP if compared to those with less severe forms of sepsis. These higher levels of GRP may explain why septic shock patients develop multiple organ dysfunctions and present the highest mortality rate among sepsis patients.

The study also shows that in animal models, administration of RC-3095 limits the spread of infection beyond the abdominal cavity, indicating the potential of RC-3095 in preventing the complete breakdown of the host's system.

Besides its clinical relevance, the study provides new insights on the roles of key players involved in the complex communication network triggering extreme inflammatory responses. Together, these findings may open new avenues for the development of effective therapeutic strategies to treat sepsis and related inflammatory diseases.

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