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Roles and mechanisms of DAMPs in sepsis

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Statement of the Problem: The most common pathological change in critical illness is multiple organ failure, which often leads to death. However, the underlying mechanisms are not fully understood. Recently, the secondary hit by cell breakdown products causes great attention.

Methodology & Theoretical Orientation: Both septic animal models and patients with sepsis were investigated. Circulating histones released after cell death, the most abundant damage-associated molecular pattern (DAMPs), were detected and their association with organ injury markers was analyzed. Intervention with anti-histone reagents was carried out to confirm the cause-effect relationship.

Findings: Circulating histones were dramatically elevated in both animal models and septic patients. Their levels were strongly associated with the severity of organ injury, particularly lung and cardiac injury. Using anti-histone scFv or non-anticoagulant heparin could significantly reduce organ injury as well as mortality rates. In addition, histones binding prothrombin initialized coagulation and significantly contribute to dysregulated coagulation leading to disseminated intravascular coagulation (DIC). Extracellular histones could interrupt integrity of cell membrane and cause calcium influx to damage cells, stimulate cytokine release and cause cardiac arrhythmia.

Conclusion & Significance: DMAPs, particularly histones, play critical roles in sepsis, including inflammation, coagulation activation, and multiple organ injury. This lays a foundation for future anti-histone intervention to reduce the unacceptably high mortality rates of sepsis.

Biography

Guozheng Wang is a Reader in University of Liverpool, UK, focuses on critical care medicine, particularly sepsis, using molecular and cellular approach, animal models and clinical investigation to understand the molecular mechanisms, develop diagnostic and therapeutic tools.

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