Title

In sepsis hydrogen peroxide release accompanies neutrophil chemotaxis to organs, artesunate prevents this neutrophil-mediated organ infiltration, cytokine storm and NET release

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Abstract

Sepsis is a systemic inflammatory condition that claims the lives of over 11 million people each year. Neutrophils are usually an essential protective part of the innate immune system, however, during sepsis they can become dysregulated and 'mis-localise' to the organs of patients in large numbers. Here, through their inflammatory

capabilities including cytokine and chemokine release and neutrophil extracellular trap (NET) production, they can induce organ damage and death. The reason for this 'mis-localisation' remains an unexplained phenomenon. Here, we show that hydrogen peroxide is released from multiple organs (lungs, liver and kidneys) during sepsis and that neutrophils preferentially migrate towards hydrogen peroxide under inflammatory conditions. We observe that once in the organs, neutrophils release high levels of the cytokines IL-1β and IL-6, and chemokines CXCL1 and CXCL2, along with NETs. Our group have previously shown that the antimalarial compound artesunate potently inhibits neutrophil and macrophage chemotaxis, cytokine, chemokine and NET release in pre-clinical models of CoVID-19. Here we observe that artesunate can also inhibit neutrophil migration to multiple distinct organs, and reduce cytokine, chemokine and NET production during sepsis. This work suggests that artesunate may be of value as a novel therapy in preventing the neutrophil-mediated multiple-organ damage associated with sepsis and other systemic inflammatory conditions.

Key words

Sepsis, neutrophil, inflammation, cytokines, artesunate, organ damage

Biography of Presenting Author

Dr Morad holds a PhD in Neuroimmunology from King's College London. He is currently a Lecturer in Immunology at the University of Westminster. Dr Morad's research focusses on preventing the damaging over-activation of immune cells in the pathophysiology of inflammatory conditions, such as sepsis, ARDS and CoVID-19. He has a great interest in translating projects from basic science through to the clinic. For example, during the COVID-19 pandemic, Dr Morad and collaborators repurposed the drug, artesunate from an antimalarial to a potent anti-inflammatory, and this compound is now undergoing Phase III clinical trials in collaboration with the World Health Organisation (WHO), as part of their 'SOLIDARITY' initiative to treat patients seriously ill with CoVID-19.

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