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P2506 Studying the impact of leucocyte response to infections on endothelial cells reveal novel druggable pathways in sepsis

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Background: Sepsis kills more people than 6 million people every year worldwide. Although, research into sepsis in the past years has heavily focused on suppressing leucocyte response to infections, all the clinical trials of immunosuppressive therapy to dampen or prevent excessive inflammation in sepsis have yielded disappointing results. However, it is unclear which mechanism is responsible for poor outcome in sepsis patients even after suppressing inflammation.

Materials/methods: In the present study, we have taken unbiased approach to this biological problem. Using a combination of global transcriptional analysis, circulatory proteomics and systems genetics, we have characterized the role of interaction between human leucocytes and endothelial cells in response to sepsis-causing pathogens such as *Streptococcus Pneumonia*, *Pseudomonas aeruginosa* and the fungus *Candida albicans*. Furthermore, by blocking TNF-α and IL-1 pathways, we identify an important role for interferon response by endothelial cells to affect sepsis progression.

Results: By analyzing global gene expression changes in human leucocytes in response to wide range of sepsis-causing pathogens we show striking enrichment of pathways involved in activating endothelial cells and regulating cell-cell adhesion processes. To validate this further, either supernatant containing humoral signals secreted by activated leucocytes or heat-killed pathogens were added to endothelial cells for 6 hours. By measuring cytokine profiles and transcriptional changes in endothelial cells, we show that endothelial cell activation is much stronger in response to leucocyte-released factors compared to direct pathogen stimulation. By systematically blocking by IL-1 and/or TNF-α signaling pathways in endothelial cells, we show for the first time, significant up-regulation of interferon response by endothelial cells in response to leucocyte released factors. Using genetic data from sepsis patient cohorts, we also validate the role of this interferon pathway in determining sepsis progression.

Conclusions: Our data, for the first time, demonstrate the crucial role for endothelial cell induced interferon pathway in determining sepsis outcome. Our results also suggest that the inter-individual variability in this pathway can be exploited to develop better therapies for sepsis.