

P029 Enhanced secretion of functional sMD-2 by the endothelium during inflammation; a novel component of the innate immune system?

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In this study we showed that soluble MD-2 (sMD-2) circulates in plasma of healthy individuals as a polymeric protein. In septic plasma, the total sMD-2 amount was strongly elevated and contained beside polymers also sMD-2 monomers representing the putative biologically active form of MD-2. Moreover, during experimental human endotoxemia, the monomeric and total sMD-2 content in plasma increased with the kinetics of an acute phase protein. The increase in sMD-2 monomers was paralleled by enhanced TLR4 costimulatory activity. Immunodepletion of sMD-2 from plasma confirmed the presence of circulating functional sMD-2 during endotoxemia and sepsis.

To identify the source of the enhanced sMD-2 release during systemic inflammation, immunohistochemistry was performed on lung and liver tissues of both controls and patients that died of sepsis. MD-2 expression was strongly enhanced on endothelium and multiple inflammatory cells in lung and liver of septic patients. sMD-2 release appeared to be restricted to endothelial cells and dendritic cells. Release of sMD-2 by endothelial cells was strongly enhanced by LPS and TNF-alpha stimulation. Taken together, this study demonstrates the increase of both circulating polymeric and functional monomeric sMD-2 during endotoxemia and sepsis, and evidence is provided that endothelium is crucially involved in this process.