Abstract:

It has been postulated that an early systemic inflammatory response syndrome (SIRS) and a subsequent compensatory anti-inflammatory response syndrome (CARS) occur sequentially in sepsis. Co-existence of both is referred to as mixed antagonist response syndrome (MARS). Pro- and anti-inflammatory cytokine production was investigated in patients with postoperative sepsis, a murine peritonitis model and in vitro to further delineate the interaction of hyper- and hypo-inflammation in sepsis. IL-6 and IL-10 were measured in serum samples from 80 patients on d1 and d2 of postoperative sepsis and were similarly determined at various time points after induction of septic peritonitis in mice. Cytokine production of RAW264 macrophages was stimulated in vitro using TLR agonists. IL-6 and IL-10 were measured in supernatants. All cytokine measurements were performed by ELISA. In patients, the initial phase of the immune response to sepsis was characterized by a concomitant elevation of serum IL-6 and IL-10 levels. IL-10 levels were correlated with IL-6 levels in an exponential manner (p<0.001), which could be confirmed in a mouse model of septic peritonitis. In vitro experiments revealed that the observed exponential correlation may occur as function of TLR signaling intensity. Early postoperative sepsis seems to be characterized by a primary MARS.
Sepsis severity was positively correlated with a disproportionate elevation of the anti-inflammatory response relative to the pro-inflammatory response, a pattern reminiscent of TLR-driven responses. Detailed characterization of immune responses in sepsis may help to direct standard therapies and to develop effective immunomodulatory strategies.