Mechanisms involved in the innate immune-dysfunction induced by severe sepsis

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Clearance of pathogens during infections depends on efficient neutrophil migration. Using animal models and neutrophil from patients, we are showing a defect in neutrophil recruitment into infectious focus during severe sepsis, which is followed by a reduced bacterial clearance. This impairment of neutrophil migration experimental animals or patients associated with the down-regulation of CXC chemokines receptors in this cell type. Investigating the mechanism involved in the neutrophil migration to infection focus during sepsis, we are demonstrating that in parallel with CXCR1/2 internalization, the CCR5 is expressed in the neutrophil surface. It seems that the CCR5 expression is a compensatory mechanism in an attempt to reestablish the migration of this cell type to infection focus. The CCR5-/- mice have a more pronounced reduction of neutrophil migration into the infection focus, compared with WT mice. Both events (CXCR1/2 down-regulation and CCR5 expression) are due to activation of Toll-like receptors (TLRs). Neutrophils harvested from TLR-2 or -4 deficient mice submitted to polymicrobial (CLP) sepsis do not present chemotactic response to CXCR2 agonists, but become responsive to CCR5 agonists. Although TLR activation induces both events, the signaling mechanisms are different. The CXCR1/2 internalization in neutrophils harvested form septic mice or patients or from naïve mice and stimulated in vitro with LPS associates with the increase of the expression and the activity of G-protein-coupled receptor kinases (GRK-2/-5). On the other hand, the CCR2 expression in the same cells depends on TNF-α production. The expression of GRKs and down-regulation of CXCR1/2 were prevented by pharmacological inhibition of iNOS (1400W)/soluble guanulate cyclase (ODQ)/PKG (KT5823) pathway. In conclusion, these results, by a side, emphasize the harmful role of TLRs/iNOS/NO-GC-cGMP-PKG pathway on down-regulation of CXCR1/2 receptors expression in neutrophils via induction of GRKs expression, and by other side, highlight a compensatory pathway (TLRs/TNF-α production) in an attempt to reestablish the neutrophil migration. Financial Support: CNPq, FAPESP and Timer-EC