alveolar neutrophil accumulation and lung edema at 8 and 24 hours post-administration[58]. Neutralizing HMGB-1 antibodies have been reported to reduce mortality in experimental models of acute lung injury or ischemia/reperfusion injury [55].

IL-10

IL-10 plays an important role in the anti-inflammatory response. This protein is produced simultaneously with the pro-inflammatory cytokines, but peaks hours later. One of the functions of IL-10 is the negative feedback on the production of TNF-α, IL-6 and IL-8. The cytokine IL-10 plays a pivotal role in the suppression of monocyte function as it directly decreases MHC-II expression [59]. IL-10 causes the MHC-II molecules on the surface of monocytes and macrophages to be internalized [60]. Increased levels of IL-10 have been shown to correlate with the development of sepsis or adverse outcome during sepsis. However, IL-10 is unable to discern outcome or severity of illness on an individual level. In addition, the biological activity of IL-10 is dependent on the pH and temperature, which is often altered in severely injured or septic patients [61]. It is unclear, whether increased IL-10 levels have a causal relationship with the development of complications, or whether it is a sign of a struggling host.

Complement factors

Complement is a collection of proteins, which are involved in the protection against micro-organisms. It is one of the most preserved defense mechanisms during the evolution of the immune system. Next to activation by immune complexes complement can bind conserved bacteriological compounds (e.g. bacterial carbohydrates, bacterial antigens) and altered self-products (e.g. free DNA) via mannose binding lectin, ficolins or complement factor C1q [62]. Complement can opsonize bacteria by complement factor C3b, a split product of C3. Opsonisation leads to attraction of leukocytes and enhances phagocytosis of bacteria. In the absence of bacterial or altered self products, the complement system can be activated by a connection with the coagulation system. The coagulation cascade and the complement cascade are connected through plasmin, a product of the trombolytic route that regulates homeostasis in the coagulation. Due to injury large scale activation of the coagulation cascade occurs. In trauma both coagulation factors and tissue damage activate the complement cascade [63]. This leads to neutrophil homing to the tissues and activation on the site of injury. Several studies have shown a correlation between activated complement factors (C3a/C3 ratio and C5a) and mortality after trauma [64]. *In vitro* is shown that C5a regulates two important aspects of neutrophil function; i) adhesion associated processes and ii) cytotoxic associated processes [65]. Complement is one of the most important factors contributing to neutrophil dysfunction, likely due to this dual function. In recent experimental studies, blocking of complement lead to a reduction in pulmonary and intestinal permeability [66]. The accumulation of neutrophils in the lung was reduced by blocking the complement factor C5. This is a promising finding, which can lead to novel therapeutic probabilities.

Tissue involvement

Trauma not only activates the innate immune response, but also alters the barrier integrity of several organs. Intramedullary osteosynthesis of femur fractures is thought to stimulate the innate immune response on a systemic level and is associated with an increased incidence of ARDS [67]. On the other hand, isolated thoracic injury induces local injury but is associated with the occurrence of ARDS as well [68,69]. When additional injury to the lungs is present during intramedullary osteosynthesis, the incidence of ARDS can increase two-fold [70]. This phenomenon suggests a synergistic mechanism between the activation of innate immunity and the loss of tissue barrier function (Fig. 4). The contribution of the loss of barrier function comes to attention not only in pro-inflammatory complications such as ARDS, but also in anti-inflammatory complications such as sepsis. A correlation has been shown between increased intestinal permeability and the occurrence of infectious complications [71]. It is thought that bacterial translocation due to increased intestinal permeability cause septic complications in an immunocompromised host [72]. In the pro-inflammatory phase, organ failure often precedes infection and an additional infection "only" deteriorates the remainder of the organ functions. This can be explained by the danger model, which states that innate immunity is already triggered after trauma, but can receive an additional stimulus in the form of invading bacteria. During the anti-inflammatory phase infection often precedes organ failure, giving it a more prominent role in the development of this severe complication. Despite the clear correlations between increased intestinal permeability and the incidence of sepsis in experimental settings, the relation in the clinical setting is less clear [73,74]. It is also known that the interpretation of immunological signals by cells of the innate immune system is dependent on environmental and tissue specific factors and for complications to become clinically evident, a threshold needs to be reached in specific tissues.

A cut-off point of >800 pg/ml IL-6 has been proposed as a prognostic marker and has been suggested for immunomonitoring in the damage control strategy. Unfortunately, at present no scoring system or prognostic tool is conclusive enough to adequately predict an adverse outcome on an individual level. The complexity of organ failure and the often ambiguous role of the different factors prevents a clear cut target for therapy. Many studies inves-