the negative effects of a dysfunctional innate immune system.

Multiple organ failure

Multiple organ failure after trauma has a multifactorial etiology, which can be divided in endogenous and exogenous factors. Endogenous factors, such as genetic predisposition and physical condition form the basis of the patient s susceptibility for the development of organ failure. Recent studies have shown that genetic variations (e.g. TNF-α polymorphisms) are strongly associated with the development of organ failure [2]. Exogenous factors, like the injury itself (the "first hit" or "trauma-load") and the resuscitation or surgical intervention (the "second hit" or "intervention load") play a key role in the development and clinical presentation of organ failure. Organ damage and subsequent organ failure is the result of a dysfunctional immune system. A localized inflammatory reaction after injury is physiological, which can be explained by the "danger model", an immunological theory coined by Matzinger. The "danger model" explains that alarm signals can provoke an inflammatory reaction [3]. These alarm signals can be secreted by healthy cells or released by necrotic cells, which are present after injury is sustained. The combination of type of tissue and type of alarm signal decides what kind of response follows. Neutrophils and macrophages (effectors) are involved in immune surveillance and injury control and after trauma are activated through mediators (cytokines, chemokines and complement). This local inflammatory response can exacerbate and a systemic inflammatory response (SIRS) develops. When SIRS leads to a multiple organ dysfunction syndrome (MODS) mortality can increase up to 50–80% (Fig. 1) [2,4,5].

To restore the equilibrium of the excessive pro-inflammatory reaction, an anti-inflammatory response is evoked. In a propitious case, homeostasis is achieved. However, an overreaction of the anti-inflammatory response can lead to either a compensatory anti-inflammatory response (CARS), or a mixed antagonist response (MARS) [6]. In the latter syndrome the pro-inflammatory and anti-inflammatory responses counterbalance each other. In both situations (CARS and MARS), the body is in a state of immune paralysis and is unable to produce an adequate reaction to a new threat (i.e. infection). In this state the patient is extremely prone to micro-organisms as there is a defect in an important defense mechanism formed by the cells of the innate immune system [7]. Resulting infections can cause serious complications like sepsis and septic shock with subsequent organ failure [8]. In conclusion, SIRS and sepsis (predisposed by CARS or MARS), despite different pathophysiological processes, can all result in multiple organ failure (Fig. 2).

Cellular response: neutrophils

Tissue damage leads to the activation of neutrophils and macrophages [9]. Hemorrhagic shock induces ischemia and this causes the tissue to change its metabolism to anaerobic. During resuscitation, thus reperfusion, oxygen is transported to the ischemic area in the tissue and radical oxygen species (ROS) are formed. These ROS are chemoattractants and activators of neutrophils (Fig. 3) [10,11]. Polymorphonuclear granulocytes (PMNs) have an important role in the defense and debridement of the injured tissue from the first 10 minutes until 3 days after injury [12]. Priming, or pre-activation, is an essential step for neutrophils which enhances functional responses of these cells [13,14].

Priming

Priming is the result of pre-exposure to priming agents, like granulocyte macrophage colony stimulating factor (GM-CSF) or tumor necrosis factor (TNF-α) [15,16]. These priming agents are found in increased concentrations in the peripheral blood of severely injured patients and several priming enhanced functions of neutrophils have been demonstrated in traumapatients and patients undergoing major abdominal surgery [17,18]. The enhanced functional response after priming encompasses chemotaxis, adhesion, rolling, diapedesis and the oxidative burst.

Oxidative burst

The increased oxidative burst (a cytotoxicity associated response) is necessary to prepare the neutrophils for invading micro-organisms. This increased functional response in the form of oxidative radical production correlates with the incidence of SIRS and MOF [19]. It is thought that the increased cytotoxic potential of neutrophils is a sign of an uncontrolled inflammatory reaction, which causes damage to tissues and leads to early MOF. Maximum increased priming for cytotixicity (after *in vitro* stimulation) was found between 3 and 24 hours after trauma [20]. An elevated priming index (elevation of the spontaneous oxidative burst from normal values) was found between day 2 and 5 after trauma and remained above normal until day 13 after trauma [21]. This increased oxidative burst is thought to cause additional damage to the tissue. Furthermore, the newly formed ROS contribute to the attraction and subsequent activation of neutrophils, which attributes to the accumulation of activated neutrophils in the tissue [11]. The harmful effects of neutrophil activity can only occur when these cells enter the tissue, therefore, an interaction between the neutrophil and endothelium has to occur. Interactive processes with the endothelium, like rolling, adhesion and diapedesis, are necessary for leukocytes to exert their function in the target tissue. These leukocyte functions are altered after trauma and during early organ failure.