percentage of MAC-1 positive neutrophils of critically ill surgical patients with severe disease as compared with surgical intensive care patients with less severe disease [30].

ICAM-1, normally expressed by activated entothelium, also exists as a soluble factor in serum (sICAM-1) and increased concentrations in septic patients correlate with the incidence of organ failure and mortality [26,29]. Expression of MAC-1 or sICAM give an indication on the activation of neutrophils or tissue and are both related with the development of organ failure. A high activation state of neutrophils is associated with SIRS, whereas a low activation state is related with sepsis. The activation state of neutrophils changes over time and could provide a partial explanation for the biphasic pattern of MOF [8].

Apoptosis

Billions of neutrophils are produced by the bone marrow on a daily basis [31]. Neutrophils, which have completed their function in the tissue, go into apoptosis. Apoptosis is necessary to limit the absolute number of neutrophils present in the tissues. After trauma a delayed programmed cell death (delayed apoptosis), has been demonstrated [21]. This delay is seen directly after trauma and can last up to 3 weeks [32]. Delayed apoptosis causes accumulation of neutrophils in the tissue, where they can produce more cytotoxic products (oxygen radicals and proteases) and promote tissue damage. This delayed apoptosis is found in patients with sepsis as well [33]. Bacterial products can inhibit apoptosis. In contrast to the large population of neutrophils which show decreased apoptosis, a relative larger subgroup of neutrophils exhibits signs of apoptosis in whole blood [34].

Neutrophils are essential in the pathophysiology of trauma-related organ failure [35]. Blocking or depletion of neutrophils in experimental models results in a reduction of organ failure in the pro-inflammatory (early) phase. However, overall organ failure increased due to an increased incidence of organ failure caused by severe infections during the anti-inflammatory (late) phase [36]. For future studies it seems more favorable to regulate the neutrophil compartment instead of shutting this important defense mechanism down.

Cellular response: macrophages

Neutrophils are important in the first response to injury, as they form the first natural immunological defense against micro-organisms and occur within 10 minutes after injury is sustained. Subsequent to the initial responders, monocytes/macrophages are recruited. These cells orchestrate the mechanisms involved in wound healing [37]. They function in wound debridement and secrete biologically active substances, called growth factors (e.g. TGF). TGF plays an important role in cell growth and tissue repair and thus essential in the wound repair after trauma [38]. Macrophages have a lasting influence on the subsequent phases of proliferation and tissue differentiation. Most of the macrophages are derived from blood monocytes. Differentiation of monocytes into macrophages and activation of macrophages takes place at the wound site. The cells reach the wound area in great numbers, attracted by chemotactic signals from injured tissue, the cytokines produced by immune cells and the presence of bacterial products. A macrophage can phagocytose micro-organisms and, in addition, is also capable of modulation of the adaptive immune response by mediating antigen presentation to lymphocytes. Antigens are taken up and partially degraded by the macrophage and then presented to a T-lymphocyte for recognition by MHC-II molecules. In injured patients, macrophages form the bridge between innate and adaptive immunity.

Down-regulation of MHC-II expression leads to decreased antigen presentation capacity and therefore higher susceptibility for infectious complications. Several authors have shown MHC-II suppression after trauma, which correlated with the incidence of infectious complications. MHC-II suppression on monocytes and macrophages is considered to be one of the most important features of immune suppression after injury. Some authors have suggested CARS to be defined as less than 30% expression of MHC-II on monocytes [29].

Cytokines and chemokines

In past years many studies focused on the relation between pro- and anti-inflammatory cytokines and the development of SIRS and CARS. Tissue damage causes the endothelial cells, fibroblasts, lymphocytes and tissue-macrophages to produce these cytokines [39]. At first, pro-inflammatory cytokines, such as TNF-α, GM-CSF, interleukin 1β (IL-1β), IL-6 and IL-8 are produced [40].

TNF-α and IL-1β

TNF-α and IL-1β are situated at the beginning of the pro-inflammatory cascade (Fig. 3). IL-1β acts primarily locally, but induces a systemic release of TNF-α and IL-6 by stimulation of hepatic cells. IL-1β and TNF-α increase the concentration of neutrophils in the circulation, trigger an increased chemotactic response, decrease the apoptosis ratio, amplify phagocytosis and cause an increased permeability of the endothelium. These actions lead to accumulation of activated inflammatory cells in the tissue [41,42]. IL-1β has been identified as an important cytokine in patients with the acute respiratory distress syndrome (ARDS), a neutrophil mediated disease. Only small amounts of biological active IL-1β are necessary to induce inflammation in the pulmonary compartment [41,43]. TNF-α has a more ambiguous role as its function is depending on the context of the tissue. It participates in