Local versus systemic inflammatory response in shock, trauma and sepsis

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Studying systemic levels of inflammatory mediators, especially cytokines, and trying to block their effects by various strategies has not helped in improving survival of patients at risk of SIRS and MODS. Apparantly an important part of the sequence of events escapes our attention. This manuscript identifies a number of problems illustrating why systemic cytokine levels may not be representative of the pathophysiological process : 1. blood counts and function of circulating fagocytes and plasma levels of inflammatory mediators do not reflect regional and/or local levels and function. 2. low systemic levels of soluble (i.e.) cytokine may leave the active cellmembrane- bound cytokine undetected. 3. changes in time of plasma levels do not reflect changes in time of local levels.

It is by now largely accepted that SIRS, or as previously coined "generalized inflammation" (1), is the result of a systemic, excessive, self-destructive response to a variety of severe insults such as shock, trauma and severe infection. Although inflammation is intended to be a

localized process, activation of inflammatory cells and a systemic spill-over of inflammatory products and mediators may be expected in patients with severe trauma and peritonitis, resulting in damage to remote organs. Systemic levels of various cytokines have been shown to be predictive of SIRS and its satellite syndromes ARDS, MODS and sepsis (2-5).

However, studying systemic levels of inflammatory mediators, especially cytokines, and trying to block their effects by various strategies, such as the administration of anti-TNF monoclonals and of various receptor antagonists, has not helped in improving survival of patients at risk. Apparantly an important part of the sequence of events escapes our attention. As inflammation basically is a local proces, designed to deal with the local problem of tissue damage and bacterial invasion, studying systemic levels and functions of circulating inflammatory cells and mediators may not reflect what is going on at the primary site of injury/infection and within distant organs such as the lung and the liver.

In this manuscript a brief and necessarily sketchy attempt is made to follow inflammatory cells and their mediators throughout the body and throughout time during the illness process, identifying a number of problems. Some of the problems this exploration will illustrate is that;
1. blood counts and function of circulating fagocytes and plasma levels of inflammatory mediators do not reflect regional and/or local levels and function. The sampling site thus is crucial.
2. low systemic levels of soluble (i.e.) cytokine may leave the active cellmembrane-bound cytokine undetected. Measuring cell-bound as well as circulating substances thus is crucial.
3. changes in time of plasma levels do not reflect changes in time of local levels. Obtaining a time scale at various sampling sites thus is crucial.

1. Fagocytes and adhesion molecules

Pulmonary sequestration of impressive numbers of PMN's is one of the early phenomena in "shock-lung" (6), while concommitantly leukopenia may be present. Indeed, leukopenia is an early indicator of subsequent MODS in trauma patients (7). Therefore, studying the function of circulating PMNs in trauma, shock, sepsis/SIRS, and MODS may not be relevant, since biologically active PMNs marginate and leave the circulation. After diapedesis, PMNs may behave completely differently than in blood, as local chemokines activate their full inflammatory potential (8). PMNs present in blood samples thus may not be representative for the activated population. This fact was illustrated nicely in a rodent model in which priming was induced by superior mesenteric artery occlusion, followed by reperfusion (9). Following this priming event, activation was induced with a low dose of endotoxin. Primed PMNs were released from the postischemic mesenterial bed, entered the systemic circulation, and were subsequently sequestered in the pulmonary vascular bed, where they were relatively harmless until activated by low dose endotoxin. These activated PMNs then migrated across the endothelium and released reactive oxygen metabolites (9).

Activated leukocytes express surface glycoproteins (integrins) such as L-selectin and E-selectin. The soluble form sL-selectin is a marker for neutrophil activation and, in a dose-dependent way, inhibits leukocyte attachment to the endothelium by occupying receptors, while at a high concentration it may completely block adhesion. Low levels of plasma sL-selectin may be associated with a high risk of ARDS. Cocks et al (10) compared cell-bound versus sL-selectin levels in 41 trauma patients 1 and 20 hours post-injury. Expression on the cell surface of monocytes and PMNs of L-selectin was strongly increased after injury, while

sL-selectin remained unchanged at either stage as compared to normal controls. Furthermore, monocytes, lymphocytes and neutrophils all showed a highly significant early increase in cell surface L-sectin expression as measured by mean channel fluorescence, persisting in later samples, while this increase only persisted in the later phase in monocytes. Thus, there were marked differences in the later response of the three populations, which may represent different control of their behaviour.

In another study, sE-selectin could not identify patients developping SIRS (11). sICAM-1 and sE-selectin could not be shown in blood samples of patients with tourniquet ischemia of a mean time of 105 minutes, despite signs of systemic cytokinemia. Increased systemic levels only occured in a group of severely traumatised patients, while these levels were significantly higher from the third to 5 fifth day postinjury in patients developping MODS (12).

2. Cytokines

At the site of inflammation, PMNs and macrophages release numerous active substances, such as proteolytic enzymes (e.g. elastase), toxic oxygen radicals, vasoactive substances (PAF, leukotrienes, PGE2), wound hormones (M-CSF, GM-CSF), cytokines (TNF-a, IL-1, IL-6) or metabolic products (e.g. neopterin).

2.1 Problems with systemic cytokine levels.

Systemic cytokine levels are influenced by a score of confounding factors. Firstly, half life of some cytokines is extremely brief, making their detection cumbersome. Changes in renal function may further cause problems in the interpretation of plasma levels. Also, especially in trauma cases, dilution by intravenous infusion influences plasma levels.

2.1.1. soluble cytokine receptors

Also the techniques of measurement utilised are important. In some human studies, sustained high plasma TNF-a levels correlated well with severity of illness and mortality (13), and plasma TNF levels were significantly higher in trauma patients with ARDS than in patients at risk but without ARDS (2). Others found no relation to outcome (14). A reason for this confusion may be that soluble TNF receptors (sTNFr) have a variable effect on the ability of the different assays to detect TNF (15).
Also early after major trauma, 55-kd and 75-kd sTNFr levels were significantly elevated above those of controls, while TNF levels were not increased (15,16). The authors concluded that the presence of sTNFr may be indirect evidence that TNF is present early after trauma despite low measured levels. Also a positive correlation between outcome and elevated concentrations of sTNFr or a decrease in cell surface TNF receptor values has been demonstrated (17). On the other hand, a recent study showed that the only independent predictor of death in critically ill patients was the presence of biologically active TNF (18).

2.1.2. Cell-associated cytokines

Some forms of cytokines are cell-associated and function by cell-contact, eventually in the absence of any circulating form. In patients with sepsis syndrome, high levels of cell associated IL-1ra and IL-8 could be detected in circulating erythrocytes, mononuclear cells and PMNs (19). On a per cell basis, 2000 to 7000 times the amount of IL-8 was found associated with PMN sthan with erythrocytes. Therefore, measurement of cell associated proinflammatory and anti-inflammatory cytokines may more reliably reflect their production than measurement of plasma levels (19).

2.2. Local versus systemic levels.
The local concentrations of inflammatory mediators are much higher than the plasma levels, while plasma levels may not reflect the local situation at all. Assessing the local production of these substances in clinical patients is limited to i.e. sampling BAL-fluid, CSF-fluid, peritoneal fluid or fluid from fracture hematoma or surgical wounds.

In peritonitis patients, the peritoneal concentration of TNF-a was 18 times higher than in the plasma, IL-6 was 993 times higher, and endotoxin 7 times higher (20). In another study in patients after elective gastrointestinal surgery, only directly after operation a significant correlation could be established between plasma and peritoneal levels of IL-6 and IL-10. Peritoneal TNF-a levels were at the 800 pg/ml level, whereas circulating TNF-a could be found in only one patient (21). Postoperative complications could be identified early by a secondary increase in peritoneal TNF-a concentrations (22). In another study, systemic and portal cytokine levels were monitored during abdominal aortic surgery (22). Levels of portal TNF-a were significantly higher than those in systemic blood after bowel manipulation and especially after reperfusion.

In experimental peritonitis, systemic levels of TNF-a correlated well with the clinical condition of the experimental animals during their 12-day threefasic illness. However, peritoneal macrophage TNF-a production was only elevated during days 3-7, when no circulating TNF-a could be measured (23).

Keel et al (24) measured cytokine levels in BAL fluid in patients with severe chest injury. While no measurable TNF-a was found, IL1-ß and IL-8 were strongly increased in BALF, while not measurable in the plasma. Only the levels of IL-1ra and sTNFr correlated for both sampling points. Suter et al (25) demonstrated that patients developping ARDS after shock or trauma had a 100-fold increase in BAL-levels of TNF, while also sTNFr were increased six-fold in the absence of changes in plasma levels. IL-1a concentrations in BAL-fluid are substantially elevated in ARDS patients and appear to be related to outcome (13,25). On the other hand, no consistent correlations could be demonstrated between plasma IL-1a levels and severity or mortality of ARDS, SIRS or MODS (2,26). This discrepancy may be explained by the fact that IL-1a probably acts merely as a local paracrine pro-inflammatory cytokine.

The first 72 hours after trauma and major surgery serum concentrations of IL-6 are elevated (2-4,13,27), correlating with the severity of injury and extend of surgery (4). The relation between elevated IL-6 levels and subsequent complications was clear in some studies (4,28), but absent in another (29). The first 24 hours after major surgery, IL-6 is increased in serum, and 100 to 500-fold higher in wound drainage fluid (29-32), while sIL-6r concentrations in drainage fluid were 4,5-fold lower than the generous concentrations in serum (31,32).

Elevated levels of IL-6 were found in the femoral vein of lower extremities with long bone fractures, in contrast to the femoral artery (33). In fracture/soft tissue hematomas, IL-10 was present in high concentrations during the first 24 hours post-injury, while IL-10 was rarely detectable in plasma of these patients (34).

In patients with severe brain injury, cerebrospinal fluid concentrations of IL-6 were 30 fold higher than in serum, while these high levels were followed by a profound acute-phase response in patients with signs of SIRS (35). Indeed, brain injury induces IL-6 production by human astrocytes (36).

In experimental haemorrhagic shock, elevated levels of TNF and IL-6 could be demonstrated in the portal blood, while these levels in cardiac blood were much less elevated, indicating that the gut may be a major source of cytokine production after shock, but that systemic levels are inaccurate for a proper assessment (37).

To evaluate the impact of lung and/or intrathoracic infection, Marie et al (38) compared systemic and pleural effusion levels of various cytokines and their soluble receptors and antagonistes. The levels of IL-6 and sTNFr in pleural effusion were higher in plasma than in the pleural effusion, whereas the levels of IL-1ra and sIL-6R were higher in plasma. There was no correlation between the levels of cytokines (IL-6, IL-8, TNF) in plasma and in pleural effusion. In contrast, a significant correlation was observed for the sIL-6R and sTNFR. The authors concluded that, as cytokines can be trapped by the surrounding cells in their environment, measurable levels of cytokines in biological fluids represent the tip of the iceberg, which is not the case for soluble receptors. The correlation of these latter markers between plasma and pleura strongly suggestes that exchanges between both compartments can occur in both directions (38).

2.3 Systemic versus local functions, and local differenced in function according to site.
After experimental ischemia/reperfusion of the gut, PMN superoxide production of portal PMNs is 25 times higher than from PMNs sampled from the aorta. In the studies of Hauser et al (39,39), it was demonstrated that fluid from a fracture hematoma suppresses healthy donor natural killer cell (mononuclear cell) function more readily than peripheral plasma. Also monocytes obtained from human long bone fracture hematoma were upregulated as to their mTNF expression, more so than circulating monocytes or control monocytes, while both fracture and circulating monocytes expressed far less HLA-DR antigen than control monocytes (40).

IL-6 mRNA was demonstrated in leukocytes from the wound area the first 48 hours after operation, while no IL-6 mRNA could be detected in peripheral blood (34). These findings indicate that IL-6 is produced in the area of primary injury, while sIL-6r is being produced in other areas and is consumed within the area of local injury.

Wickel et al (41) demonstrated that in experimental peritonitis induced by CLP, neutrophil migration into the peritoneum is P-selectin dependent, but sequestration in lungs is selectin independent.

In acute pancreatitis in rats, uptake of labelled bacteria showed tremendous differences between Kuppfer cells, pulmonary, intestinal and blood macrophages. This function significantly decreased in Kuppfer cells, while increasing by a factor4 in blood macrophages, a factor 2 in intstinal and pulmonary macrophages (42).

An impressive demonstration of the systemic vesrsus local role of a cytokine is IL-8. Blood-IL-8 seems to have an important anti-inflammatory role, while tissue IL-8 is pro-inflammatory (8). What is going on in the blood thus actually may be opposite of what is going on in the tissues.

2.4. Changes vary with time
Combined trauma and hemorrhaghic shock in mice results within 24 hours in a severe depression of splenic macrophage antigen presentation and in a decreased production of TNF-

a and IL-6. Seven days later, however, these cells produce significantly increased amounts of TNF-a, IL-6 and nitric oxide with a persisting functional defect in antigen presentation (43).

In an experimental peritonitis model, Plama TNF-a, as well as peritoneal macrophage TNF-a production showed a clear trifasic changes, though - as quoted earlier- these changes were in the opposite direction for the sites measured (23). (Fig. 1)

3. Conclusion.

For various reasons, interpreting the results of plasma-levels of pro-and anti-inflammatory substances should be performed with caution, as they do not necessarily reflect the local disease process. This leads to the inevitable conclusion that, today, our knowledge about the intricate pathophysiology of SIRS and MODS is insufficient to tamper with the immune system of our patients. An effective, proper-balanced and individualised modulation of the immune response can be designed only after full inventarisation and understanding interpretation of the local and systemic role of various cells and mediators at each stage of the disease process.

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