TREM-1 Expression on Monocytes is not a Parameter Specific for Infectious Etiology of Systemic Inflammatory Response Syndrome

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Abstract: Determination of mTREM-1 expression on monocytes has been investigated as a perspective diagnostic method to distinguish infectious from non-infectious etiology of the inflammation. The aims of our study were: i) to investigate the expression of TREM-1 on monocytes in septic patients and in those after elective spinal surgery without infection; ii) to assess the dynamics of mTREM-1 expression on monocytes and its association with the outcome in patients with severe sepsis. Fifty two patients with severe sepsis, 20 healthy volunteers, and 20 patients after elective spinal surgery were involved in our study. TREM-1 expression on monocytes was evaluated by flow cytometry. Compared with the group of healthy adults (median 42.0, interquartile range (IQR) 30.3–76 MFI), mTREM-1 expression was increased in the group of septic patients both at entry (median 138.4, IQR 78.4–187.5 MFI) and the last examination (median 136.5, IQR 69.0–170.0 MFI) as well as in patients 24 hours after spinal surgery (median 138.5, IQR 45.3–165.5 MFI). The increase was statistically significant. mTREM-1 expression in patients undergoing spinal surgery and those with severe sepsis did not differ. TREM-1 expression on the monocytes in survivors was higher than in

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non-survivors (p=0.007). TREM-1 levels in septic non-surviving patients correlated weakly with TNF-α levels (r=0.38; p=0.003) and with HLA-DR/CD14 levels (r=0.38; p=0.003). Increased TREM-1 expression on monocytes is not associated exclusively with the presence of systemic infection.

Introduction

Sepsis is characterized by a strong systemic inflammatory response as a result of the presence of infection. Characteristic features of the mechanisms mediating sepsis are amplification and diversification. Triggering receptor expressed on myeloid cells (TREM-1) is one of the molecules involved in this inflammatory response. TREM-1 is a cell surface receptor expressed on the myeloid cells and a member of the immunoglobulin superfamily. The family of TREM proteins includes different types, providing for positive and negative regulation in the process of myeloid cell activation and differentiation. While TREM-1 is a regulatory component of the inflammatory response, TREM-2 controls the development of dendritic cells, microglia and osteoclasts (Colonna, 2003). Cooperation of TREM-1 with DAP-12 (DNAX activating protein of 12 kDa) is essential for the formation of an immunoreceptor tyrosine-based activation motif (ITAM) (Lanier, 2003) resulting ultimately in inflammatory signal amplification (Bouchon et al., 2001). In addition to mTREM-1, which is expressed on monocytes, sTREM-1 can be detected in the serum or bronchoalveolar lavage (Radsak et al., 2007; Tejera et al., 2007). *In vitro* studies have shown TREM-1 upregulation after the administration of lipopolysaccharide, and led to studies assessing TREM-1 as a potential diagnostic parameter in septic patients (Gibot et al., 2004; Knapp et al., 2004). Studies designed to determine mTREM-1 monocyte determination have been sparse.

The aims of this study were: i) to investigate the expression of TREM-1 on monocytes in septic patients in addition to its expression on monocytes of patients after elective spinal surgery without infection; ii) to assess the dynamics of mTREM-1 expression on monocytes and its association with the outcome in patients with severe sepsis; iii) to correlate TREM-1 expression to HLA-DR expression on monocytes and TNF-α production after stimulation by lipopolysaccharide (parameters of immunoparalysis).

Material and Methods

Patient selection

We investigated 52 consecutive patients hospitalized in the Intensive Care Unit of Na Homolce Hospital and in the Department of Anesthesiology and Resuscitation of Thomayer University Hospital. The patients were 35 men and 17 women, with a mean age of 55 ± 15 years. Severe sepsis was defined according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine consensus conference (Bone et al., 1992). Exclusion criteria were as follows: patients with current immunosuppression at the time of collection of peripheral

blood samples – patients with oral intake of corticosteroids, those after blood marrow or organ transplantation, patients with leucopenia <1000/mm^3, and those with a hematological malignancy. A control group consisted of 20 healthy adult volunteers aged 23 to 63 years and of 20 patients after elective spinal surgery. All neurosurgical patients underwent spondylosurgery under general anesthesia. Blood samples of healthy adult volunteers were taken just once.

The observed values of all study parameters had no effect whatsoever on the course of therapy. The protocol was approved by the Institutional Review Board according to European and Czech legislation.

The following characteristics were obtained in all patients with severe sepsis: age; sex; severity of the medical condition stratified according to the APACHE II and SOFA scores, site of infection, and etiological organisms. A control group of neurosurgical patients was investigated within 24 hours of the procedure.

Blood sampling

Collection of peripheral blood samples was initiated within the first 24 h of meeting criteria of severe sepsis and continued at a 2- to 3-day interval, until the patient died or was discharged from the ICU. Nine millilitres of whole blood was drawn into tubes coated with lithium heparin (Vacuette, Greiner GmbH, Kremsmuenster, Austria) for "*ex vivo*" lipopolysaccharide (LPS) stimulation and measurement of constitutive tumor necrosis factor-α (TNF-α), procalcitonin (PCT), and C-reactive protein (CRP). Three millilitres of whole blood was drawn into tubes coated with K3 EDTA for flow cytometry, white blood cells (WBC), and differential counts. Blood samples were immediately stored on ice for measurement.

Determination of cell-surface TREM-1 expression and HLA-DR on monocytes

EDTA-anticoagulated blood was drawn and processed within 1 hour of the time of blood collection. Whole blood was washed three times in an isotonic phosphate buffer by centrifugation at 500× *g* for 5 minutes. Cells to be used for staining were Fc-blocked by treatment with human IgG for 15 minutes at room temperature. To visualize the expression, phycoerythrin-conjugated anti-TREM-1 antibody (R&D Systems) and fluorescein isothiocyanate conjugated anti-CD14 FITC, clone MF P9 (BD Biosciences, San Jose, CA, USA) were used. Granulocytes were defined according to their scatter pattern and monocytes as CD14+ cells. Isotype-matched control antibodies were used to exclude nonspecific staining – IgG1 PE clone DAK-G01 (Dako, Glostrupp, Denmark). Samples were analyzed by flow cytometry using a FACsCalibur cytometer (Becton-Dickinson, Franklin Lakes, NJ, USA). Data evaluation was performed using CellQuest software. TREM-1 expression on monocytes was measured in terms of mean fluorescence intensity (MFI).

HLA-DR expression on monocytes was determined by flow cytometry. Fresh EDTA whole blood was immediately stained at room temperature. Samples were

lyzed with the FACS lyzing solution (BD Biosciences, San Jose, CA, USA) and immediately analyzed. Monocytes were gated out from other cells on the basis of labelling with FITC-CD14. Results were expressed as the percentage of monocytes expressing HLA-DR and as MFI (anti/HLA-DR/PE, BD Biosciences Pharmingen (San Jose, CA, USA) The absolute number of leucocytes and monocytes were determined using an Advia analyzer (Bayer, Leverkusen, Germany).

CRP and PCT determination

CRP concentration was measured routinely by turbidimetry, with a lower limit of detection of 0.5 mg/l (Beckman Diagnostics, Florida, USA). For PCT, an immunoassay with the sandwich technique and a chemiluminiscent detection system were used according to the manufacturer's instructions (Lumitest; B.R.A.H.M.S. GmbH Diagnostica, Berlin, Germany). The detection limit for PCT was 0.08 ng/ml.

"Ex vivo" LPS stimulation

The capacity of monocytes to produce TNF-α after stimulation by a certain amount of LPS was assessed using a commercially available test kit (Ex Vivo Stimulation Kit, Milenia Biotec GmbH, Bad Nauheim, Germany). Fifty microliters of heparinized whole blood was added to a pyrogen-free stimulation solution containing 500 pg/ml of LPS in culture medium (RPMI 1640, pyrogen-free). After 4 h of incubation at 37 °C, tubes were centrifuged, and supernatants were stored at –70 °C for further measurement of TNF-α on an Immulite semi-automated chemiluminescent immuno-assay analyzer (DPC, Los Angeles, California, USA).

Statistical analysis

All tests were performed with STATA 9 statistical software. Descriptive results of continuous variables were expressed as a mean (±SD) or median (interquartile range). Relationships between two continuous variables were analyzed using Spearman's rank correlation tests. Variables were tested for their association with the diagnosis using the Pearson chi-square test for categorical data. The different groups were compared by using the Mann-Whitney U test (or nonparametric Kruskal-Wallis test when appropriate) for numerical data. The association of a low level of TREM-1 with the outcome was tested using logistic regression. For this purpose, the value of TREM-1 was dichotomized at the 20^{th} percentile of all tests performed in patients with sepsis. A two-tailed P-value of less than 0.05 was considered statistically significant.

Results

Demographic data of patients

In the group of patients with severe sepsis, there were 33 survivors (63.5%) and 19 deaths (36.5%). We demonstrated a significant difference in the APACHE II

Table 1 – Etiology of sepsis

Nosocomial infection	38 (73%)
Pulmonary	21 (40%)
Non pulmonary	31 (60%)

Absolute number of patients 52

Table 2 – Demographic characteristics of septic patients and patients after spinal surgery, PCT and C-reactive protein levels

	Septic patients	Spinal surgery	
Number of patients	52	20	
Age	55 ± 15	53 ± 11	
Sex (M/F)	47/15	15/5	
Procalcitonin (ng/ml)	3.1 (0.1–256)	0.83 (0.28–1.78)	p<0.001
C-reactive protein (mg/l)	121.9 (6–530)	42 (18–74)	p<0.001

score between the groups of survivors and non-survivors (15 ± 6 and 22 ± 7, respectively; p<0.0001) as well as in the SOFA score (6 ± 4 and 9 ± 3.6, respectively; p=0.0043). Demographic characteristics of patients, etiology of sepsis as well CRP and PCT levels in septic patients and the control group are shown in Tables 1 and 2. No postoperative infectious complications occurred in the group of neurosurgery patients and no neurosurgical patient required either blood transfusion or vasoactive drug support.

Increased mTREM-1 expression in patients with severe sepsis and in patients after a neurosurgical procedure

TREM-1 expression on monocytes of septic patients at entry and the last examination and its expression in healthy controls and in patients who underwent spinal surgery was determined. Compared with the group of healthy adults (median 42.0, interquartile range (IQR) 30.3–76 MFI), mTREM-1 expression was increased

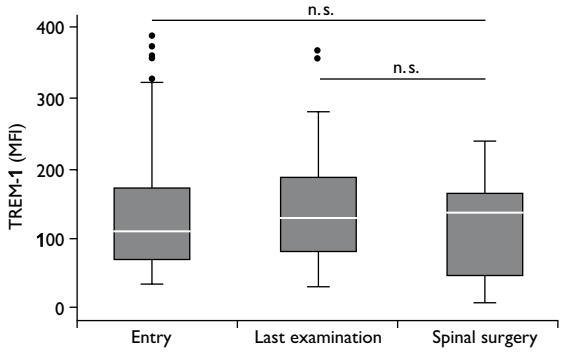

Figure 1 – TREM-1 expression on monocytes of septic patients at entry and the last examination and its expression in patients who underwent spinal surgery. Expression of mTREM-1 in patients undergoing spinal surgery and those with severe sepsis did not differ.

in the group of septic patients both at entry (median 138.4, IQR 78.4–187.5 MFI) and the last examination (median 136.5, IQR 69.0–170.0 MFI) as well as in patients 24 hours after spinal surgery (median 138.5, IQR 45.3–165.5 MFI). The increase was statistically significant. Expression of mTREM-1 in patients undergoing spinal surgery and those with severe sepsis did not differ (Figure 1).

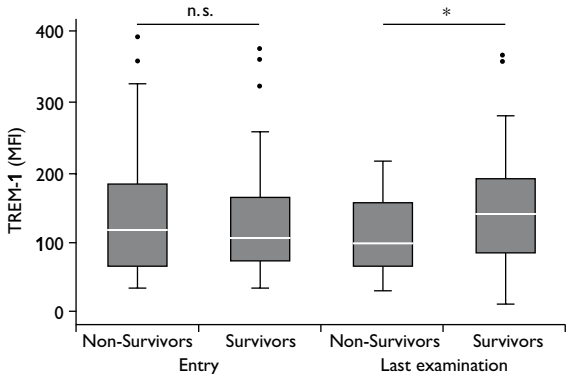

Figure 2 – TREM-1 levels did not differ between the two groups of septic patients at entry, p=0.790. At the last examination, TREM-1 expression was higher in the survivor group (n=33) compared to non-survivors (n=19), p=0.03.

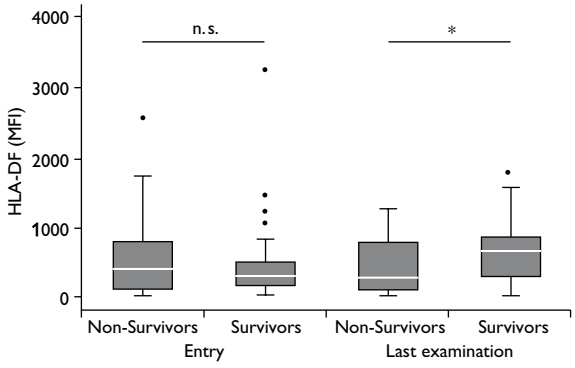

Figure 3 – HLA-DR expression did not differ between the two groups of septic patients at entry. At the last examination, HLA-DR expression was higher in the group of survivors, p=0.03.

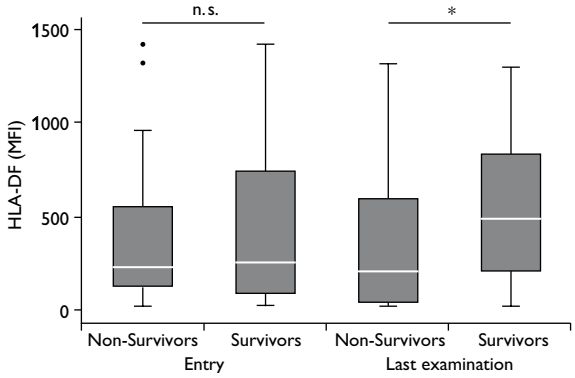

Figure 4 – TNF-α production "ex vivo" did not differ at entry between survivors and non-survivors. At the last examination, it was significantly higher in the group of survivors, p=0.03. In the group of survivors, TNF-α levels obtained at the last examination was significantly higher compared with entry (p=0.01).

The dynamics of TREM-1 expression in septic patients
TREM-1 expression on the monocytes in survivors (median 138.5 MFI, IQR 88.8–138.5 MFI) was higher than that in non-survivors (median 100.5 MFI, IQR 65.8–138 MFI), p=0.007. TREM-1 levels did not differ between the two groups at entry (non-survivors median 115, IQR 60.0–172.0; survivors median 104, IQR 70.5–169.0), p=0.790, while, at the last examination, TREM-1 expression was higher in the survivor group (median 143, IQR 94.0–212.5 and 98, respectively; IQR 52.0–165, P=0.035; Figure 2).

Septic patients showing, during the course of severe sepsis, a TREM-1 level lower than 71 MFI (20^{th} percentile) were significantly more likely to die (odds ratio 3.1; 95% CI 1.40–6.8; p=0.005). This correlation became even stronger after excluding entry examination (OR 6.5; CI 2.1–20.2; p=0.001).

Decreased HLA-DR expression and TNF-α production in non-survivors with severe sepsis
HLA-DR expression on monocytes at entry did not differ significantly between non-survivors and survivors with severe sepsis while being significantly lower in non-survivors at the final examination. TNF-α production following stimulation by lipopolysaccharide was significantly lower in non-survivors both at entry and the last examination. While increases in HLA-DR expression and TNF-α production were seen in the group of survivors, this dynamics was not documented in non-survivors (Figures 3 and 4).

Correlation of TREM-1 with "ex vivo"-produced TNF-α after stimulation by LPS and HLA-DR expression on monocytes
TREM-1 expression in septic non-survivors correlated weakly with TNF-α levels upon stimulation by LPS (r=0.38; p=0.003) and with HLA-DR/CD14 (r=0.38; p=0.003).

Discussion

In recent years, TREM-1 has been studied as a factor mediating the inflammatory response of the body to infection, and determination of the levels of its soluble form (sTREM-1) or determination of expression of TREM-1 on monocytes (mTREM-1) has been investigated as a prospective diagnostic method to distinguish infectious from non-infectious etiology of the inflammation. Most clinical trials have addressed sTREM-1 determination in the serum or bronchoalveolar lavage (Richeldi et al., 2004; Determann et al., 2005; Gibot et al., 2005; El Solh et al., 2008). The site of sTREM-1 production and regulation continues to be the focus of studies as it still is not well understood (Plachouras et al., 2006). Studies designed to determine mTREM-1 monocyte determination have been sparse. In terms of practical use in septic patients, ELISA-based sTREM-1 determination does not allow immediate analysis and availability of results. In contrast, use of flow cytometry is quick and available.

Our results document increased TREM-1 expression on the monocytes of patients with severe sepsis as well as in those undergoing elective neurosurgery compared with a control group of healthy donors. We did not demonstrate a significant difference between monocyte TREM-1 expression in the groups of severe sepsis patients and neurosurgical patients. This is consistent with the concept that inflammation as a compensatory response by the macroorganism to stress – in its effector mechanisms – is identical in infectious and non-infectious inflammation within the first hours of insult. A number of mediators in SIRS (systemic inflammatory response syndrome) of infectious and non-infectious etiology are increased. Monocyte TREM-1 expression is thus a marker of not only systemic inflammatory response of infectious origin; it is also increased in patients after surgical trauma. Similar findings have been reported in other mediators such as procalcitonin. Procalcitonin also responds by an increase even to non-infectious inflammation or to surgical stress (Dörge et al., 2003; Maier et al., 2009). Results similar to those obtained in our study have been reported by Ferat-Osorio et al. in surgical patients, with increased monocyte TREM-1 expression demonstrated in infection-free surgical patients as well as in septic patients. SIRS pre-existing prior to surgery predicted preoperative and postoperative TREM-1 upregulation (Ferat-Osorio et al., 2008). The same authors reported increased mTREM-1 expression in patients with acute pancreatitis; this increase was not associated with the presence of infection or mortality (Ferat-Osorio et al., 2009).

sTREM-1 upregulation in non-infectious SIRS has been reported independently by two studies conducted by German and French investigators (Adib-Conquy et al., 2007; Bopp et al., 2009). Recent paper by German authors failed to show a difference in sTREM-1 levels between healthy controls and patients with SIRS, severe sepsis, and septic shock within the first 3 days. sTREM-1 levels likewise did not differ between surviving and non-surviving patients (Bopp et al., 2009). Similar results were obtained in a Spanish study. In critical patients admitted with SIRS, sTREM-1 has a poor discriminative power to identify patients with infection, and sTREM-1 levels do not add diagnostic information to that provided by other routinely available clinical tests (Latour-Pérez et al., 2010).

The dynamics of TREM-1 expression is also of interest. In our study, baseline TREM-1 was unable to distinguish surviving patients from deceased ones; by contrast, there was a difference in the value of TREM-1 of the last examination, which was lower in non-surviving patients. Similar to us, Ferat-Osorio et al. reported a higher TREM-1 expression in surgical septic patients who survived compared with the deceased ones, while there was no significant difference between the groups at 72 hours post surgery. TREM-1 expression varies significantly over time, as evident in our and the above studies. No differences in baseline TREM-1 expression were seen, which could possibly distinguish the groups of survivors from the deceased ones. By contrast, the situation changed subsequently. While, in septic surgical patients, there was no longer a difference

between septic patients and healthy controls within 72 hours of the procedure, the final value of monocyte TREM-1 expression in our group of patients with severe sepsis was higher in the survivor group (Ferat-Osorio et al., 2008). In a French study with patients in septic shock, Gibot et al. did not find a difference in their baseline TREM-1 expression. However, TREM-1 expression differed between the two groups in the ensuing course (day 3), with TREM-1 expression declining in the surviving group while remaining the same in the non-surviving one (Gibot et al., 2005). These different results indicate that the amplification of the inflammatory response differed in its intensity among patients with sepsis, severe sepsis, and septic shock, and exceeding a certain threshold value of intensity may result in different mTREM-1 expression.

It is a well-known fact that the parameters characterizing immune system functionality in septic patients are HLA-DR expression on monocytes and TNF-α production following stimulation by lipopolysaccharide. These parameters also serve as a prognostic marker for septic patients (Frazier and Hall, 2008). Their decrease is characteristic of a condition referred to as immunoparalysis (Döcke et al., 2005; Ploder et al., 2006; Monneret et al., 2008). In our study, we also demonstrated characteristic alterations, with characteristic dynamics present in our group of surviving patients with increases in both parameters, while these alterations were absent in the group of deceased patients (Figures 3 and 4). TREM-1 expression correlated only weakly with TNF-α production by monocytes after stimulation by lipopolysaccharide as well as with monocyte HLA-DR expression. Interestingly, another finding of our study was the fact that patients developing TREM-1 levels lower than 71 MFI (20^{th} percentile) during severe sepsis were more likely to have a lethal outcome by a factor of 3.1

Limitations of the study

We were unable to investigate sTREM-1 in the groups of septic and neurosurgical patients with TREM-1. Correlating sTREM-1 with mTREM-1 will make an appropriate and useful addition to our efforts to clarify the relations between these two parameters.

Conclusion

Monocyte TREM-1 expression is not associated exclusively with the presence of systemic infection. It is also increased in patients undergoing elective spinal surgery without infection.

TREM-1 expression correlates weakly with HLA-DR levels and TNF-α production in septic patients.

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