Tumour Necrosis Factor-α and Interleukin-10 Production in Septic Patients and the Regulatory Effect of Plasma

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ABSTRACT

Objective: To investigate the capacity of patients' whole blood to produce proinflammatory and antiinflammatory cytokines in severe sepsis and to relate abnormalities to the effect of the patients' plasma on cytokine production in healthy donor blood.
Design: Open, prospective clinical study.
Setting: Teaching hospital, Germany
Patients: Ten patients in the surgical intensive care unit with shock and a systemic inflammatory response syndrome (SIRS), a mean APACHE II score of 27, and dysfunction of at least two organ systems at the time of investigation, resulting in 70% mortality.
Main outcome measures: Tumour necrosis factor-α (TNF-α) and interleukin-10 (IL-10) concentrations.
Results: TNF-α and IL-10 production of the whole blood in response to lipopolysaccharide (LPS) was reduced from 2000 pg/ml to 90 pg/ml and from 9163 pg/ml to 622 pg/ml, respectively ($p < 0.01$). When the plasma of these septic patients was added to the whole blood cells of healthy donors TNF-α production decreased by 38% to 1238 pg/ml ($p < 0.01$) and IL-10 production by 36% to 5857 pg/ml ($p = 0.03$).
Conclusion: The effect of plasma from septic patients on the cytokine production in healthy donor blood cells paralleled the decreased production of proinflammatory TNF-α and antiinflammatory IL-10 in the whole blood of septic patients. Efforts to modulate cytokine production in septic patients therefore need to take account of the signals from the plasma as well as the functional capacity of the cells.

Key words: sepsis, plasma cytokines, whole blood cytokines, TNF-α, IL-10, immunomodulation.

INTRODUCTION

High plasma concentrations of proinflammatory and antiinflammatory cytokines have been reported in patients with septic shock (11, 18). Cytokines are essential mediators of the immune response that are directed towards elimination of invasive microorganisms. However, if they are produced in excess, they cause life-threatening symptoms that give the clinical picture of septic shock (9, 26). Reduced cytokine production has been reported in the whole blood of septic patients (10, 23), in contrast to raised concentrations in plasma. These data raise the question of whether cytokine production should be blocked or stimulated to stop autodestruction and to restore an effective immune response (8, 15, 21). So that treatment may be planned it is necessary to clarify whether dysregulated cytokine production in sepsis is the consequence of the primed state of immunoactive cells (29, 30) or whether it is the response of an otherwise normal-reacting cell to irregular signals from the environment (28). Our aim was to find out whether the production of tumour necrosis factor-α (TNF-α) and interleukin-10 (IL-10) in the whole blood of septic patients is dependent on the presence of the autologous plasma (the natural environment of the mediator-producing cells), and whether the plasma of septic patients gives out signals that modulate cytokine production in normal donor cells. In addition we investigated changes in the production of proinflammatory TNF-α and antiinflammatory IL-10 production in septic patients.

SUBJECTS AND METHODS

Subjects

Patients in the surgical intensive care unit were eligible for the study if they had life-threatening septic shock. The inclusion criteria were: APACHE II score over 18, the presence of a severe systemic inflammatory response syndrome (SIRS) (2), and the dysfunction of at least two organ systems at the time of investigation. We considered a patient to have cardiovascular dysfunction if catecholamines were required to maintain a systolic blood pressure of at least 100 mm/Hg;

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pulmonary dysfunction if artificial ventilation was necessary; and renal dysfunction if urine production was less than 40 ml/hour for at least 12 hours. Patients were investigated during the first four days after the inclusion criteria had been met.

Measurements

Heparinised blood (10 IU/ml) was drawn at 0800 hours from each septic patient and from one AB-compatible healthy control subject and processed immediately. Aliquots of samples were centrifuged at 400 *g* for 15 minutes; the plasma was then removed and the remaining blood cells were resuspended in phosphate buffered saline (PBS) and centrifuged again at 400 *g*. The PBS was removed and the original volume was reconstituted by adding either the patient's plasma or that of the healthy control. Lipopolysaccharide (LPS) in a final concentration of 1.0 μg/ml was added where appropriate. Samples were incubated at a slow rotation at 37°C in 5% carbon dioxide. After five hours (for measurements of TNF-α production) and 18 hours (for IL-10 production) samples were centrifuged, supernatants removed, and they were stored at −70°C until assayed.

To achieve a dose response curve for the effect of different concentrations of plasma from septic patients on donor blood cells, 100%, 33%, 11%, and 4% of the plasma volume of the blood of the control was replaced by plasma from septic patients. The rest (up to 100% of the initial volume) was replaced by autologous plasma from the (control) donor.

A control experiment was required to assess the effect of the substitution of the autologous donor plasma by plasma from other healthy donors. Samples were processed as described above and the original plasma volume was restored with autologous or homologous plasma from the other donors. In this experiment all blood samples and all plasma samples were derived from healthy controls as assessed by the absence of clinical signs of disease and normal white cell counts.

TNF-α was measured with a bioassay. Briefly, the assay measures the cytolytic activity of biologically active TNF-α on a sensitive target cell, and we used the murine connective tissue cell line L929. TNF-α is able to lyse these cells in a dose-dependent manner in the presence of actinomycin-D, as measured by monotetrazolium MTT dye staining of residual viable cells. The optical density allows calculation of concentrations by means of a standard curve derived from standards of mouse recombinant TNF-α. The detection limit was set at 50 pg/ml.

TNF-α concentrations in the control experiment, which was done after the end of the study, were measured with the new Immulite® TNF-α-assay (Biermann, Bad Nauheim, Germany). IL-10 was measured with a commercially available kit (Immunotech, Hamburg). The assay is based on a sandwich technique with a monoclonal antibody against IL-10 as the capture antibody and a second biotinylated monoclonal antibody as the detection antibody. This second antibody reacts with streptavidin-peroxidase. The bound enzymatic activity is measured by adding chromogenic substrate and measuring the resulting coloured solution with a spectrometer. The concentration of the sample can be calculated by means of a standard curve.

Clinical follow up

Patients were followed up until death in the surgical intensive care unit or until discharge from hospital.

Data presentation and statistical analysis

Data are expressed as mean (SEM). The non-parametric Wilcoxon test was used to assess the significance of differences between two groups. Probabilities of less than 0.05 were accepted as significant. If cytokine production was measured in samples containing plasma derived from patients, plasma concentrations were subtracted.

RESULTS

The mean APACHE II score in 10 patients with septic shock was 27 (Table I). Seven deaths were reported in the study group. The length of stay in the intensive care unit ranged from six to 64 (mean 31) days.

Production of proinflammatory TNF-α in the whole blood of septic patients was below the detection limit of the assay or much lower than in healthy controls (90 (56) pg/ml compared with 2000 (132) pg/ml, Fig. 1A, $p < 0.01$). Substitution of septic plasma by healthy donor plasma in the blood samples of these patients did not result in normal TNF-α production (195 (68) pg/ml). Production of antiinflammatory IL-10 in septic patients was also reduced (916 (339) pg/ml compared with 9163 (918) pg/ml, Fig. 1B, $p < 0.01$). The addition of healthy donor plasma to the whole blood cells of septic patients did not normalise IL-10 production (1262 (680) pg/ml).

If serum of septic patients was added to blood from the controls, TNF-α production decreased by 38% (2000 (132) pg/ml compared with 1238 (193) pg/ml, Fig. 1A, $p < 0.01$) and IL-10 production decreased by 36% (9162 (918) pg/ml compared with 5857 (956) pg/ml, Fig. 1B, $p < 0.03$). In addition, the effect of various concentrations of plasma from septic patients on TNF-α production was tested with the plasma of three patients. TNF-α production was reduced in a dose-dependent manner (Fig. 2).

Table I. *Diagnoses and outcome in 10 patients*

Case number	Diagnosis	APACHE II at investigation	Length of ICU stay	Outcome
1	Multiple injuries	21	35	Survived
2	Multiple injuries, ARDS, peritonitis	25	39	Survived
3	Neck infection, mediastinitis	27	6	Died
4	Cholangiocarcinoma, postoperative pneumonia	22	8	Died
5	Colonic carcinoma, anastomotic leak, peritonitis	28	64	Died
6	Ischiorectal abscess, peritonitis, Fournier's gangrene	27	31	Died
7	Multiple injuries	29	46	Died
8	Plasmocytoma, splenectomy, pneumonia	27	35	Died
9	Perforated appendicitis, peritonitis	28	28	Survived
10	Perforated diverticulitis, peritonitis	36	28	Died

In the control experiment the blood and the plasma of five apparently healthy donors was used. Neither the LPS stimulated production of TNF-α, 13937 pg/ml in the sample reconstituted with autologous plasma compared with 13544 pg/ml in the samples reconstituted with plasma from the other healthy donors, nor the production of IL-10, 26425 pg/ml compared with 27992 pg/ml were different. Plasma from different healthy donors therefore did not modulate TNF-α and IL-10 production of the whole blood cells of healthy donors.

DISCUSSION

Previously, "sepsis" has been defined as a systemic response to infection (2). However, in many clinical studies the term "sepsis" has been used without further classification of its severity. We therefore used the term "septic shock" in this study to show that only cases of severe sepsis were enrolled. This was confirmed by a mean APACHE II score of 27 in the patients enrolled, and by a high mortality (70%).

In addition to the severity of the sepsis, the identification of the septic phase may be important. Patients were studied within the first four days after the diagnosis had been confirmed and inclusion criteria had been met. In this phase they were at risk of dying of acute cardiopulmonary failure and did not have any secondary complications. In the period that followed, however, they were at risk of acquiring additional nosocomial infections in the ICU, as a result of severely depressed antibacterial host defence, and ultimately of dying of multiple organ dysfunction.

Our aim was to identify dysregulated immune reactions. This is a basic requirement of any therapeutic approach to the restitution of an effective immune response after survival of the initial phase of the septic shock. We investigated the production of an inflammatory cytokine, TNF-α, and of an antiinflammatory cytokine, IL-10. Both cytokines are potent modulators of the immune response. Excessive production of TNF-α mediates septic shock (19). In contrast, elimination of TNF-α increases infection rates (3, 22). IL-10 is a highly potent monocyte inhibitory factor, which counteracts hyperactivation (6, 13, 17). However, the downregulation of the cellular immune response may facilitate the development of infections in septic patients.

The objective of ongoing multicentre studies is to neutralise TNF-α and to show that neutralisation of TNF-α in the early phase of sepsis increases the survival of the patients (25, 27). However, recently published data do not support this hypothesis (14). IL-10 is supposed to be involved in the development of "immunoparalysis" (7, 28). The potential benefit of this antiinflammatory action in septic shock may be outweighed by its potentially deleterious long term effect.

Cytokine production is influenced not only by the relationship of proinflammatory and antiinflammatory cytokines in the environment, but also by the state of cellular activation and various other signals from the environment of the cell. These signals include endotoxin and other antigens that are presented to the cell. Depending on the type of antigen presented, different signal transduction pathways may be activated that have different effects on cellular activation. Previous stimulation or the influence of various cytokines in the environment modulate the cellular response, of which tolerance to endotoxin is an example (31). In septic shock both these aspects are involved. Monocytes may already have responded to signals from the environment, having changed their state of activation (16). To discriminate between the properties of cytokine-producing cells in septic shock and the influence of environmental factors in the plasma we had to separate cells and plasma. The cells were stimulated in their natural environment and in parallel in healthy donor plasma, which is an environment without the presumed

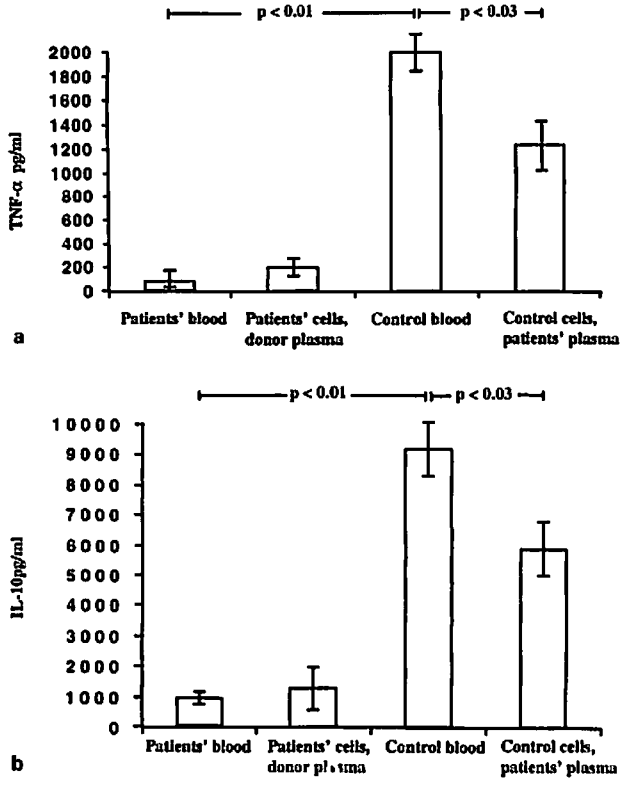

Fig. 1(a). LPS-stimulated TNF-α production in the whole blood of patients with septic shock. *(b)* LPS-stimulated IL-10 production in the whole blood of patients with septic shock. Figures are expressed as mean (SEM).

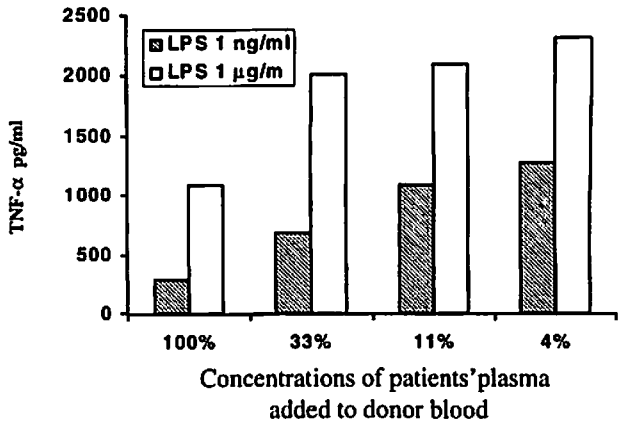

Fig. 2. TNF-α production in whole blood cells of healthy donors modulated by serum derived from patients in septic shock. Figures are expressed as means of three tests.

modifications found in the plasma of septic patients. We then added the plasma of septic patients to healthy donor blood to test the effect of septic plasma on normal cells. We found that production of both proinflammatory and antiinflammatory cytokines were reduced. The results for TNF-α confirmed previous data on cytokine production in the whole blood of septic patients. In addition to previous reports (10) we found evidence that antiinflammatory cytokine production was also low compared with healthy individuals. Low production of TNF-α and IL-10 were also found when the cells of septic patients were incubated in healthy donor plasma. These data confirm that cells from septic patients have a different and decreased response to endotoxin compared with those of healthy donors; this suggests a tolerance mechanism of endotoxin rather than a shift from proinflammatory to antiinflammatory cytokine production in septic shock (1, 24). If healthy donor blood cells were incubated with plasma from septic patients, production of both cytokines was reduced. This is evidence that signals from the plasma downregulate the cellular response to endotoxin. A control experiment confirmed that the effect was not seen if plasma of other healthy controls was used to modulate the response to LPS. This excluded an artificial effect of the method itself. The question was raised whether changes of cell numbers or cell subsets in the patient's blood subsequent to sepsis may have caused the difference in cytokine production which was described. Such changes are likely to have occurred and may have contributed to the results (12). Future studies based on flow cytometry, which are under way, will address this issue. However, the effect of the plasma from the septic patients on cytokine production of the whole blood cells derived from healthy donors which was tested in vitro cannot be the result of changes of the cell population.

The data also suggest a tolerance mechanism different from the well known tolerance to LPS after previous application of low doses of LPS. Healthy donor cells were not exposed to LPS before stimulation in the septic environment. In contrast to tolerance, which follows initial cytokine production after stimulation, the cytokine secretion of these cells was reduced immediately. The results were not explained by potential LPS-binding proteins in the plasma, because high doses of LPS did not increase maximum TNF-α production.

In summary, we have shown that decreased production of TNF-α and IL-10 in septic patients was the result of a modulated cellular response as well as the consequence of the regulatory effects of the plasma. For trials of immunotherapy this is important. The data do not support therapeutic strategies to block inflammatory TNF-α production at the time of investigation (4, 5, 20, 25, 27) nor do they support the idea that excessive IL-10 production continues to cause systemic "immunoparalysis". The reduced capacity of the cells to produce TNF-α, however, fits into the clinical

picture of a reduced antibacterial host defence in such patients. We may speculate that stimulation of cells in septic patients (21) can be effective only if signals from the plasma that render the cells tolerant are neutralised at the same time.

This may explain why treatment that mainly focused on neutralisation of endotoxin or inflammatory cytokines failed to improve outcome in septic patients. Identification of abnormal reactions in the immune response may offer target variables for immunotherapy. The monitoring of cytokine production in the whole blood and of regulatory effects of plasma derived from septic patients in a standardised fashion may provide a more reliable way of describing the immune function of patients in severe sepsis.

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RÉSUMÉ

But: Etudier la capacité du sang total des patients ayant un sepsis grave de produire des cytokines de l'inflammation et anti-inflammatoires et confronter ces anomalies à l'effet du plasma de ces patient sur la production de cytokine chez les donneurs de sang bien portants.
Type d'étude: Clinique, ouverte, prospective.
Provenance: Hôpital universitaire, Allemagne.
Patients: Dix patients hospitalisés en unité de soins intensifs chirurgicaux pour un état de choc avec un syndrome de réponse inflammatoire systémique (SRIS), un score APACHE II moyen de 27, et une défaillance d'au moins deux appareils au moment de l'étude, et une mortalité de 70%.
Principaux critères de jugement: Les concentrations de facteur de nécrose tumorale α (TNF α) et d'interleukine-10 (IL-10).
Résultats: La production de TNF α et d'IL-10 dans le sang total en réponse à la présence de lipopolysaccharide (LPS) est respectivement passée de 2000 pg/ml à 90 pg/ml et de 9163 pg/ml à 622 pg/ml ($p < 0.01$). Lorsque le plasma de ces patients était ajouté au cellules du sang total des donneurs bien portants, la production de TNF α a diminué de 38% pour atteindre 1238 pg/ml ($p < 0.01$) et celle d'IL-10 de 36% pour atteindre 5857 pg/ml ($p = 0.03$).
Conclusions: Les effets du plasma des patients septiques sur la production de cytokine par les cellules sanguines de donneurs bien portants suivent parallèlement la baisse de production des cytokines de l'inflammation TNF-α et anti-inflammatoire IL-10 dans le sang total des patients septiques. Les efforts faits pour moduler la production de cytokine chez les patients septiques doivent par conséquent prendre en compte aussi bien les signaux plasmatique que la capacité fonctionnelle des cellules

ZUSAMMENFASSUNG

Ziel: Die Untersuchung der Fähigkeit des Vollbluts von Patienten bei schwerer Sepsis pro-inflammatorische und anti-inflammatorische Cytokine zu produzieren und die Abnormitäten der Patientenplasma mit gesundem Blutspenderblut in Beziehung zu setzen.
Studienanordnung: Offene, prospektive klinische Studie.
Studienort: Lehrkrankenhaus, Deutschland.
Patienten: Zehn Patienten einer chirurgischen Intensivstation mit Schock und "systemic inflammatory response syndrome" (SIRS), durchschnittlicher APACHE II-Punktzahl von 27, und Dysfunktion von mindestens zwei Organsystemen während der Untersuchung, die in einer 70%-igen Mortalität resultierten.
Endpunkte: Tumor necrosis factor α (TNF-α) und Interleukin-10 (IL-10) Konzentrationen.
Ergebnisse: Die TNF-α- und IL-10-Erzeugung von Vollblut als Antwort auf Lipopolysaccharid (LPS) wurde von 2000 pg/ml auf 90 pg/ml reduziert bzw. von 9163 pg/ml auf 622 pg/ml ($p < 0,01$). Wenn das Plasma der septischen Patienten zu dem Vollblut gesunder Blutspender zugegeben wurde, sank die TNF-α-Produktion um 38% ab auf 1238 pg/ml ($p < 0,01$) und die IL-10-Produktion um 36% auf 5857 pg/ml ($p = 0,03$).
Schlussfolgerung: Die Wirkung des Plasmas septischer Patienten auf die Cytokinproduktion von gesunden Spenderblutzellen verlief parallel mit der verminderten Produktion von pro-inflammatorischem TNF-α und anti-inflammatorischem IL-10 im Vollblut septischer Patienten. Versuche zur Modulation der Cytokinproduktion von septischen Patienten müssen daher sowohl die Signale des Plasmas als auch die funktionelle Kapazität der Zellen berücksichtigen.

РЕЗГОМЕ

Цель: Изучить возможности продукции крови пациентов проинфламаторных и антиинфламаторных цитокинов при тяжелых формах сепсиса, а также влияние плазмы пациентов на продукцию цитокинов в здоровой крови доноров.
Характер исследования: Открытое проспективное клиническое исследование.
Клиника: Учебный госпиталь, Германия.
Пациенты: 10 пациентов хирургического отделения интенсивной терапии с явлениями шока и системного инфламаторного респонссиндрома (SIRS), средние данные APACHE II score составляли 27 при нарушении функции, по крайней мере, двух систем с 70% летальностью.
Задачи исследования: Изучение Tumor Necrosis Factor-α (TNF-α), интерлейкин-10 (IL-10).
Результаты: Продукция TNF-α и IL-10 в цельной крови в ответ на липосахариды была редуцирована от 2000 pg/ьд до 90 pg/ьд и от 9163 pg/ьд до 622 pg/ьд соответственно ($p < 0.01$). Когда плазма этих септичеких пациентов была добавлена в клетки цельной крови здоровых доноров, продукция TNF-α уменьшалась в 38% случаев до 1238 pg/ьд ($p < 0.01$) и продукция IL-10 у 36% до 5857 pg/ьд ($p = 0.03$).
Выводы: Влияние плазмы септических пациентов на продукцию цитокинов здоровой донорской крови протекает параллельно с уменьшением продукции проинфламаторного TNF-α и антиинфламаторного IL-10 в цельной крови септических пациентов. Попытки модуляции продукции цитокинов у септических пациентов следует рассматривать как плазматические сигналы, а также как функциональные возможности клеток.

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