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Update on the Mechanisms of Immune Suppression of Injury and Immune Modulation

E. Faist, M.D., C. Schinkel, M.D., S. Zimmer, M.D.

Department of Surgery, Ludwig-Maximilians University, Klinikum Grosshadern, Marchioninistrasse 15, 81377 Munich, Germany

Abstract. Major trauma results in massive impairment of immunologic reactivity, the clinical consequence of which consists in the high susceptibility of the traumatized individual toward serious infection. Whereas parts of the immune system are stimulated within a systemic, nondiscriminant, excessive whole-body inflammation, other functions within the complex of cell-mediated immunity (CMI) are dramatically paralyzed. Immune abnormalities in the aftermath of trauma occur in a sequence of states of cellular activation and within a complex order of events that is not yet well understood. Traumatic stress is causing disintegration of the intact monocyte (Mϕ)–T cell interaction, which is associated with profound changes in Mϕ forward-regulatory capacities and substantial depression of T cell function. Extensive tissue destruction results in the generation of numerous stimuli, such as phagocytosis, immune complexes, complement split products, and endo- and exotoxins, all of which contribute to excessive Mϕ activation. Mϕ then rapidly produce and release prostaglandin E_2 (PGE_2), a powerful endogenous immune suppressant. PGE_2 is an inhibitor of T cell mitogenesis, interleukin 2 (IL-2) production, and IL-2 receptor expression; and it has a massive impact on the quality of B cell antibody synthesis. Most importantly, PGE_2 represents an important cofactor for the induction of T-helper lymphocyte (T_H) activity toward the T_H2 direction. T_H2 cells are associated with the synthesis of immunosuppressive cytokines, such as IL-4 and IL-10. Although immunosuppressive substrates are inhibitory for T_H1 cells—the functional carriers of CMI—they support T_H2 activity, which predisposes the host to develop infection. The endogenous ability of the organism to survive overwhelming trauma is insufficient and requires major exogenous support. Immune modulatory interventions, depending on the immune abnormalities seen in the traumatized host, should be started as early as possible after trauma in a preventive fashion to protect against organ tissue destruction. Ideally, it should protect all cellular host defense compartments from hyperactivation as well as from exhaustion. We do believe that only a combination of drugs can effectively control the posttraumatic dyshomeostasis of the various cell systems.

Trauma of sufficient magnitude to induce a large volume of tissue injury and hypovolemic hemorrhagic shock results in massive impairment of immunologic reactivity. As inadequate defense against invasion by pathogenic organisms inevitably leads to the development of disease, injury-induced anergy has been postulated to represent a major determinant for the high susceptibility of trauma victims toward serious infection. Anergy, one of the fundamental mechanisms of endogenous immune suppression indicating the loss of specific host defense function, results from two immune mechanistic entities that occur as the dire consequence of severe trauma: systemic, nondiscriminant, excessive whole-body inflammation and a dramatic paralysis of cell-mediated immune function. We have learned that parts of the immune system are stimulated, whereas others are depressed, in a complex order of events that is not yet well understood. As depicted in Figure 1, a sequence of states of cellular activation are observed in the aftermath of trauma, and to a certain degree they can also be associated with consecutive clinical states such as the acute-phase response, anergy, infection, and organ failure. Within the monocyte/macrophage (Mϕ) lineage, immediate hyperactivation with the excessive release of proinflammatory cytokines is followed in most patients by substantial paralysis of cell function, which is then overcome after 3 to 5 days [1] with newly recruited Mϕ that probably lack the full spectrum of activity because of immaturity. Episodes of gram-negative infection toward the end of the first week after trauma can stimulate the Mϕ again toward substantial synthesis of inflammatory mediators, which then trigger the activation of polymorphonuclear neutrophils (PMNs) and endothelial cells. It is commonly agreed that T cells show an immediate functional paralysis following trauma, the degree and length of which are proportional to the injury severity. The functional quality of newly recruited lymphocytes is also most likely characterized by immaturity or fragility, resulting in continued restriction of immunologic reactivity.

We further postulate that within the different states of depressed T cell function the deletion of certain cellular subpopulations via apoptosis should play an important role. Currently a number of investigators are trying to determine if there are triggering biologic events, such as excessive plasma levels of tumor necrosis factor α (TNFα), that under stressful conditions induce programmed cell death in Mϕ, lymphocytes, and endothelial cells and make apoptosis a crucial issue for the development of trauma-associated immunodeficiency. Support of host resistance is becoming important. Incentive for the development of therapeutic regimens comes from the recognition that infection is a major contributor to late morbidity and mortality after injury (second phase MOF) [2]. Such therapy is based on studies of the down-regulatory mechanisms responsible for injury-related immune problems.

Correspondence to: E. Faist, M.D.

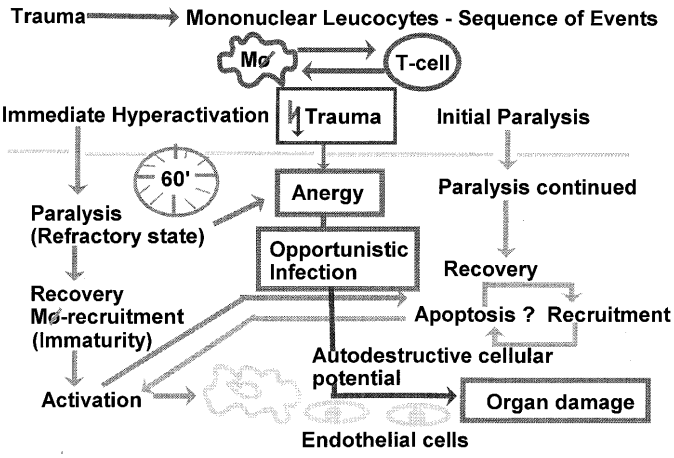

Fig. 1. Sequence of functional alterations of Mϕ and T cells associated with crucial clinical events during the posttraumatic course.

Table 1. Trauma-related cellular immune defects.

T and B lymphocytes
Myelodepression
Thymic paralysis
Lymphopenia
DTH responses ↓ ↓ ↓
$CD4^+$ ↓ ↓
CD4/CD8 ↓
TAC-CD25 expression (mitogen) ↓ ↓
Proliferative capacity ↓ ↓
Lymphokine synthesis/release ↓ ↓ ↓ (IL-2, IL-3, IFNγ)
Shift from $T_H1 \rightarrow T_H2$ subpopulation?
NK cell activity ↓
Monocytes/macrophages (Mϕ)
Relative monocytosis
Phenotypic expression of: HLADR antigen ↓ ↓ ↓ (< 20%)
CD11b ↓
Immunosuppressive property, via PGE_2 synthesis ↑ ↑ ↑ ⇒ angry macrophage
Release of thrombotic factors: TXA_2 ↑ ↑, PCA ↑ ↑, PAI ↑ ↑
Altered metabolic activity (neopterin release) ↑ ↓
Differential (↑ ↓) alteration of proinflammatory cytokine (TNFα, IL-1, IL-8) release
Polymorphonuclear neutrophils (PMNs)
PMN chemotaxis ↓
Phagocytic capacity ↓
Respiratory burst ↓
Degranulation
Altered receptor expression (CD11, CD16, CD18, CD35)
β-Integrin expression ↓
LTB_4 synthesis ↓
Release of O_2 radicals ↓ ↑
Release of elastase ↑ ↑

DTH: delayed-type hypersensitivity; NK: natural killer; TXA_2: thromboxane A_2; PCA: procoagulant activity; PAI: plasminogen activator inhibitor; LTB_4: leukotriene B_4.

Derangement of Cell-Mediated Immunity after Injury

Many immunologic derangements occur after shock, trauma, burns, and extensive surgical procedures. From the wide array of parameters (Table 1), that have been demonstrated to reflect and characterize the functional alterations of immune cells, this review focuses somewhat arbitrarily on just a few crucial immune mechanistic issues—primarily on those that seem to the authors to fit as useful targets for therapeutic intervention to correct posttraumatic immunosuppression. The massive impact on the balance of cell-mediated immune regulation is caused primarily through a simultaneous attack on Mϕ and T cells, causing disintegration of the intact Mϕ–T cell interaction. Traumatic stress not only affects the capacity of adequate specific performance of each cell type; probably more important it effects the loss of control capacity and modulatory surveillance that physiologically the Mϕ and T cells possess for each other within a number of regulatory loops. This loss of regulatory function occurs instantaneously at the moment of injury.

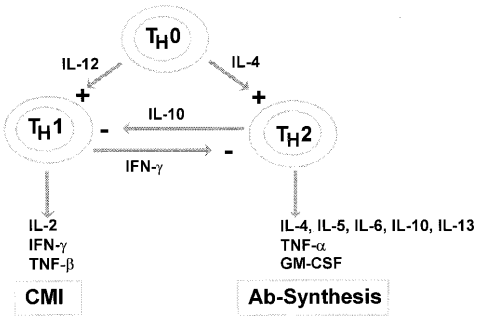

Fig. 2. T_H1/T_H2 conception of T-helper cell activation.

Under stressful conditions Mϕ are easily triggered to rapidly produce and release prostaglandin E_2 (PGE_2), which is probably the most powerful endogenous immune suppressant. Whereas the intensity of posttraumatic synthesis of proinflammatory monokines is dependent on certain environmental conditions, PGE_2 has been demonstrated to be uniformly up-regulated for as long as 21 days after trauma [3]. PGE_2 is an inhibitor of T cell mitogenesis, IL-2 production, IL-2 receptor (IL-2R) expression, and IgM antibody synthesis by B cells [4]. The inhibitory effects of PGE result from its binding to a PGE receptor, which then stimulates production of the second messenger cyclic 3′5′-adenosine monophosphate (cAMP). Via intracellular elevation of cAMP levels, PGE also negatively controls the Mϕ synthesis of TNFα and IL-1.

We demonstrated that therapeutic administration of the cyclooxygenase inhibitor indomethacin could partially restore adequate synthesis of IL-2, IL-1, and TNFα in patients undergoing cardiac surgery under extracorporeal circulation [5, 6]. Mosmann et al. [7] have noted that under certain conditions T-helper (T_H) lymphocytes can be subdivided into two functionally distinct subsets, T_H1 and T_H2, depending on their pattern of lymphokine secretion and related functional activities. Since that finding, it has appeared to be feasible to reevaluate some major immune regulatory mechanisms, as they were described to be crucial under traumatic stress, to gain further insight into their clinical relevance. Since the original description of the murine subset model in 1986, it has evolved to encompass several newly discovered cytokines, and importantly it has been validated in humans. T_H1 cells are defined by their production of IL-2, interferon γ (IFNγ), and TNFβ; and T_H2 cells are defined by their production of IL-4, IL-5, IL-6, IL-10, IL-13, TNFα, and granulocyte macrophage colony-stimulating factor (GM-CSF) [8] (Fig. 2).

Interestingly, T_H1 cells secrete IFNγ, which suppresses T_H2 activity, and T_H2 cells are suppressor-active toward the T_H1

potential via IL-4 and IL-10. $CD4^+$ T_H precursor cells (T_HP or T_H0) are directed to differentiate toward the T_H1 subtype, primarily via the monokine IL-12, and IL-4 likely represents the major driving force for the noncommited T_H to become T_H2. The T_H1 and T_H2 subsets likely represent differentiated helper-T cells, and their development may reflect particular types of antigenic stimulation.

Immunosuppression, Cytokine Networking, and Polarization

As critically injured individuals are known to lack delayed hypersensitivity and to manifest impaired IL-2 production (both T_H1 activities), it seemed appropriate to look for increased T_H2 activity in states of traumatic and septic stress in patients and relevant animal models [9].

In the search for trauma-induced mechanistics that might explain a shift of polarization in the T-helper cell population toward a T_H2 phenotype, we strongly propose a PGE_2-dependent pathway. Agents that increase cAMP, including PGE_2, have been used as probes to identify the signaling pathways that operate in T_H subsets [9]. An interesting, consistent response pattern has emerged: PGE_2 and other agents that elevate cAMP profoundly decrease T_H1 subset production of IL-2 and IFNγ. In contrast to these findings, no inhibitory effects were observed on the production of IL-4 by T_H2 cells [10]. The elevation of intracellular cAMP appears to act by down-regulating RNA for the autocrine growth factor IL-2 but not IL-4. PGE not only affects the balance of IL-2 and IL-4, it also affects IFNγ. This cytokine, which is important for the up-regulation of major histocompatibility complex (MHC) class II molecules and in an autoregulatory mode for IL-2 synthesis and IL-2R expression, is down-regulated by PGE_2.

Ayala et al. demonstrated that a decrease in T cell proliferation was associated with enhanced release of lymphocytic IL-10 from hemorrhaging mice [11]. The IL-10 release was further elevated by addition of PGE_2 and was prevented by addition of the cyclooxygenase inhibitor ibuprofen. It was demonstrated further that the PGE_2 effect must have been of an indirect nature, as the incorporation of monoclonal antibody IL-4 prevented the release of IL-10 by PGE_2-treated cells from the traumatized animals (Fig. 3). It was concluded by the authors that autocrine release of PGE_2 during hemorrhage increases IL-10 production via an IL-4-mediated pathway. In our still ongoing investigations in patients who had sustained major burns and extensive blunt injury (Injury Severity Score $\geq$ 30 points) we frequently found elevated IL-10 plasma levels during the initial phase after injury; in addition, it was seen that there was a good correlation between peak values of IL-10 and the development of septic complications. In contrast, the cytoplasmatic detection of IFNγ revealed a clear deficit of IFNγ synthesis (up to −25%) compared to control values from healthy volunteers (unpublished data). In an experimental series Kobayashi and coworkers demonstrated that the increased susceptibility of thermally injured mice to herpes simplex virus (HSV) and *Candida albicans* infections was produced by an imbalance of T cell responses induced by burn-associated type 2 T cells that were identified as $CD8^+$, $CD11^+$, $TCR\gamma\delta^+$ T cells that produced IL-4 and IL-10. The resistance of the burned animals to HSV infection was completely restored after administration of a mixture of monoclonal antibodies (mAbs) for IL-4 and IL-10 [12].

Further evidence that the trauma-induced predominance of the T_H2 lymphocyte phenotype is essentially associated with decreased resistance to infection has been most recently demonstrated by O'Sullivan et al. [13]. These authors reported on studies in 24 patients early after major burn and mechanical injury and on a series of mice with a 20% burn injury. Human phytohemagglutinin (PHA)-stimulated peripheral blood mononuclear cells (PBMCs) produced significantly less (−45%) IFNγ but significantly more (+90%) IL-4 than PBMCs in healthy controls.

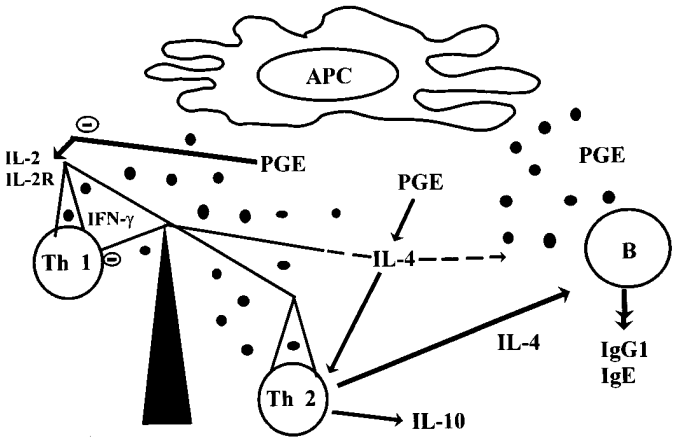

Fig. 3. Monocytic prostaglandins of the E series, predominantly PGE_2, regulate B and T cells. PGE_2 can inhibit the synthesis of T_H1 cytokines (IL-2, IFNγ) but not the synthesis of IL-4 by T_H2 cells. Thus PGE_2 secretion may tip the balance in favor of a T_H2 type response, leading also to a switch in B cell production from IgM to IgG1 and IgE. (Modified from [4], with permission of the publisher.)

In the burned mice a significant decrease in IL-2 and IFNγ was found in contrast to a significant increase in IL-4 and IL-10 on the transcriptional and protein levels compared to those in sham-burned animals. Furthermore, production of IL-12, the T_H1 "promoter monokine," was significantly suppressed in burned animals compared to controls. In another experiment burned and sham-burned animals were treated with IL-12 (25 ng/day) for 5 days after injury until a septic challenge [cecal ligation and puncture (CLP)] was carried out. The in vivo IL-12 treatment resulted in clearly decreased mortality due to CLP on day 10 (85% versus 15%), identical to that in the sham-burned mice, and an impressive increment of splenocyte IFNγ synthesis toward supranormal levels.

From the most recent studies of Zimmer et al. (personal communication) in human volunteers has come valuable information in respect to lipopolysaccharide (LPS)-induced effects on the T_H1/T_H2 cytokine response in humans. Immediately following intravenous administration of *Escherichia coli* (4 ng/kg body weight) there was a shift toward a cytokine type 2 response with up to 11-fold elevated IL-10 and significantly suppressed IL-2 plasma levels.

We believe from the wide spectrum of available data, as outlined above, that major trauma and associated inflammation and infection clearly induce polarization of the T-helper lymphocyte activity with a clear shift in the T_H2 direction. We suppose that the development of such a response dominated by T_H2-associated lymphokines may be mainly supported by activated Mϕ. Depending on the state of Mϕ activation induced by stimuli such as phagocytosis, immune complexes, complement split products, and endotoxin, there is massive PGE_2 release, as we and

others have described [14, 15]. Therefore the trauma-associated quality and quantity of various antigens that induce PGE_2 release from Mϕ may crucially influence the development of a T_H1- or T_H2-dominated response.

Rationale for Immune Modulatory Therapy after Injury

It is our understanding that the endogenous ability of the organism to survive overwhelming trauma is insufficient and requires major exogenous support. Posttraumatic immune abnormalities consist of two mechanistic entities: inappropriately hyperactive inflammatory processes and profound depression of cell-mediated immune function. Thus immune modulation must include restoration of depressed immune responses but should also encompass down-regulation, rather than complete abrogation, of hyperinflammation.

It must be the principal goal of modern immunotherapy to prevent a state of systemic inflammatory response in an immunocompromised host from converting to a state of bacterial sepsis. Several strategic approaches to prevent the development of late multiple organ dysfunction and failure (MODS/MOF) seem feasible. The clinical trials in septic patients with gram-negative bacterial infections that have employed therapeutic tools such as anti-LPS monoclonal antibodies, anti-TNF antibodies, soluble TNF receptors, or an IL-1 receptor antagonist have not shown an overall valid, clinically important, reproducible, statistically significant treatment benefit. Based on these studies it appears to us that the earliest possible blockade—alleviation of the systemic inflammatory response syndrome—may prove to be the most efficacious approach to avoiding an irreversible, autodestructive inflammatory process in organ tissue. Immune therapeutic interventions must be employed in a calculated preventive fashion as early as possible after trauma. They should protect lymphocytes and macrophages as well as granulocytes and the endothelial cell system from cell hyperactivation and cell exhaustion. Because of this enormous demand on the design and efficacy of the therapeutic approach it is becoming evident that only a combination of several drugs can be effective in controlling the posttraumatic dyshomeostasis of the various cell systems.

It cannot be overemphasized that for rational immune modulatory therapy of posttraumatic immunodeficiency a profound understanding of the cytokine and immunologic abnormalities present is required. We have learned that many of the crucial cytokines described so far have actions that overlap those of others, and cytokines with overlapping actions are released in the same clinical situation. The actions of one cytokine may synergize with those of another to produce an observed clinical effect. Thus it is impossible to ascribe any clinical syndrome or phenomenon within the context of traumatic stress to the action of one particular cytokine. Likewise, only rarely can one immunologic disorder be accounted for by an isolated abnormality of a single cytokine [16].

Bearing in mind that despite the enormous progress that has been made in understanding the pleiotropic synergistic and antagonistic activities of cytokines within the cytokine network, we must continue to assess the roles of many mediators in the induction or inhibition of immunosuppressive and inflammatory processes associated with injury. However, despite the incomplete concept of the "mediator orbit," we deem it justifiable to design and carry out immune therapeutic studies now. We should do that preferably in a preventive fashion, employing, step by step, a number of cytokines in combination with each other as well as with other agents. Thus by continuous modification via the mode of "trial and error" it should be possible to reach a basic platform of therapy.

We propose the following combined therapeutic strategy: (1) prevention of excessive macrophage stimulation via neutralization of circulating endo- and exotoxins with high doses of polyvalent immunoglobulins and soluble complement receptors; (2) global short-term ($\leq$72 hours) down-regulation of inflammatory Mϕ and PMN activity; and (3) restoration of cell-mediated immune performance in order to overcome posttraumatic functional paralysis.

Antiinflammatory Therapeutic Approaches

Colony-stimulating factors (CSFs) are hematopoietic growth factors that regulate granulocytopoiesis and monocytopoiesis. Recombinant human granulocyte colony-stimulating factor (rG-CSF) has been used in several studies. The use of G-CSF for sepsis prophylaxis in neutropenic patients (e.g., patients with congenital agranulocytosis or cancer patients during chemotherapy), is well established and has been reported to accelerate recovery of granulocyte counts and to be effective for infection prophylaxis. Moore and associates [17] found that patients with major torso trauma had inadequate granulocytopoiesis and CSFs were deficient. Cioffi and associates gave GM-CSF to a group of patients with burns and compared them with controls. White blood cell (WBC) function improved in those treated, and WBC counts increased significantly after a lag time of about 1 week. This study demonstrated the safety of giving this substance to patients with a burned surface area up to 75% [18].

Hartung and colleagues [19] demonstrated in healthy volunteers an additional sepsis prophylactic property of G-CSF. LPS-inducible TNFα and IL-1β release were attenuated by about 50% within 20 hours after treatment. In contrast, LPS-inducible sTNF-R p75 was not detectable in incubated blood from untreated donors, but increased dramatically 44 hours after G-CSF treatment. After LPS challenge the IL-1ra was increased 10-fold by G-CSF. The authors concluded from these findings that G-CSF treatment switches peripheral leukocytes to an antiinflammatory state, characterized by attenuation of IL-1- and TNF-releasing capacity and augmentation of the release of cytokine antagonists.

Another promising approach to attenuate an excessive systemic inflammatory response consists in the use of xanthine derivatives such as pentoxifylline (POF). It is known that POF selectively inhibits the formation of TNFα, likely by causing accumulation of intracellular cAMP [20]. Furthermore, POF is able to counteract neutrophil adherence to the endothelium and protect from increased pulmonary vascular permeability in the lung. Consequently, POF was found to improve survival in various models of hemorrhagic and endotoxic shock. Meanwhile, at our institution a clinical trial with POF has been carried out in patients with early states of systemic inflammatory response following cardiac surgery. First evaluations of the data derived from these investigations demonstrate clear alleviation of the posttraumatic acute-phase reactions in terms of a reduction of elastase or selectin levels compared to a untreated control group [21]. Oismüller et al. studied the effect of POF on PMN respiratory burst activity in septic patients in whom the drug (5 mg/kg IV) was administered over 180 minutes. They found that POF treatment clearly resulted

in a decrease of respiratory burst activity compared to the PMN function in untreated controls [22].

In an immune mechanistic study we found evidence that addition of the human recombinant IL-13 (hrIL-13) T cell lymphokine to cell cultures of Mϕ from patients with major injury resulted in effective down-regulation of the synthesis of proinflammatory mediators such as TNFα, IL-1β, IL-6, and IL-8, as well as nitric oxide [23]. From other preexisting studies we have learned that hrIL-13, in addition to its antiinflammatory functional properties, supports cell-mediated immune (CMI) responses in terms of the up-regulation of MHC class II antigen presenting capacity as well as the IFNγ synthesis from large granular lymphocytes. We believe that the biologic properties of hrIL-13 call for this cytokine to be tested as a biologic response modifier in states of posttraumatic inflammation.

Restoration of CMI Function

During several clinical investigations we have scrutinized the therapeutic administration of the cyclooxygenase inhibitor indomethacin and the thymomimetic pentapeptide TP-5 via either single drug use or combined therapy. We found that the combined administration of indomethacin and TP-5 in patients undergoing major cardiac surgery [24] restored practically every essential element within the forward-regulatory pathway of CMI responses—IL-1 and IL-2 synthesis, IL-2 receptor expression, lymphoproliferation, IFNγ synthesis—and that it could normalize the in vivo immunoreactivity. The treatment also down-regulated Mϕ driven acute-phase reactions as expressed through reduced release of the Mϕ metabolite neopterin as well as IL-6.

As adequate Mϕ activation and forward-regulatory function depend on sufficient delivery of IFNγ to these cells, it appears to be a reasonable approach to substitute the lymphokine during trauma-induced states of IFNγ deficiency. Two trials have been conducted to assess the efficacy of IFNγ to reduce infection and deaths in patients sustaining severe injury [25]. One preliminary trial indicated that the administration of IFNγ reverses trauma-induced diminution of Mϕ expression of MHC class II HLA-DR antigen; however, no difference between treatment arms was noted in terms of the infection rate or mortality. Patients in the trauma II trial experienced comparable infection rates with or without IFNγ therapy, although the patients treated with IFNγ experienced fewer deaths related to infection. These findings agree with those from a number of experimental studies that show that IFNγ administration in patients with surgical infections it is associated with improved outcome [26]—decreases translocation following transfusion and thermal injury [27] and that it reduces susceptibility to sepsis following hemorrhagic shock [28]. However, under certain conditions IFNγ mediates the lethality of endotoxin and TNFα via its overwhelming inductive capacity for TNFα release in a LPS-activated Mϕ [29, 30]. Thus a good deal of caution and prudence in respect to the appropriate timing of its administration is warranted. Most recently, also in our laboratory, is was demonstrated that IFNγ can induce the production of its own promoting cytokine IL-12 within a positive feedback mechanism [31, 32]. As the experimental studies of Mannick and Rodrick's group demonstrated, exogenous IL-12 can restore T_H1 cytokine production and resistance to infection under traumatic stress. We agree with these authors that the therapeutic administration of IL-12, a proximal mediator within the cytokine cascade, may be a powerful weapon for the counterregulation of trauma-induced immunodeficiency [13]. Down-regulation of PGE_2-driven T_H2 pathways together with the simultaneous up-regulation of T_H1 regulatory loops as a concerted approach to minimize the risk of injury-associated infection should represent a promising, progressive strategy to improve survival rates after injury.

Résumé

Un traumatisme majeur perturbe fortement l'activité immunologique, avec comme corollaire une sensibilité accrue à l'infection grave. Alors que certains mécanismes du système sont stimulés d'une façon non discriminante et parfois excessive, d'autres mécanismes, notamment à l'intéricur du complexe de l'immunité cellulaire (CIC), sont totalement paralysés. Les anomalies immunologiques constatées après la survenue d'un traumatisme sont composées d'une séquence d'activation cellulaire dont le mécanisme et la séquence sont encore peu élucidécs. Le stress traumatique est responsable d'une désintégration résultant de l'interaction du monocyte intact avec la cellule T (Mϕ/T-cell), associée à de profonds changements dans la capacité de régulation positive de la cellule Mϕ et une diminution substantielle de la fonction de la cellule T. La destruction tissulaire excessive génère de nombreux stimuli comme la phagocytose, la production de complexes immuns et de produit de dégradation du complément, d'endo et d'exotoxines, tous facteurs qui contribuent à une activation excessive des Mϕ. Ensuite, les Mϕ produisent et larguent rapidement dans la circulation la prostaglandine E_2 (PGE_2), un immunodépresseur endogène puissant. La PGE_2 est un inhibiteur de la mitogénèse de la cellule T, de la production de l'IL-2, de l'expression du récepteur IL-2 et retentit massivement sur la qualité de la synthèse des anticorps par les cellules-B. Plus important encore, la PGE_2 est un co-facteur dans l'induction de l'activité du lymphocyte «T-helper» (T_H) envers les cellules T_H2. Les cellules T_H2 sont impliquées dans la synthèse des cytokines immunodépressives tels l'IL-4 et l'IL-10. Les substrats immunosuppresseurs sont inhibiteurs pour les cellules T_H1, le support fonctionnel du CIC; et renforcent l'activité des T_H2, ce qui prédispose l'hôte à l'infection. Les défenses de l'organisme vis-à-vis du trauma d'origine endogène sont insuffisantes et ont besoin d'un soutien exogène important. On doit commencer les interventions immunomodulaires, choisies en fonction des anomalies constatées chez l'hôte traumatisé le plus tôt possible après le traumatisme dans le but de prévenir l'organisme des agressions provenant de la destruction tissulaire. Idéalement, ce traitement devrait protéger tous les compartiments cellulaires de l'hôte de l'hyperactivation ainsi que de l'épuisement des systèmes immunitaires. Nous croyons que scule la combinaison de plusieurs médicaments sera efficace dans le contrôle de l'homéostasie de ces systèmes.

Resumen

El trauma mayor resulta en interferencia masiva con la reactividad inmunitaria, cuya consecuencia clìnica es una alta susceptibilidad del individuo traumatizado a la infecciòn grave. En tanto que algunos componentes del sistema inmunitario son estimulados en el marco de una inflamaciòn corporal sistèmica indiscriminada y excesiva, otras funciones en el complejo de la inmunidad celular aparecen dramàticamente paralizadas. Las anormalidades inmunitarias luego de ocurrido el trauma se presentan en una

secuen cia de estados de activaciòn celular y dentro de un complejo orden de eventos que todavìa no es bien comprendido. El estrès del trauma causa una desintegraciòn de la interacciòn del monocito intacto (Mϕ/cèlula-T que se halla asociado con cambios profundo s en las capacidades regulatorias del Mϕ y una depresiòn sustancial de la funciòn celular-T. Una extensa destrucciòn tisular resulta en la generaciòn de numerosos estìmulos tales como fagocitosis, complejos inmunitarios, productos de lisis del complemento, endo- y exotoxinas, todo lo cual contribuye a una excesiva activaciòn del Mϕ. El Mϕ luego produce ràpidamente y libera prostagalandina E_2 (PGE_2), un muy poderoso agente inmunosupresor endògeno. La PGE_2 es un inhibidor de la mitogènesis de las cèlulas-T de la producciòn de IL-2, de la expresiòn de receptores de IL-2 y ejerce un impacto masivo en la calidad de la sìntesis de anticuerpos de cèlulas-B. Lo màs importante, la PGE_2 representa un importante co-factor para la inducciòn de actividad de los linfo citos-T ayudadores (T_H) en la direcciòn de T_H2. Las cèlulas T_H2 se asocian con la sìntesis de citocinas inmunosupresoras tales como IL-4 e IL-10. En tanto que los sustratos inmunosupresores son inhibidores de las cèlulas TH_1 -los transportadores funcional es de CMI- a su vez dan soporte a la actividad TH_2, lo cual predispone al huèsped al desarrollo de infecciòn. La provisiòn endògena del organismo para sobrevivir al trauma masivo resulta insuficiente y requiere soporte exògeno mayor. Las intervenciones in munomodulatorias, dependiendo de las inmunoanormalidades que se observan en el huèsped traumatizado, deben ser iniciadas tan pronto como sea posible luego de ocurrido el trauma en una forma preventiva a fin de protegerlo de la destrucciòn de tejidos orgàn icos. Idealmente, debe proteger tanto de la hiperactivaciòn como del agotamiento a todos los compartimientos de defensa celular del huèsped.

References

1. Faist, E., Storck, M., Hueltner, L., et al.: Functional analysis of monocyte (Mϕ) activity via synthesis patterns of interleukin 1, 6, 8 (IL-1, IL-6, IL-8) and neopterin in surgical intensive care patients. Surgery *112*:562, 1992
2. Faist, E., Baue, A.E., Dittmer, H., Heberer, G.: Multiple organ failure in polytrauma patients. J. Trauma *23*:775, 1983
3. Faist, E., Mewes, A., Baker, C.C., et al.: Prostaglandin E_2 (PGE_2) dependent suppression of interleukin-2 (IL-2) production in patients with major trauma. J. Trauma *27*:837, 1987
4. Phipps, R.P., Stein, S.H., Roper, R.L.: A new view point of prostaglandin E regulation of the immune response. Immunol. Today *12*:10, 1991
5. Faist, E., Markewitz, A., Fuchs, D., et al.: Immunomodulatory therapy with thymopentin (TP-5) and indomethacin: successful restoration of interleukin-2 (IL-2) synthesis in patients undergoing major surgery. Ann. Surg. *214*:264, 1991
6. Faist, E., Ertel, W., Cohnert, T., et al.: Immune protective effects of cyclooxygenase inhibition in patients with major surgical trauma. Surg. Forum *34*:114, 1988
7. Mosmann, T.R., Cherwinsk, H., Bond, M.W., Giedlin, M.A., Coffman, R.L.: Two types of murine helper T-cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J. Immunol. *136*:2384, 1986
8. Kelso, A.: T_H1 and T_H2 subsets: paradigms lost. Immunol. Today *16*:374, 1995
9. Mannick, J.A.: Trauma, sepsis and immune defects. In Host Defense Dysfunction in Trauma, Shock and Sepsis: Mechanisms and Therapeutic Approaches, E. Faist, J.L. Meakins, F.W. Schildberg, editors. New York, Springer-Verlag, 1993, pp. 15–21
10. Betz, M., Fox, B.S.: Prostaglandin E_2 inhibits production of T_H1 lymphokines but not of T_H2 lymphokines. J. Immunol. *146*:108, 1991
11. Ayala, A., Lehmann, D.L., Herdon, C.D., Chaudry, I.H.: Mechanisms of enhanced susceptibility to sepsis following hemorrhage: interleukin-10 suppression of T-cell response is mediated by eicosanoid-induced interleukin-4 disease. Arch. Surg. *129*:1172, 1994
12. Kobayashi, M., Pollard, R.B., Suzuki, F.: $CD4^+$ contrasuppressor T-cells improve the resistance of thermally injured mice infected with HSV. J. Leukoc. Biol. *58*:159, 1995
13. O'Sullivan, S.T., Lederer, J.A., Horgan, A.F., Chin, D.H.L., Mannnick, J.A., Rodrick, M.L.: Major injury leads predominance of the T_H2 lymphocyte phenotype and diminished IL-12 production associated with decreased resistance to infection Ann. Surg. *222*:482, 1995
14. Faist, E., Mewes, A., Strasser T., et al.: Alteration of monocyte function following major injury. Arch. Surg. *123*:287, 1988
15. Miller-Graziano, C.L., Fink, M., Wu, J.Y., Szabo, G., Kodys, K.: Mechanisms of altered monocyte prostaglandin E_2 production in severely injured patients. Arch. Surg. *123*:293, 1988
16. O'Riordain, M.G., Mannick, J.A., Rodrick, M.L.: Cytokine response to surgery, trauma and burns. In Clinical Applications of Cytokines: Role of Pathogenesis, Diagnosis and Therapy, J.J. Oppenheim, J.L. Rossio, A.J.W. Gearing, editors. New York, Oxford University Press, 1993, pp. 301–305
17. Moore, F.A., Peterson, V.M., Moore, E.E.: Inadequate granulopoiesis after major torso trauma: a hematopoietic regulatory paradox. Surgery *108*:667, 1990
18. Cioffi, W.G., Jr., Burleson, D.G., Jordan, B.S., et al.: Effects of granulocyte-macrophage colony-stimulating factor in burn patients. Arch. Surg. *126*:74, 1991
19. Hartung, T., Krieger, G., Volk, H.D., Wendel, A.: Reduced proinflammatory cytokines and increased antagonists in LPS-stimulated blood from G-CSF-treated volunteers. J. Intensive Care Med. *20*:142, 1994
20. Schade, F.U., Zabel, P.: Modulating effects of pentoxifylline on cytokine release syndromes. In Sepsis: Current Perspectives in Pathophysiology and Therapy, K. Reinhart, K. Eyrich, C. Sprung, editors. New York, Springer-Verlag, 1994, pp. 371–381
21. Hoffman, H., Reichert, K., Faist, E., Markewitz, A., Jochum, M.: Supplemental treatment with pentoxifylline in patients at risk for sepsis: a pilot study. Presented at the Surgical Infection Society, Fifteenth Annual Meeting, 1995, p. 14
22. Oismüller, C., Mayer, N., Micksche, M., Steltzer, H., Hammerle, A.: In-vivo modulation of human neutrophil function by pentoxifylline in patients with septic syndrome. Shock *4*:161, 1995
23. Kim, C., Faist, E., Minty, A., et al.: Interleukin-13 (IL-13) effectively downregulates a monocyte inflammatory potential during traumatic stress. Arch. Surg. (in press)
24. Faist, E., Markewitz, A., Fuchs, D., et al.: Immunomodulatory therapy with thymopentin (TP-5) and indomethacin: successful restoration of interleukin-2 (IL-2) synthesis in patients undergoing major surgery. Ann. Surg. *214*:264, 1991
25. Dries, D.J., Polk, H.C. Jr.: Interferon gamma on trauma related sepsis: results of two large multicenter studies. J. Intensive Care Med. *20*:123, 1994
26. Hershman, M.J., Sonnenfeld, G., Mays, B.W., et al.: Effects of interferon-gamma treatment on surgically simulated wound infection in mice. Microb. Pathog. *4*:165, 1988
27. Gennari, R., Alexander, W., Eaves-Pyles, T.: IFN-γ decreases translocation and improves survival following transfusion and thermal injury. J. Surg. Res. *56*:530, 1994
28. Ertel, W., Morrison, M.H., Ayala, A., Dean, R.E., Chaudry, I.H.: Interferon-γ attenuates hemorrhage-induced suppression of macrophage and splenocyte functions and decreases susceptibility to sepsis. Surgery *111*:177, 1992
29. Silva, A.T., Cohen, J.: Role of interferon-γ in experimental gram-negative sepsis. J. Infect. Dis. *166*:331, 1992
30. Jurkovich, G.J., Mileski, W.J., Maier, R.V., Winn, R.K., Rice, C.L.: Interferon-γ increases sensitivity to endotoxin. J. Surg. Res. *51*:197, 1991
31. Faist, E., Licht, K., Schinkel, C., et al.: Gamma-interferon (γ-IFN) driven monocytic cytokine release patterns are highly differentiated and depend on inflammation induced states of cellular preactivation. In Abstract Book, no. 32. American Association for the Surgery of Trauma, Fifty-Fifth Annual Meeting, 1995
32. Trinchieri, G., Scott, P.: The role of interleukin-12 in the immune response, disease and therapy. Immunol. Today *15*:460, 1994