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Monocyte-related immunopathologies in trauma patients

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Summary

Mechanical trauma is one of the most important causes of morbidity in the developed world. The response of the immune system to mechanical insult is of paramount importance for the patient's recovery. Shortly after trauma, the indiscriminate systemic inflammatory response syndrome (SIRS) is mediated by circulating monocytes (MØs) and other innate immunity components. Then acquired immunity, limited to the offending pathogen and the site of injury, gradually preponderates. SIRS is followed by the compensatory anti-inflammatory response syndrome (CARS), where the initial inflammatory response is quenched by anti-inflammatory mediators. This precisely regulated process of immune system activation in response to trauma can be easily deviated, resulting in multi-organ failure (MOF) and increased mortality. Excessive activation of inflammatory MØs in the SIRS phase, premature or exorbitant CARS, a predominance of macrophages (Macs) in the blood stream and peripheral tissues, as well as a depletion of dendritic cells are often seen in trauma patients and contribute to the development of MOF. Here we explore several mechanisms of pathological MØ activation in patients with severe mechanical traumatic injury without accompanying sepsis.

Key words: mechanical trauma • monocyte • dendritic cell • macrophage • inflammatory monocyte

Abbreviations: CARS – compensatory anti-inflammatory response syndrome, SIRS – systemic inflammatory response syndrome, MØ – monocyte, DC – dendritic cell, Mac – macrophage, MOF – multi-organ failure, TLR – Toll-like receptor, M-CSFR – M-CSF receptor, GM-CSFR – GM-CSF receptor; IFN-γ – interferon γ, LPS – lipopolysaccharide, HSP – heat shock protein, MHC II – major histocompatibility complex type II, TGF-β – transforming growth factor β, mTNF-α – membrane-bound tumor necrosis factor α, sTNF-α – secreted TNF-α, COX-1 – cyclooxygenase 1, ROS – reactive oxygen species, HMG-1 – high-mobility globulin 1.

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INTRODUCTION

Severe mechanical trauma is one of the leading causes of morbidity in the developed world⁴¹. Appropriate performance of the immune system is crucial for the prompt recovery of trauma victims. However, in 20–30% patients, increased leukocyte apoptosis, aberrant monocyte (MØ) activation and differentiation, T cell anergy, or other immune system pathologies are present^{2, 4, 7, 8, 9, 26, 27, 31, 32, 40, 45, 47, 59, 62, 64}. We believe that aberrations in the function and/or differentiation of monocyte-lineage cells are pivotal in the development of trauma-related immunopathologies. Since MØs bridge innate and adaptive immunity, their dysfunction profoundly affects the whole immune system, inevitably leading to unfavorable clinical outcome^{5, 13, 14, 23, 43, 44}. Our review is intentionally limited to data obtained exclusively from human studies, since there are several differences between human and animal models³⁶. We also focus our analysis on data obtained from trauma victims without sepsis, since this co-morbidity has several distinctive characteristics^{21, 22}.

IMMUNE SYSTEM ACTIVATION AFTER MECHANICAL TRAUMA

Even minor trauma, such as laparoscopic surgery, results in a profound reaction from the immune system^{50, 51}. Thus it is not surprising that major traumatic events (a car accident, fall, body injury due to assault) have a significant effect on the immune system^{7, 13, 19, 24}. Tissue injury and the invasion of various pathogens into the organism result in the activation of the coagulation cascade, platelets, neutrophils, and MØs, providing optimal response to the mechanical insult. This generalized and unspecific response is called the systemic inflammatory response syndrome (SIRS) and is mediated by the MØ-Toll-like receptor (TLR) system and other components of innate immunity (Fig. 1)^{9, 35, 43, 44, 48}. Later in SIRS, the unopposed pro-inflammatory innate response is gradually replaced by dendritic cell (DC)-controlled T and B cells^{34, 43, 48}. Excessive SIRS may lead to collateral tissue damage and multi-organ failure (MOF), but in the majority of patients in SIRS it is followed by the compensatory anti-inflammatory response syndrome (CARS; Fig. 1)^{32, 33, 55}. The magnitude of CARS-stage immunosuppression is directly related to the initial magnitude of the SIRS response. CARS results from the delayed production of anti-inflammatory interleukin (IL)-10, transforming growth factor (TGF)- β , and PGE₂, the emergence of T helper (Th)2 cells, stimulation of the leukocytes by apoptotic and necrotic cell bodies, and cytokine- and activation-induced MØ apoptosis^{13, 23, 31}. However, if

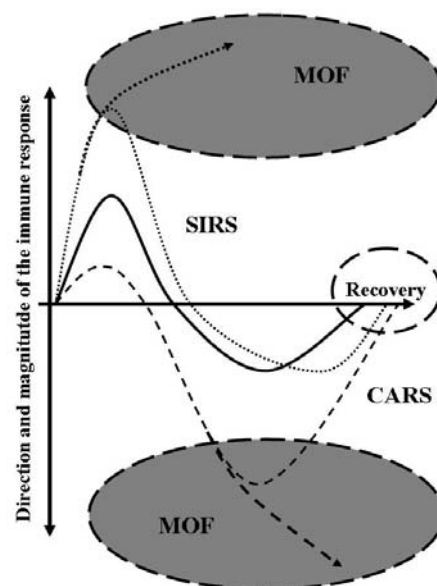


Figure 1. Several trajectories of the immune response may develop in trauma patients, leading to recovery or multi-organ failure (MOF). Solid line depicts the classical immune response to severe mechanical trauma. Dotted lines describe situations with exaggerated SIRS response, leading to recovery or death. Broken lines represent subjects with premature or overwhelming CARS response, leading to recovery or MOF.

CARS occurs prematurely, or if there is an additional insult (e.g. sepsis or respiratory failure), profound, CARS-related MØ deactivation might result in an unfavorable clinical outcome due to the suppressed functions of the immune system (Fig. 1).

MØ FUNCTIONS UNDER RESTING CONDITIONS AND AFTER TRAUMA

After emerging from the bone marrow, MØs circulate in the blood stream for 1–3 days²³. These MØs are naive, pluripotent cells which can become activated MØs or differentiate into several offspring cells, such as DCs, macrophages (Macs), osteoblasts, endothelial cells, smooth muscle cells, fibroblasts, or microglia cells (Fig. 2)^{5, 13, 23, 63, 64}. This extraordinary developmental plasticity is a hallmark of MØs and is surpassed only by stem cells.

Based on flow cytometry, several subpopulations of peripheral blood MØs can be distinguished^{5, 64}. Some of these cells are precursors of various DCs (IL-4R⁺GM-CSFR⁺, CD11c⁺ MØ) and macrophage (M-CSFR⁺ MØ) populations, whereas the majority of MØs are sentinel, immature cells^{9, 23, 61}. These MØs express TLR and several cytokine receptors (M-CSFR, GM-CSFR, IL-6R, IL-4R, IL-3R, IL-10R), and are characterized by moderate phagocytosis and antigen-presenting cell capabilities (Fig. 3A and B,

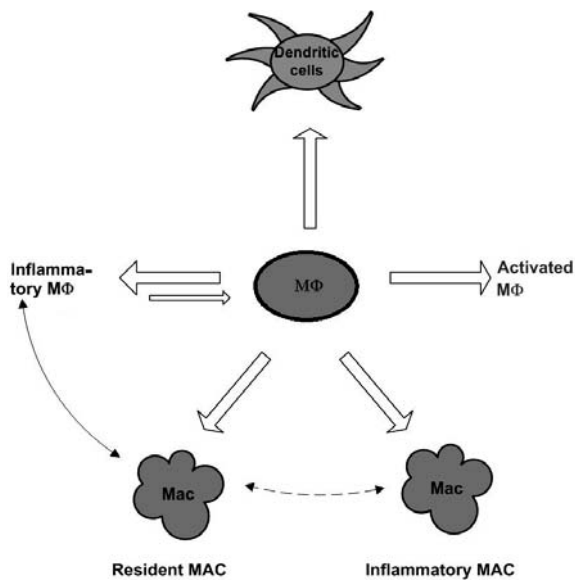


Figure 2. Activation and differentiation of MØs into DCs or Macs.

Table 1)^{5, 12, 13, 14, 23, 31, 64}. These functions can be rapidly activated upon stimulation by lipopolysaccharide (LPS), Gram-positive bacterial compounds, heat shock proteins (HSP), fibrin split products, dead cells, and complement^{12, 13, 31}. Under moderate stimulation by the aforementioned products, naïve MØs become activated cells characterized by significantly increased production of interleukin (IL)-1 β ($\uparrow\uparrow\uparrow$), moderate secretion of secreted tumor necrosis factor (sTNF)- α ($\uparrow$), and up-regulated surface expression of MHC class II molecules (Table 1)^{1, 11, 13, 27, 49}. MØ activation is further supported by Th1-secreted interferon (IFN)- γ , whereas Th2-specific cytokines rather quench or alter classical MØ activation^{13, 23, 31, 62}. In general, MØ activation causes an increase in the core

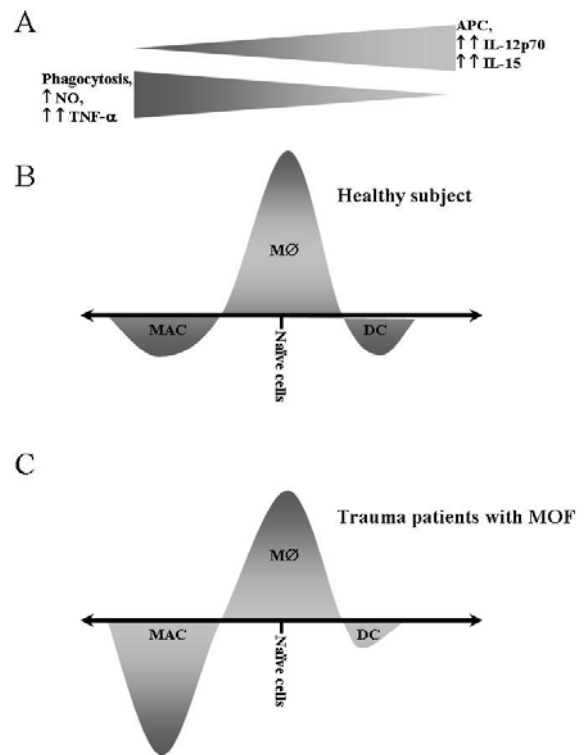


Figure 3. Specific features of MØs, Macs, and DCs create a functional continuum (A) which is well-balanced in healthy subjects (B). However, in trauma patients a significant shift is observed related to the pathological reaction to injury (C).

body temperature, expression of the new MHC class II molecules on non-classical immune system cells (endothelia, fibroblasts), hemodynamic changes (heart rate, vascular tone, glomerular filtration rate), and general activation of the immune system⁴⁹.

Table 1. Receptors and cytokines characteristic of different MØ subpopulations

	Resting MØ	Activated MØ	Inflammatory MØ	DC	Resident Mac	Inflammatory Mac
Surface receptors	TLR2, TLR4 GM-CSFR, M-CSFR, IL-6R, IL-4R, IL-13R CD11c ⁺ , CD11b ⁺ , CD14 ⁺ HLA-DR ⁺	MHC II $\uparrow\uparrow\uparrow$ TLR4 $\uparrow$, TLR2 $\uparrow$ GM-CSFR $\uparrow$, M-CSFR $\uparrow$, IL-6R $\uparrow$, IL-4R $\uparrow$, IL-13R $\uparrow$, CD11b $\uparrow$	CD14 ⁺ CD16 ⁺ HLA-DR ⁺ CD64 ⁺ $\uparrow\uparrow$ CD25 ⁺ CD11b ⁺	CD1a ⁺ CD83 ⁺ CD209 ⁺ BDCA3 ⁺	Microsialin ⁺ , ED2 ⁺ , SIGLEC-1 ⁺ , MARCO ⁺ , CD206 ⁺	CD163 ⁺ MRP8/14 ⁺ CD16 ⁺
Cytokine production	none	sTNF- α $\uparrow\uparrow$ IL-1 β $\uparrow\uparrow$	mTNF- α $\uparrow\uparrow\uparrow$ PGE ₂	IL-12 $\uparrow\uparrow\uparrow$ IL-15 $\uparrow\uparrow$	Mac-specific factors	mTNF- α $\uparrow\uparrow\uparrow$ IL-18 $\uparrow\uparrow$ IL-4 $\uparrow\uparrow$
Compounds responsible for differentiation to mature offspring	naïve cells	LPS, SEB, complement product, HSP, fibrin split product, IL-13. IFN- γ	M-CSF, GM-CSF, combined stimulation by LPS, SEB, complement, HSP, fibrin, and other danger signals	IL-4+GM-CSF IL-13+GM-CSF IL-3	Local tissue environment – tissue specific factors, M-CSF, IL-6, GM-CSF	IL-13, IFN- γ , IL-4 alone eotaxin, M-CSF, IL-6, GM-CSF
Another secreted products		NO ROS	NO $\uparrow\uparrow\uparrow$ ROS $\uparrow\uparrow\uparrow$			NO $\uparrow\uparrow\uparrow$ ROS $\uparrow\uparrow\uparrow$

Ultimately, the offending pathogens are expunged and damaged tissues are repaired, with important MØ contribution^{19, 23, 28}. Then the activated MØs undergo spontaneous or IL-4-mediated apoptosis, or their action is inhibited by Th2-specific cytokines such as IL-10, TGF- β , and PGE₂^{13, 31}.

Another aspect of MØ function is their ability to differentiate into Macs or DCs^{5, 8, 22, 46}. Under resting conditions, the emergence of mature offspring from specific MØ precursors has a low turnover, but this can be greatly enhanced by the maturation of naïve peripheral blood MØs in trauma²³. This pool of naïve MØs provides the immune system with great flexibility in response to stimuli. Macs are characterized by an extraordinary phagocytic activity and the ability to produce pro-inflammatory cytokines (sTNF- α ↑↑↑, IL-1 β ↑) and free radicals (ROS)^{13, 23, 49}. Under physiological conditions, MØ→Mac differentiation employs a complicated process involving chemokine-driven taxis, endothelium-MØ interactions, and the intertissue lattice environment^{5, 13, 23, 31}. These emerging cells are described as resident macrophages and exhibit several tissue-specific features²³. Resident Macs cannot proliferate and their turnover is very slow, so they cannot be rapidly expanded. The slow physiological process of MØ→resident Mac differentiation can be greatly enhanced by the rapid emergence of inflammatory macrophages, since activated MØs are more sensitive to Mac-differentiation stimuli due to the increased expressions of M-CSFR, IL-6R, IL-4R, and GM-CSFR (Table 1)^{9, 13, 27}. Additionally, the serum cytokine environment (↑IL-6, ↑TNF- α) supports intravascular Mac differentiation from circulating MØs^{31, 49, 52}. After the inflammatory process ceases, inflammatory Macs undergo apoptosis or adapt to the particular tissue environment, with subsequent transformation into resident, tissue-specific Macs^{23, 31}.

DCs are crucial elements of acquired immunity since they can capture, process, and present different antigens to effector cells^{5, 22}. By stimulating antigen-specific clones of T and B cells, they transform indiscriminate, innate immunity into a highly specific and effective immune response^{43, 44}. This transformation of immune system activation from an innate type to an acquired one is crucial, since the acquired immune response is limited to the insult and/or offending pathogen. As innate immunity lacks such specificity, it often harms healthy tissues and has adverse systematic effects (e.g. MOF). The extraordinary DC potency to induce and regulate acquired immunity results from their very high surface expression of MHC II molecules, the presence of a variety of modulating molecules (CD80, CD86, ICOS-L, PD-1L1,

PD-1L2, CTLA-4), and their secretion of several stimulatory cytokines, such as IL-12 and IL-15^{12, 15, 43, 44, 56}. A great deal of controversy exists as to the origin of different DC subpopulations^{5, 14, 23, 56}. It was shown that not only CD34⁺ precursors, but also naïve MØs, specific precursory monocyte populations (CD11c⁺), and even granulocyte progenitor cells differentiate into DCs under certain conditions^{43, 44, 65}. In healthy subjects, the differentiation of specific precursors (CD11c⁺, CD34⁺) is the main source of DCs. However, in trauma the population of circulating MØs is probably a much more important source of DC precursors, since they can differentiate into DCs *in vitro* and are easy to recruit.

ABERRANT MØ ACTIVATION IN TRAUMA

Under normal activation, MØs produce large quantities of pro-inflammatory cytokines (sTNF- α ↑, IL-1 β ↑↑↑) and ROS and migrate and differentiate into the nidus of infection^{13, 34, 35}. Usually, such a response is continuously adjusted to prevent unfavorable collateral tissue damage and systemic symptoms (MOF, septic shock syndrome). However, in some trauma patients an overwhelming, uncontrolled pro-inflammatory monokine production, with subsequent MOF, ensues (Figs. 1 and 3C)^{34, 35, 37, 41}. Several mechanisms might be responsible for such a pathological, aberrant activation of MØs. Simultaneous and excessive stimulation by LPS, HMG1, tissue debris, complement system, and/or junk immunoglobulins (Ig) is usually a triggering event^{18, 34, 35, 48, 54}. This multimodal stimulation activates concomitantly several MØ kinases, limiting the MØ ability to self-regulate. Excessive MØ response is usually counterbalanced by IL-10, TGF- β , IL-4, PGE₂, and M-CSF and up-regulation of the mannose receptors. However, in some trauma patients, the cells' sensitivity to the inhibitory signals is significantly reduced even if the aforementioned anti-inflammatory compounds are abundant^{12, 13, 23, 26, 31, 62}. It has also been suggested that T cell anergy contributes to unopposed MØ activation, since anergic T cells do not produce inhibitory IL-4, IL-10, or IL-13⁸. Thus, aberrant MØ activation results from an imbalance between stimulatory and inhibitory signals, leading to anomalous signal transduction and faulty inflammatory cytokine processing^{11, 27}. For example, TNF- α is predominantly manufactured by activated MØs in its sTNF- α ¹¹. However, in the aberrant, inflammatory MØs or Macs of trauma patients, a highly cytotoxic form of membrane-bound TNF- α (mTNF- α) is predominantly manufactured^{11, 27}. Physiologically, TNF- α production is limited by the short half-life of the mRNA for TNF- α and by the activity of cleaving enzymes. An aberration in surface-receptor expres-

sion and co-stimulation by bacterial and tissue debris products result in increased stability of the mRNA for TNF- α ¹¹. This increased mRNA stability results in excessive production of TNF- α , whereas a defect in cleaving enzyme activity causes the formation of the membrane-bound form of this cytokine⁴¹. mTNF- α has a longer half-life than secreted TNF- α . Ultimately, excessive production of long-lived mTNF- α results in excessive activation of apoptosis, necrosis, predominant differentiation of MØs into MACs, and MOF. MØs retaining mTNF- α represent a population of circulating inflammatory MØs/Macs and are characterized by an unrestrained production of inflammatory mediators. Their phenotype has been described as CD14⁺CD16⁺HLA-DR⁺^{11, 13, 26, 27, 52, 53}. Additionally, their resistance to apoptotic signals further enhances the unfavorable effects of their emergence.

The above-described pathology represents only one example of MØ pathology in trauma. Some researchers have linked diminished MØ HLA-DR expression, the presence of LPS tolerance, and aberrant MØ-T cell interaction to the unfavorable clinical outcome of trauma^{1, 17, 19, 31, 39, 64}. We believe that all these mechanisms are clinically important. The one we described in greater detail was chosen to show the complexity of the MØ-related pathology which is typical of trauma-related immunoaberrancies. This example of immune system intricacy requires a novel approach to correct immunoaberrancies in trauma victims. Instead of the single-drug approach, which has failed in numerous clinical trials, a holistic approach must be applied, aimed at multiple levels of immune system function^{21, 24}.

MACROPHAGE PREDOMINANCE AND THEIR PATHOLOGICAL ACTIVATION IN TRAUMA VICTIMS

The Mac population consists of a variety of tissue-specific phagocytes which are critical for removing bacteria and tissue debris in wound healing^{13, 23}. M-CSF, IL-6, IL-10, LPS, PGE₂, TNF- α , and IFN- γ are major inducers of MØ→Mac emergence, and some of them are also Mac activators^{26, 31, 38, 46}. Under resting conditions, this process takes place in peripheral tissue. However, in some severely traumatized patients, MØ→Mac differentiation occurs in the blood. This skewed MØ→Mac differentiation is driven by increased serum levels of Mac-supporting mediators (IL-6, GM-CSF, IL-10, LPS, TNF- α) and increased expressions of receptors for these signals (IL-6R, M-CSFR) on the surface of trauma patients' MØs^{9, 18, 35, 41, 54}. Additionally, circulating Mac-like MØs secrete much higher amounts of several

macrophage-differentiating monokines (M-CSF, TNF- α , IL-10) in response to bacterial pathogens than do naive or activated MØs, further tipping the balance of MØ differentiation towards Mac offspring, with all of the adverse results (Fig. 3C). This process of intravascular Mac differentiation overlaps with excessive stimulation via various inflammatory reagents, leading to the emergence of Macs with predominantly aberrant inflammatory characteristics.

Inflammatory Macs produce large quantities of nitric oxide, mTNF- α , PGE₂, and free radicals which can damage vascular and pulmonary endothelium as well as activate the coagulation cascade^{23, 31, 47, 57}. Since secretion of all these immunologically active compounds occurs in the blood, instead of being contained in the peripheral tissue, systemic effects are often seen^{6, 48, 54}. A dramatic decrease in blood vessel tone and hypotension, damage to the pulmonary epithelium with subsequent pulmonary distress, impairment of heart function, as well as an excessive rise in core body temperature with accompanying profound metabolic disturbances are all mediated by inadequate intravascular release of pro-inflammatory cytokines by circulating inflammatory MØs and Macs^{19, 23, 31, 57, 58}. This is the underlying cause of MOF^{24, 32, 39, 58}. In tissues, an exaggerated activation of inflammatory Macs results in mTNF- α -mediated damage to healthy tissue in the mechanism described in the previous section. The excessive production of inflammatory cytokines is further enhanced by the prolonged turnover of inflammatory Macs, since they do not undergo apoptosis easily and stay for a prolonged time in tissue or the blood stream, even after the offending pathogen has been removed²².

DEPLETION OF DCs IN TRAUMA

DCs constitute an alternate differentiation pathway for MØs. Their action is crucial for prompt recovery, but several researchers have reported a decreased ability of MØs to differentiate into DCs (MØ→DC) in trauma, suggesting that the diminished DC number is responsible for the exaggerated immune system response^{9, 12, 23, 46}.

Trauma-related DC depletion is probably not related to an insufficient number of precursory cells. We believe that CD34⁺ stem cells play a limited role in supplying DC precursors, whose conversion into DCs requires a considerable amount of time. It is the population of circulatory MØs that is the important source of DCs, since they can be recruited rapidly, and MØ-derived DCs (MØ-DC) exhibit several features typical of fully functional DCs. A brisk hemopoiesis is driven by the increased serum IL-6 level in

trauma, supplying enough precursory myeloid cells^{10, 20, 30, 52, 60}. Some studies showed a profound dysfunction of the bone marrow in burn patients, septic shock, and in advanced stages of MOF, but such bone marrow insufficiency does not occur shortly after trauma, as shown by the unaltered frequency of CD11c⁺ precursors in the circulation of trauma victims^{3, 9, 30, 60}. However, naive or activated precursory MØs are immediately subjected to the serum environment driving them towards macrophages, thus limiting the cell pool available for prospective DCs. HSPs, TNF- α , IL-6, and IL-10 are the most known factors inhibiting DC emergence, and they are abundant in the serum of trauma patients^{16, 25, 42, 46, 56}. Additionally, trauma patients' MØs have decreased surface receptor expressions for IL-4, IL-13, and GM-CSF, which are responsible for driving the MØ→DC process, further diminishing their capability to differentiate into DCs, even in an optimal cytokine environment⁵. Concomitantly, increased expression of the Mac-differentiation receptor on circulating trauma patients' MØs has been reported ($\uparrow$ M-CSFR)⁹. All these observations indicate that trauma patients' MØs developed into Macs, limiting the chance for MØ-derived DC emergence. We hypothesize that an altered response to pathogen is of pivotal importance in the emergence of this phenomenon. Since some trauma patients' MØs manufacture aberrant cytokines, such as mTNF- α and PGE₂, we speculate that a skewed production of Mac-differentiating cytokines could be a crucial factor. In fact, we showed that trauma patients' MØs produce much higher levels of M-CSF in response to TLR-specific stimulation than do those of healthy controls⁹. M-CSF stimulation results in increased M-CSFR expression, diminished IL-4 effects, and Mac differentiation. M-CSF also has some anti-inflammatory features and can induce self-secretion in a positive feedback loop. All these effects are observed in trauma patients with MØ→DC defects. Therefore, disproportionate M-CSF production in response to pathogen stimulation drives MØ intravascular differentiation into aberrant Macs and prevents DC emergence (Figs. 2 and 3C)^{13, 18}. The M-CSF-mediated MØ→Mac differentiation commitment in trauma can be broken only by adding a neutralizing M-CSF antibody⁹. A similar M-CSF-driven MØ→DC differentiation defect has been described in some tumor environments, showing the universality of this mechanism²⁹. Theoretically, the DC-stimulating environment provided by the action of Th2 cells could offset the dominant influence of secreted and serum cytokines promoting MØ→Mac differentiation^{5, 7, 23, 25}. Th2-dependent cytokines (IL-4, IL-13, and GM-CSF) are induced in the late stages of SIRS and have been shown to stimulate MØ-DC

emergence *in vitro*^{4, 24, 49}. However, some trauma patients' T cells are anergic, rendering them unable to produce any cytokines^{1, 9, 45}. This T cell anergy is rather a global phenomenon and does not result from a predominance of Th2 or Th3 populations. All of the above mechanisms result in a predominant intravascular Mac-emergence and DC depletion in trauma victims^{8, 40, 45}. If sepsis occurs, enhanced apoptosis disseminates the population of DCs already existing^{21, 22}.

DCs have the unique ability to regulate the immune system. Their action stimulates the emergence of Th2 cells and selects the pathogen-specific clones of effector cells (B cells and T cells). The action of these pathogen-specific clones is selective and focused. Thus it prevents an excessive production of unspecific junk Ig and limits collateral tissue damage by limiting the activation of complement and the coagulation cascade as well as lowering the serum concentrations of HSP, fibrin split product, and other inflammatory mediators^{31, 49, 52, 58}. These mediators are crucial for multimodal aberrant MØ activation and the skewed differentiation of MØ→Mac due to M-CSF induction in trauma patients. DC-stimulated Th2 cells emerged late in trauma. They effectively redirect pro-inflammatory MØ activity towards wound healing and tissue repair in the CARS phase. Summarizing, DC cells are crucial for both the emergence of pathogen-specific clones and the resolution of inflammation. Therefore it is not surprising that their depletion in trauma patients result in increased mortality and MOF^{9, 16, 22, 23, 46}.

CONCLUSION

Major mechanical trauma presents a severe challenge to the immune system. Although its role in the mediation of MOF is often overlooked, more and more researchers are focusing their attention on MØ-related immunopathologies. MØs and their offspring are the cornerstones of the immune system. They can regulate both innate and acquired immunity and act as major responders to insult. In trauma, their aberrant activation is characterized by an excessive production of pro-inflammatory cytokines, reduced ability to respond to immuno-inhibitory signals, and resistance to apoptosis. Furthermore, the ability of the host's immune system to limit aberrant immune system activation can be further impaired by a lack of DCs and the presence of inflammatory MØ/Macs in the peripheral blood, driving an overwhelming and ineffective immune response (Figs. 1 and 3C). All these phenomena are cumulative and are responsible for several MOF-specific pathologies and increased mortality in trauma patients.

REFERENCES

- Adamik B., Zimecki M., Wlaszczyk A. and Kubler A. (1997): Immunological status of septic and trauma patients. II. Proliferative response and production of interleukin 6 and tumor necrosis factor alpha by peripheral blood mononuclear cells from septic survivor, nonsurvivor and trauma patients: a correlation with the survival rate. *Arch. Immunol. Ther. Exp.*, 45, 277–284.
- Aller M. A., Arias J. L., Nava M. P. and Arias J. (2004): Posttraumatic inflammation is a complex response based on the pathological expression of the nervous, immune, and endocrine functional systems. *Exp. Biol. Med.*, 229, 170–181.
- Amos R. J., Deane M., Ferguson C., Jeffries G., Hinds C. J. and Amess J. A. (1990): Observations on the haemopoietic response to critical illness. *J. Clin. Pathol.*, 43, 850–856.
- Angele M. K. and Faist E. (2002): Clinical review: immunodepression in the surgical patient and increased susceptibility to infection. *Crit. Care*, 6, 298–305.
- Ardavin C., Martinez del Hoyo G., Martin P., Anjuere F., Arias C.F., Marin A.R., Ruiz S., Parrillas V. and Hernandez H. (2001): Origin and differentiation of dendritic cells. *Trends Immunol.*, 22, 691–700.
- Cook R., Cook D., Tilley J., Lee K., Marshall J. and Canadian Critical Care Trials Group. (2001): Multiple organ dysfunction: baseline and serial component scores. *Crit. Care Med.*, 29, 2046–2050.
- Coronel A., Boyer A., Franssen J. D., Romet-Lemonne J. L., Fridman W. H. and Teillaud J. L. (2001): Cytokine production and T-cell activation by macrophage-dendritic cells generated for therapeutic use. *Br. J. Haematol.*, 114, 671–680.
- De A. K., Kodys K. M., Pellegrini J., Yeh B., Furse R.K., Bankey P. and Miller-Graziano C. L. (2000): Induction of global anergy rather than inhibitory Th2 lymphokines mediates posttrauma T cell immunodepression. *Clin. Immunol.*, 96, 52–66.
- De A. K., Laudanski K. and Miller-Graziano C. L. (2003): Failure of monocytes of trauma patients to convert to immature dendritic cells is related to preferential macrophage-colony-stimulating factor-driven macrophage differentiation. *J. Immunol.*, 170, 6355–6362.
- DeLong W. G. Jr. and Born C. T. (2004): Cytokines in patients with polytrauma. *Clin. Orthop. Relat. Res.*, 422, 57–65.
- Furse R. K., Kodys K., Zhu D. and Miller-Graziano C. L. (1997): Increased monocyte TNF-alpha message stability contributes to trauma patients' increased TNF production. *J. Leukoc. Biol.*, 62, 524–534.
- Gallucci S. and Matzinger P. (2001): Danger signals: SOS to the immune system. *Curr. Opin. Immunol.*, 13, 114–119.
- Gordon S. (2003): Alternative activation of macrophages. *Nat. Rev. Immunol.*, 3, 23–35.
- Gordon S. (2004): Pathogen recognition or homeostasis? APC receptor functions in innate immunity. *C. R. Biol.*, 327, 603–607.
- Granucci F., Andrews D. M., Degli-Esposti M. A. and Ricciardi-Castagnoli P. (2002): IL-2 mediates adjuvant effect of dendritic cells. *Trends. Immunol.*, 23, 169–171.
- Granucci F., Ferrero E., Foti M., Aggujaro D., Vettoretto K. and Ricciardi-Castagnoli P. (1999): Early events in dendritic cell maturation induced by LPS. *Microbes. Infect.*, 1, 1079–1084.
- Griswold J. A. (1993): White blood cell response to burn injury. *Semin. Nephrol.*, 13, 409–415.
- Hanada T. and Yoshimura A. (2002): Regulation of cytokine signaling and inflammation. *Cytokine Growth Factor Rev.*, 13, 413–421.
- Haupt W., Riese J., Mehler C., Weber K., Zowe M. and Hohenberger W. (1998): Monocyte function before and after surgical trauma. *Dig. Surg.*, 15, 102–104.
- Heike T. and Nakahata T. (2002): Ex vivo expansion of hematopoietic stem cells by cytokines. *Biochim. Biophys. Acta*, 1592, 313–321.
- Hotchkiss R. S. and Karl I. E. (2003): The pathophysiology and treatment of sepsis. *N. Engl. J. Med.*, 348, 138–150.
- Hotchkiss R. S., Tinsley K. W., Swanson P. E., Grayson M. H., Osborne D. F., Wagner T. H., Cobb J. P., Coopersmith C. and Karl I. E. (2002): Depletion of dendritic cells, but not macrophages, in patients with sepsis. *J. Immunol.*, 168, 2493–2500.
- Hume D. A., Ross I. L., Himes S. R., Sasmono R. T., Wells C. A. and Ravasi T. (2002): The mononuclear phagocyte system revisited. *J. Leukoc. Biol.*, 72, 621–627.
- Kox W. J., Volk T., Kox S. N. and Volk H. D. (2000): Immunomodulatory therapies in sepsis. *Intensive Care Med.*, 26 (suppl. 1), S124–128.
- Kuipers H., Hijdra D., De Vries V. C., Hammad H., Prins J. B., Coyle A. J., Hoogsteden H. C. and Lambrecht B. N. (2003): Lipopolysaccharide-induced suppression of airway Th2 responses does not require IL-12 production by dendritic cells. *J. Immunol.*, 171, 3645–3654.
- Kunkel S. L., Spengler M., May M. A., Spengler R., Larrick J. and Remick D. (1988): Prostaglandin E2 regulates macrophage-derived tumor necrosis factor gene expression. *J. Biol. Chem.*, 263, 5380–5384.
- Laudanski K., De A., Brouxhon S., Kyrkanides S. and Miller-Graziano C. (2004): Abnormal PGE(2) regulation of monocyte TNF-alpha levels in trauma patients parallels development of a more macrophage-like phenotype. *Shock*, 22, 204–212.
- Liese A. M., Siddiqi M. Q., Siegel J. H., Deitch E. A. and Spolarics Z. (2002): Attenuated monocyte IL-10 production in glucose-6-phosphate dehydrogenase-deficient trauma patients. *Shock*, 18, 18–23.
- Lin E. Y. and Pollard J. W. (2004): Macrophages: modulators of breast cancer progression. *Novartis Found. Symp.*, 256, 158–168; discussion 168–172, 259–269.
- Livingston D. H., Anjaria D., Wu J., Hauser C. J., Chang V., Deitch E. A. and Rameshwar P. (2003): Bone marrow failure following severe injury in humans. *Ann. Surg.*, 238, 748–753.
- Ma J., Chen T., Mandelin J., Ceponis A., Miller N. E., Hukkanen M., Ma G. F. and Kontinen Y. T. (2003): Regulation of macrophage activation. *Cell Mol. Life Sci.*, 60, 2334–2346.
- Marik P. E. (2002): Definition of sepsis: not quite time to dump SIRS? *Crit. Care Med.*, 30, 706–708.
- Marzi I. (1994): [The significance of the liver for the course of SIRS (Systemic Inflammatory Response Syndrome) following shock, trauma and during sepsis]. *Anesthesiol. Intensivmed. Notfallmed. Schmerzther.*, 29, 41–46.
- McCarter M. D., Mack V. E., Daly J. M., Naama H. A. and Calvano S. E. (1998): Trauma-induced alterations in macrophage function. *Surgery*, 123, 96–101.
- Menger M. D. and Vollmar B. (2004): Surgical trauma: hyperinflammation versus immunosuppression. *Langenbeck's Arch. Surg.*, 389, 475–484.
- Mestas J. and Hughes C. C. (2004): Of mice and not men: differences between mouse and human immunology. *J. Immunol.*, 172, 2731–2738.
- Miller-Graziano C. L., Kodys K. and Jhaver K. (1994): Normal M phi cell-associated TNF alpha is resistant to PGE2 as well as TGF beta downregulation. *Ann. N. Y. Acad. Sci.*, 730, 307–309.
- Molloy R. G., Mannick J. A. and Rodrick M. L. (1993): Cytokines, sepsis and immunomodulation. *Br. J. Surg.*, 80, 289–297.
- Napolitano L. M., Faist E., Wichmann M. W. and Coimbra R. (1999): Immune dysfunction in trauma. *Surg. Clin. North Am.*, 79, 1385–1416.
- Pellegrini J. D., De A. K., Kodys K., Puyana J. C., Furse R. K. and Miller-Graziano C. (2000): Relationships between T lymphocyte apoptosis and anergy following trauma. *J. Surg. Res.*, 88, 200–206.
- Pellegrini J. D., Puyana J. C., Lapchak P. H., Kodys K. and Miller-Graziano C. L. (1996): A membrane TNF-alpha/TNFR ratio correlates to MODS score and mortality. *Shock*, 6, 389–396.
- Puig-Kroger A., Sanz-Rodriguez F., Longo N., Sanchez-Mateos P., Botella L., Teixeira J., Bernabeu C. and Corbi A. L. (2000):

- Maturation-dependent expression and function of the CD49d integrin on monocyte-derived human dendritic cells. *J. Immunol.* 165, 4338–4345.
43. Pulendran B. (2004): Immune activation: death, danger and dendritic cells. *Curr. Biol.*, 14, R30–32.
44. Pulendran B. (2004): Modulating TH1/TH2 responses with microbes, dendritic cells, and pathogen recognition receptors. *Immunol. Res.*, 29, 187–196.
45. Puyana J. C., Pellegrini J. D., De A. K., Kodys K., Silva W. E. and Miller C. L. (1998): Both T-helper-1- and T-helper-2-type lymphokines are depressed in posttrauma anergy. *J. Trauma*, 44, 1037–1045; discussion 1045–1046.
46. Rotta G., Edwards E.W., Sangaletti S., Bennett C., Ronzoni S., Colombo M. P., Steinman R. M., Randolph G. J. and Rescigno M. (2003): Lipopolysaccharide or whole bacteria block the conversion of inflammatory monocytes into dendritic cells *in vivo*. *J. Exp. Med.*, 198, 1253–1263.
47. Schwacha M. G. (2003): Macrophages and post-burn immune dysfunction. *Burns*, 29, 1–14.
48. Sharma S. and Kumar A. (2003): Septic shock, multiple organ failure, and acute respiratory distress syndrome. *Curr. Opin. Pulm. Med.*, 9, 199–209.
49. Sherwood E. R. and Toliver-Kinsky T. (2004): Mechanisms of the inflammatory response. *Best Pract. Res. Clin. Anaesthesiol.*, 18, 385–405.
50. Sietses C., Beelen R.H., Meijer S. and Cuesta M.A. (1999): Immunological consequences of laparoscopic surgery, speculations on the cause and clinical implications. *Langenbecks Arch. Surg.*, 384, 250–258.
51. Smit M. J., Beelen R. H., Eijssbouts Q. A., Meijer S. and Cuesta M. A. (1996): Immunological response in laparoscopic surgery. *Acta Gastroenterol. Belg.*, 59, 245–247.
52. Szabo G., Kodys K. and Miller-Graziano C. L. (1991): Elevated monocyte interleukin-6 (IL-6) production in immunosuppressed trauma patients. I. Role of Fc gamma RI cross-linking stimulation. *J. Clin. Immunol.*, 11, 326–335.
53. Szabo G., Kodys K. and Miller-Graziano C. L. (1991): Elevated monocyte interleukin-6 (IL-6) production in immunosuppressed trauma patients. II. Downregulation by IL-4. *J. Clin. Immunol.*, 11, 336–344.
54. Takala A., Nupponen I., Kylanpaa-Back M. L. and Repo H. (2002): Markers of inflammation in sepsis. *Ann. Med.*, 34, 614–623.
55. Taneja R. (2003): SIRS – a syndrome, disease or a chef d'oeuvre? *Br. J. Anaesth.*, 91, 756; author reply 756.
56. Veeraswamy R. K., Cella M., Colonna M. and Unanue E. R. (2003): Dendritic cells process and present antigens across a range of maturation states. *J. Immunol.*, 170, 5367–5372.
57. Volk T., Gerst J., Faust-Belbe G., Stroehmann A. and Kox W. J. (1999): Monocyte stimulation by reactive oxygen species: role of superoxide and intracellular Ca²⁺. *Inflamm. Res.*, 48, 544–549.
58. Volk T. and Kox W. J. (2000): Endothelium function in sepsis. *Inflamm. Res.*, 49, 185–198.
59. Wolach B., Sazbon L., Gavrieli R., Broda A. and Schlesinger M. (2001): Early immunological defects in comatose patients after acute brain injury. *J. Neurosurg.*, 94, 706–711.
60. Wu J. C., Livingston D. H., Hauser C. J., Deitch E. A. and Rameshwar P. (2001): Trauma inhibits erythroid burst-forming unit and granulocyte-monocyte colony-forming unit growth through the production of TGF-beta1 by bone marrow stroma. *Ann. Surg.*, 234, 224–232.
61. Wysocka, M., Zaki M. H., French L. E., Chehimi J., Shapiro M., Everetts S. E., McGinnis K. S., Montaner L. and Rook A. H. (2002): Sezary syndrome patients demonstrate a defect in dendritic cell populations: effects of CD40 ligand and treatment with GM-CSF on dendritic cell numbers and the production of cytokines. *Blood*, 100, 3287–3294.
62. Yadavalli G. K., Auletta J. J., Gould M. P., Salata R. A., Lee J. H. and Heinzel F. P. (2001): Deactivation of the innate cellular immune response following endotoxic and surgical injury. *Exp. Mol. Pathol.*, 71, 209–221.
63. Zhao Y., Glesne D. and Huberman E. (2003): A human peripheral blood monocyte-derived subset acts as pluripotent stem cells. *Proc. Natl. Acad. Sci. USA*, 100, 2426–2431.
64. Ziegler-Heitbrock H. W. (2000): Definition of human blood monocytes. *J. Leukoc. Biol.*, 67, 603–606.
65. Zou G. M. and Tam Y. K. (2002): Cytokines in the generation and maturation of dendritic cells: recent advances. *Eur. Cytokine Netw.*, 13, 186–199.