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Michael D. Menger
Brigitte Vollmar

Surgical trauma: hyperinflammation versus immunosuppression?

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M. D. Menger (✉)
Institute for Clinical
and Experimental Surgery,
University of Saarland,
66421 Homburg-Saar, Germany
e-mail: exmdme@uniklinik-saarland.de
Tel.: +49-6841-162-6550
Fax: +49-6841-162-6553

B. Vollmar
Department of Experimental Surgery,
University of Rostock,
18055 Rostock, Germany

Abstract *Background:* Experimental and clinical studies have brought evidence that surgical trauma markedly affects the immune system, including both the specific and the non-specific immune response. *Materials and methods:* This report reviews the present knowledge on the mechanisms of surgical trauma-induced immune dysfunction and outlines experimental and clinical approaches to find effective treatment strategies. *Results:* Major surgical trauma induces an early hyperinflammatory response, which is characterized by (1) pro-inflammatory tumour necrosis factor alpha (TNF), interleukin (IL)-1, and IL-6 cytokine release and (2) neutrophil activation and microvascular adherence, as well as (3) uncontrolled polymorphonuclear (PMN) and macrophage oxidative burst. The massive and continuous IL-6 release induces an acute phase response, but, more importantly, also accounts for the up-regulation of major anti-inflammatory mediators, such as prostaglandin (PG) E2, IL-10 and transforming growth factor (TGF)-ß. This results in surgical, trauma-induced, immunosuppression, as indicated by (1) monocyte deactivation, reflected by the lack of monocytic TNF- production upon lipopolysaccharide (LPS) stimulation, and (2) a shift of the Th1/Th2 ratio towards a Th2-dominated cytokine pattern. The imbalance between pro-inflammatory and anti-inflammatory cytokines and immuno-competent cells determines the phenotype of disease and should help the physician to compose the therapeutic strategy. In fact, recent clinical studies have shown that both the initial uncontrolled hyperinflammation and the continued cell-mediated immunosuppression represent primary targets to counteract post-surgery immune dysfunction. The balance between inflammatory and anti-inflammatory forces may be restored by interferon gamma (IFN-γ) to counteract monocyte deactivation; the anti-inflammatory PGE2 may be inhibited by indomethacin to attenuate immunosuppression; or the initial hyperinflammation may be targeted by administration of anti-inflammatory substances, such as granulocyte colony-stimulating factor (G-CSF), hydoxyethyl starch, or pentoxifylline. *Conclusions:* When drawing up the therapeutic regimen the physician should not consider hyperinflammation *versus* immunosuppression, but hyperinflammation *and* immunosuppression, aiming at restoring an appropriate mediator- and immune cell-associated balance.

Keywords Interleukin-10 · Th1/Th2 ratio · Interleukin-6 · Tumour necrosis factor-α · Interferon-γ

Introduction

Experimental and clinical studies have brought evidence that surgical trauma markedly affects the immune system, including both the specific and the non-specific immune response. While minor surgery is suggested to stimulate individual components of the immune system, it is generally agreed that major surgery, although associated with a local acute phase response, causes immunosuppression [1, 2]. During the early postoperative course this may define a state of impaired defence and increased susceptibility to infection and septic complications, in particular in patients with polytrauma, burn injury and cancer [3].

Protective immunity is critically dependent on an adequate Th1/Th2 conception of T-helper cell activation, an intact macrophage–T cell interaction, and an appropriate cytokine balance. The surgical trauma-induced deterioration of immune function is caused by disintegration of these complex regulatory systems [1]. During the past decade, experimental and clinical research has focused on the understanding of the pathophysiology of this immunoinflammatory dysfunction, because the elucidation of the mechanisms is thought to be a prerequisite for the introduction of preventive and therapeutic strategies into clinical practice.

Surgical trauma-induced inflammatory response

Pro-inflammatory cytokine response. Primarily, surgical trauma induces an acute phase response, which is capable of controlling tissue damage, killing infective organisms, and inducing repair processes in order to restore normal host function [4]. The acute phase response is initiated locally at the site of the surgical trauma by macrophages and monocytes, which release pro-inflammatory cytokines, in particular tumour necrosis factor alpha (TNF-α) and interleukin-1 beta (IL-1β) [5]. Some 10 years ago, distinct clinical studies suggested that hyperinflammation after major surgical trauma, based on excessive release of TNF-α and IL-1β, is the cause, not only of increased mortality, but also of enhanced risk of postsurgery development of an adult respiratory distress syndrome and multiple organ failure [6]. Those studies supported the concept that these syndromes are induced by an overwhelming autodestructive inflammatory response. However, while it is well confirmed that multiple trauma, blood loss, and sepsis are associated with a massive pro-inflammatory cytokine response, and that elevated plasma levels of those cytokines significantly correlate with increased infectious complications and higher mortality rates [6–8], elective major surgery may induce, during the postoperative course, only minor or even non-relevant changes in systemic TNF-α and IL-1β levels [9–12]. This might be due to the fact that pro-inflammatory cytokines exert their physiological activity close to their site of release [13], or that the peak of this pro-inflammatory cytokine response has been missed for analysis, because these cytokines have relatively short half lives of only up to 20 min [14]. The latter view is supported by a report by Baigrie and co-workers [15], who indicated an early and short-lived IL-1β response to major surgery that was detected only by intensive sampling in the peri-operative period.

Within the cytokine networking during the surgical trauma-induced acute phase response, TNF-α and IL-1β stimulate the production and release of other cytokines, including interleukin-6, which markedly peaks at 4–48 h after surgery [15, 16]. The release of IL-6 has been shown to correlate with the duration of surgery [17], and the length of mechanical ventilation in the ICU [10], however, seems also to depend on the extent of tissue trauma [18]. The conclusion that implicates the severity of tissue trauma in the IL-6 response to surgery is greatly supported by a variety of studies that demonstrate (1) that despite similar procedure times there is a greater degree of IL-6 elevation after abdominal aortic and colorectal surgery than after hip replacement [18] and (2) that there are lower IL-6 levels after laparoscopic procedures than after open operating procedures, including cholecystectomy and small bowel and colonic resections [9, 19–22].

Neutrophil response. Interleukin-6 is a primary effector in the production of acute phase proteins, such as C-reactive peptide, alpha-2 macroglobulin, other anti-proteinases and fibrinogen, which are involved in non-specific and specific immunity as inflammatory mediators, scavengers and protease inhibitors [5]. Accordingly, the increased levels of IL-6 in surgical trauma are associated with markedly elevated levels of C-reactive protein (CRP) and neutrophil elastase [21, 22]. This increase is related to the extent of the surgical trauma, because laparoscopic performance of identical operating procedures is capable of reducing the acute phase response and, thus, CRP and neutrophil elastase release [22]. In addition, IL-6 may further affect polymorphonuclear (PMN) leukocyte-mediated inflammation. IL-6 plays a major role in the proliferation of PMN progenitors in the bone marrow, and mechanical trauma has been shown to induce an early increase in circulating immature PMNs [23]. Apart from this, IL-6 may stimulate surgery-induced inflammation by modulating the functional repertoire of mature PMNs [24]. After open cholecystectomy, which is associated with higher IL-6 levels, PMN superoxide anion release and chemotaxis are increased, in comparison with the less traumatic laparoscopic approach [25]. Because anti-IL-6-treatment is effective in the successful counteraction of the PMN oxidative response [26], this cytokine has to be considered as a primary PMN stimulant in the circulation.

Microcirculatory response. Surgical trauma to tissue induces profound arteriolar constriction, which, however, is

not associated with an alteration of nutritive capillary perfusion [27]. This indicates that local tissue hypoxia is not a relevant factor in inducing the inflammatory response after major surgery. While the systemic inflammatory response to surgical trauma is characterized by an increased blood neutrophil count [28], the local microcirculatory inflammatory response is reflected by a pronounced leukocyte accumulation and adherence to the endothelial lining of postcapillary and collecting venules. The microcirculatory leukocyte response is associated with an increase in microvascular permeability, indicating the disruption of endothelial integrity [27]. This surgical trauma-induced inflammation within the microvasculature may additionally be enhanced by manipulation of the tissue. Experimental studies have indicated that, after laparotomy, the exteriorization of the mesentery results in a marked increase of venular leukocyte accumulation due to enhanced rolling and adhesion interactions [29]. The mechanisms involved in the surgical trauma-induced leukocyte endothelial interactions include endogenous TNF-α release, because in vivo microcirculation analysis has shown that both the leukocytic response and the endothelial injury can be attenuated by the application of a monoclonal antibody directed against this pro-inflammatory cytokine [27]. In inflammatory processes, the adhesion interactions of leukocytes with endothelial cells encounter a complex regulation of adhesion molecule expression and function, involving selectins for leukocyte rolling and the leukocytic β2-integrin CD11b/CD18 and the endothelial intercellular adhesion molecule (ICAM)-1 for firm adhesion [30]. These molecules seem also to be involved in the surgical trauma-induced inflammatory response, because (1) major surgery elevates serum levels of soluble P-selectin, E-selectin, ICAM-1, and vascular cell adhesion molecule (VCAM)-1 [31–33] and (2) increases leukocytic CD11a and CD11b, and endothelial ICAM-1 and VCAM-1 expression [28, 34–36]. This view has been confirmed by experiments, which demonstrated that the application of a monoclonal antibody directed against CD18 significantly reduces surgical trauma-induced leukocyte adhesion [29].

Surgical trauma-induced immunosuppression

Cytokine misbalance. Apart from its pro-inflammatory action, IL-6 also functions as an immunoregulatory cytokine [24]. In fact, IL-6 can act as an anti-inflammatory cytokine required for controlling local or systemic acute inflammatory responses [37]. IL-6, by inducing an acute phase response, enhances the synthesis of glucocorticoids, which have marked anti-inflammatory properties, and downregulates the pro-inflammatory response by inhibiting the expression of TNF-α and IL-1β [38, 39]. Further, IL-6 stimulates the macrophage expression of anti-inflammatory mediators, such as interleukin-1-receptor antagonist and soluble TNF receptors (TNFsr-I and TNFsr-II) [40]. These bind to the pro-inflammatory cytokines TNF-α and IL-1β and, thus, truncate the inflammatory response [40]. In addition, the IL-6-triggered acute phase response induces macrophages to release prostaglandin E_2 (PGE_2) [4], which is probably the most powerful endogenous immune suppressant. PGE_2 inhibits T-cell mitogenesis, IL-2 production, and IL-2 receptor expression [41]. In addition, by intracellular elevation of cyclic 3′5′-adenosine monophosphate (cAMP), PGE_2 further abrogates the inflammatory response by a negative control of macrophage TNF-α and IL-1β synthesis [41]. Finally, PGE_2 induces the release of the potent anti-inflammatory cytokine IL-10, involving interleukin-4 action [42]. Thus, IL-6 is capable of downregulating pro-inflammatory cytokines and, additionally, of exerting profound anti-inflammatory actions, resulting in a dramatic cytokine misbalance, which is clinically reflected by a compensatory anti-inflammatory response syndrome [10].

The outlined pathophysiology of IL-6-mediated immunosuppression, which is known from basic research studies with trauma, haemorrhagic shock and sepsis, is in line with the results of cytokine analysis after major surgery. Surgical trauma-induced immunosuppression is, indeed, characterized by low levels of pro-inflammatory TNF-α, IL-1β, IL-12, and interferon gamma (IFN-γ) but markedly elevated levels of anti-inflammatory IL-6, IL-10, and IL-1ra [10, 12, 24]. These results are further confirmed by studies that demonstrate that a reduction of surgical trauma by the use of a minimally invasive laparoscopic approach significantly reduces the increased serum levels of IL-6 and IL-10, and restores the decreased IFN-γ, TNF-α, and IL-2 production by T cells [22, 43].

Interestingly, IL-10-induced immunosuppression cannot be caused only by the IL-6-triggered systemic inflammatory response, but may also be caused by local brain injury in the absence of systemic inflammation, as induced in neurosurgical procedures. Local release of cytokines and other stressors can induce systemic immunodepression by downregulation of monocyte function, which is mediated by a catecholamine-induced release of IL-10 [44, 45].

Cell-mediated immune dysfunction. Appropriate cell-mediated immunity is not only based on an adequate macrophage and T cell function, but also depends on an in-tact macrophage–T cell interaction. Under stressful conditions, such as trauma and sepsis, macrophages and monocytes are triggered to produce and release PGE_2, which initiates a sequela of events, resulting in a hypo-inflammatory state [1]. Immuno-incompetence under those conditions is mainly caused by the deactivation of monocytes, which is characterized by (1) a markedly reduced human leukocyte antigen (HLA-DR) receptor expression, (2) a loss of antigen-presenting capacity, and (3) a pronounced reduction in their ability to produce TNF-α upon stimulation with

LPS in vitro [46]. Because this monocytic deactivation is associated with a profound immunodeficiency, Volk et al. [47] called this phenomenon "immunoparalysis." In fact, major surgical trauma also causes a depression of monocytic HLA-DR expression [3, 48], which is thought to correlate with sepsis severity and outcome [49, 50]. Although under septic conditions these monocytes show downregulation of LPS-induced TNF-α secretion, representing LPS desensitization and, thus, tolerance [46], a subpopulation of Fc receptor-positive monocytes can be found, which resembles the so-called angry macrophage that is characterized by high pro-inflammatory cytokine synthesis and suppressed antigen presentation [51]. This subset of cells is thought to contribute to the disintegration of the intact macrophage–T cell interaction, which may render the host anergic to opportunistic infections.

In vitro and in vivo studies have shown that PGE_2 is capable of deactivating monocytes, resulting in a lack of TNF-α and IL-6 release upon stimulation with LPS. This monocytic deactivation involves IL-10, because a neutralizing antibody against IL-10 has been shown to restore significantly the LPS-induced pro-inflammatory cytokine production [52]. This PGE_2-induced release of IL-10 also seems to play a key role in mediating the monocytic deactivation-associated immunosuppression in surgical trauma, because (1) surgery-induced reduction of monocyte HLA-DR expression significantly correlates with IL-10 gene expression [53], and (2) impaired LPS-induced up-regulation of monocyte HLA-DR expression after surgical trauma is reversed, at least in part, by the application of an IL-10 neutralizing antibody [53].

Apart from IL-10, the anti-inflammatory transforming growth factor (TGF)-beta may additionally contribute to the surgical trauma-induced monocyte deactivation. Haemorrhage, and also major surgical trauma, such as thoracoabdominal aortic aneurysm repair, induces a significant increase in circulating TGF-β [54, 55], which is associated with a marked depression of macrophage antigen presentation [54]. The idea that TGF-β, indeed, contributes to the deactivation of macrophages is further supported by experiments that demonstrated restoration of macrophage antigen presentation by using a TGF-β1,2,3 neutralizing antibody [54]. As IL-10 and TGF-β may also be involved in the mechanisms of endotoxin desensitization [56], striking similarities may be encountered between surgical trauma-induced immunosuppression and endotoxin tolerance induction.

The innate cellular immune system, which provides for the rapid production of IFN-γ by natural killer (NK) cells in response to microbial threats, is thought to be deactivated by major surgical trauma [57]. In fact, major surgical interventions are associated with a significant decrease in total systemic lymphocyte counts, including both CD4(+) and CD8(+) cells [58]. This lymphocyte depression has been shown to correlate with the duration of the surgical procedure, and the volume of blood loss, however, was not associated with the extension of the trauma, the age of the patient, or the type of intensive care intervention [58]. Deactivation of the cell system was further confirmed by the fact that after in vitro stimulation of those lymphocytes, the release of interleukins, IFN-γ and TNF-α remained low [58]. The cause of the fall in lymphocyte count due to surgical trauma may involve a dysregulated expression of apoptotic death and survival factors. Delogu and co-workers [59] could demonstrate that 24 h after surgery CD4(+) and CD8(+) cells exhibited a significantly higher frequency of apoptosis, as well as Fas, Fas ligand and caspase-1 expression, than they did preoperatively. This increase was paralleled by a marked downregulation of anti-apoptotic factors such as Bcl-2. The impact of this immune dysfunction was underlined by the result that the rate of apoptotic CD8(+) cells significantly correlated with the manifestation of infectious complications during the postoperative course [59]. This surgery-induced increase of apoptotic CD4(+) and CD8(+) cell death is associated with the elevated levels of IL-10 [60]; however, the link between overproduction of IL-10 and lymphocyte apoptosis after surgical operations still remains to determined.

A considerable number of studies have shown that modulation of T-helper lymphocytes (Th cells) is also involved in the development of immunosuppression after surgical trauma. Th cells can be subdivided into two functionally distinct subsets, e.g. Th1 and Th2 cells, according to individual functional parameters, including cytokine secretion. Th1 cells may support an inflammatory response by producing IL-2, IL-12, and INF-γ, while Th2 cells act as anti-inflammatory agents by secreting IL-4, IL-5, IL-6, IL-10, and IL-13. Hensler and coworkers [3] demonstrated that during the early postoperative course after elective major surgery the cytokine secretion of T cell-enriched fractions of peripheral blood mononuclear cells (PBMCs) stimulated by cross-linking of CD3 and CD28, was reduced for IL-2, IFN-γ, and TNF-α, which are associated with the Th1 phenotype of T-helper lymphocytes. In contrast, the anti-inflammatory cytokine IL-10 was selectively elevated during the late postoperative course, indicating a shift of the Th1/Th2 balance towards a Th2 response [3]. That this deregulation of T lymphocyte function is induced by surgical trauma is confirmed by the results of another study, which demonstrates that minimization of the trauma by laparoscopic surgery results in restoration of an adequate Th1/Th2 and pro-inflammatory/anti-inflammatory cytokine balance [43].

It is of interest that, under conditions of major surgery-associated immunosuppression, additional blood transfusion may exert a deleterious inflammatory response by a Th1 lymphocytic release of pro-inflammatory cytokines, such as IL-1, IL-2, TNF-α, IFN-γ, and granulocyte–macrophage colony-stimulating factor (GM-CSF), which attack host cells in a syndrome referred to as transfusion-

associated graft-versus-host disease [61]. On the other hand, blood transfusion may induce a shift towards a Th2-dominated response, associated with a fall in lymphocyte count, downregulation of antigen-presenting cells, and release of cortisol and sTNF-R55. This modulatory effect may result in aggravation of the surgery-induced state of immunosuppression [61, 62].

Consequences of surgical trauma-induced immunosuppression

While it is well known that immunosuppression in patients with multiple trauma, haemorrhagic shock and sepsis is associated with high morbidity and mortality [1, 63–65], the frequency of immunosuppression-associated complications after elective major surgery are less pronounced. Nonetheless, dysregulation of the cytokine balance may determine the development of postoperative complications. In fact, increased IL-10 serum levels have been shown to correlate significantly with the postoperative outcome after adult cardiopulmonary bypass operations [66] and in sepsis and multiple organ failure in children [67] and adults [68, 69]. In addition, Mokart and co-workers [10] showed that, after major surgery in cancer patients, the postoperative increase of IL-6 concentrations is associated with septic morbidity, and the raised IL-1ra concentrations may predict postoperative septic shock. In parallel, in severely injured male trauma patients the depressed interleukin-12 producing activity due to a shift towards a Th2-type lymphocyte pattern significantly correlates with the development of adult respiratory distress syndrome, infections and sepsis [70]. Accordingly, the surgical trauma-induced suppression of monocytic HLA-DR expression correlates with sepsis severity and outcome [49, 50, 71].

In addition to the immune suppression state, the early overwhelming inflammatory response after surgical trauma may also determine clinical outcome. The initial pro-inflammatory cytokine response is associated with an increased rate of adult respiratory distress syndrome (ARDS), multiple organ failure (MOF) and mortality [6]. Further, Klava et al. [34] have demonstrated that in patients undergoing major elective surgery for malignant disease, those patients who develop sepsis have greater degrees of granulocytic CD11b expression and adhesion. In line with this, the intravascular priming, which adversely affects PMN neutrophils during exudation, has been suggested to contribute to the sepsis-related mortality of anergic patients [72]. Thus, distinct components of both uncontrolled inflammation and immunosuppression after major surgery may contribute to the development of complications and mortality.

In patients who are undergoing surgery for malignant disease, the consequence of immunosuppression may not only be the development of infectious complications, but may also include progression of tumour growth and metastasis formation [73]. It may be speculated that a compromised immune status facilitates engraftment of circulating tumour cells. Experimental studies could, indeed, demonstrate that tumour cells grow more aggressively after major surgery than after minor surgery [74]. In addition, when the surgical trauma of laparotomy is reduced to a laparoscopic approach, experimental tumour growth has been shown to be significantly attenuated [75, 76]. This reduction in tumour growth seems to be due to a less pronounced immune dysfunction after the reduced surgical trauma, because (1) the accelerated tumour growth after laparotomy significantly correlates with a suppressed NK and lymphokine activated killer (LAK) cell cytotoxicity [75] and (2) the difference in tumour growth between laparotomy and laparoscopy is blunted if experiments are performed in T cell-deficient athymic mice [77]. In line with this, Wildbrett and co-workers [78] showed an increased rate of pulmonary metastases after sham laparotomy compared with CO_2 pneumoperitoneum, and successful inhibition of metastases formation by peri-operative immunomodulation. Whether, in patients, the reduction of surgical trauma or adjuvant peri-operative immunomodulation reduces local recurrence and frequency of distal metastasis, remains to be determined in prospective clinical trials.

Potentials of immunomodulation to counteract surgical trauma-induced immune dysfunction

The probably most successful way to reduce surgical trauma-induced immunosuppression is to reduce the extent of trauma. This is achieved by careful operation; however, it may imply the use of a minimally invasive approach, including laparoscopic surgery, endovascular surgery or off-pump cardiac surgery [31, 73, 79]. Reduction of operating trauma by the use of a laparoscopic approach has been shown (1) to reduce the early postoperative pro-inflammatory TNF-α, IL-1β, and IL-6 cytokine response [11, 80, 81] and CRP increase [82], (2) to attenuate the fall in lymphocyte count [48], (3) to abrogate the decrease of monocytic HLA-DR expression [48], and (4) to prevent the suppression of Th1 and, thus, the shift towards a Th2-type pattern of cytokines [43, 83, 84]. This may guarantee an adequate IFN-γ response by T cells upon stimulation [43, 83, 84], an intact plasma opsonic capacity and PMN phagocytosis [85], and a preserved monocyte-mediated tumour cell killing [86]. Similarly, endovascular aortic aneurysm repair has been shown to lead to a minor distortion of the Th1/Th2 immunobalance compared to open surgery [79], and off-pump coronary artery bypass grafting could reduce early TNF-α release and P-selectin and ICAM-1 expression compared to the conventional approach using extracor-

poreal circulation, blood cardioplegia, and hypothermic arrest [31].

An immune modulatory therapy of surgical trauma-induced immunosuppression should protect lymphocytes, macrophages, granulocytes, and endothelial cells from both hyperactivation and exhaustion. Because hyperinflammation and immunosuppression can be found simultaneously, the immune modulation should aim at restoring the distinct depressed immune responses, but should also encompass downregulation rather than abrogation of hyperinflammation [1]. This view is supported by the fact that clinical studies designed to inhibit IL-1 or TNF-α have not only failed to improve outcome, but have induced an even higher mortality if sTNF-R75 was applied [87–89].

Because monocyte activation requires delivery of IFN-γ, the substitution of this lymphokine may be a reasonable approach to counteract surgical trauma-induced monocyte deactivation. IFN-γ, ex vivo, has been shown to restore the monocytic TNF-α response to LPS after LPS desensitization [90, 91] and to normalize ex vivo monocytic TNF-α, IL-1β, IL-6, IL-8, and IL-12 response to LPS in patients after major surgery or severe injury [92, 93]. The first clinical application of IFN-γ was carried out on septic patients. The treatment resulted in restoration of the deficient monocytic HLA-DR expression and ex vivo LPS-induced TNF-α secretion [46]. Most interestingly, the recovery of monocyte function was associated with clearance of sepsis, and the authors suggested that IFN-γ treatment in carefully selected septic patients should be a therapeutic strategy worth persuing. And indeed, recently, an additional clinical study reported that in immunosuppression after major elective abdominal surgery a single dose of rhIFN-γ rescues down-modulation of antigen-specific CD4(+) T cell reactivity and concomitantly upregulates TCR-ligands on antigen-presenting cells [94]. A further study, which also analyses the effects of rhIFN-γ on immunosuppression in anergic patients who are undergoing major surgery, could demonstrate modulation of the in vitro response, with an increase in TNF-α, IL-2, IL-2r, IL-6, and PGE_2, and a decrease in IL-4, while IL-10 release and lymphocyte proliferation were not affected [95, 96]. Although the patient population was too small in these studies, and an overall lack of infectious complications did not allow a benefit of rhIFN-γ on final outcome to be detected, those first results should be considered to be of high interest and should encourage larger clinical trials to confirm the efficacy of IFN-γ in preventing immunosuppression-induced infectious complications and death after major surgery.

To counteract immunosuppression after major surgery, others have analysed the effect of blockade of the anti-inflammatory PGE_2. In an early clinical study, Faist and co-workers [97] and Markewitz and colleagues [98] could demonstrate that immunomodulatory therapy with the thymomimetic substance thymopentin and the cyclooxygenase inhibitor indomethacin effectively downregulated the macrophage-driven acute phase response, as indicated by a reduced IL-6 release, a restored IL-1, IL-2, and IFN-γ synthesis, IL-2 receptor expression, CD4(+)/CD8(+) ratio and lymphocyte proliferation, and a normalized delayed-type hypersensitivity response. Accordingly, Gogos et al. [99] showed, some years later, in patients who underwent major surgical operations, an increase in the T-helper/T-suppressor cell ratio and an improvement in delayed-type hypersensitivity response upon indomethacin treatment.

In a very recent study, the anti-inflammatory recombinant granulocyte colony-stimulating factor (G-CSF) was analysed for its efficacy to counteract major surgery-induced immune dysfunction [100]. G-CSF increased leukocyte count and serum levels of anti-inflammatory mediators such as IL-1 receptor antagonist and TNF-receptors, while the postoperative acute phase response was attenuated. Most interestingly, G-CSF was additionally capable of blunting surgical trauma-induced monocyte deactivation, as indicated by restoration of TNF-α release and HLA-DR expression, and of counteracting lymphocyte anergy, as shown by normalization of mitogenic proliferation and Th1 lymphokine release. Most importantly, the G-CSF-mediated immunomodulation was associated with a reduction in the incidence and severity of infectious complications [100].

Several additional attempts at treatment to attenuate surgery-induced immunosuppression in patients have been undertaken, including an immune-enhancing diet, the histamine-2 receptor antagonist (H2RA) ranitidine, the anti-inflammatory pentoxifylline, and the colloid hydroxyethyl starch (HES). Supplementation of enteral nutrition with glutamine, arginine, and omega-3-fatty acids modulated immunosuppressive and inflammatory responses in gastrointestinal cancer patients who were undergoing major surgery in that the diet induced higher levels of nitric oxide, total lymphocytes, T lymphocytes, T-helper cells, and NK cells. This was associated with increased phagocytosis and respiratory burst, but lowered CRP and IL-6 levels [101]. Similarly, ranitidine could be shown to modulate postoperative immune response after elective abdominal hysterectomy by lowering IL-6-induced CRP levels [102] and by reducing postoperative infectious complications in patients following acute colorectal surgery [103]. In patients with early states of a systemic inflammatory response after cardiac surgery, pentoxifylline was capable of reducing elastase and soluble selectin levels, and of decreasing the incidence of multiple organ failure [1, 104]. Finally, volume replacement by HES may attenuate the immunosuppressive state. Animal experiments have demonstrated, in trauma-haemorrhagic shock, that HES volume replacement is capable of restoring macrophage integrity and of preventing increased circulating IL-6 levels [105]. In addition, a very recent clinical study has now confirmed that in elderly patients who are undergoing major abdominal

surgery, HES can attenuate the surgery-induced increase of CRP, IL-6, and IL-8 levels and can prevent the elevation of soluble E-selectin and ICAM-1 [32].

Conclusion

A review of the literature indicates that the development of novel therapeutic strategies to counteract major surgery-induced immune dysfunction should not consider either hyperinflammation or immunosuppression, but should focus on a hyperinflammation-and-immunosuppression disease state. The treatment regimen should, thus, not mainly aim at abrogating one or the other of the mediators within the complex network and cascades, but should primarily focus on the restoration of an adequate balance between inflammatory and anti-inflammatory immune cell function. Such therapy will probably not follow an overall standardized protocol, but will have to be designed in detail for each individual patient according to the distinct failures of the non-specific and the specific immune system. Nonetheless, the relevant parameters to be monitored and values to indicate deviation from normal have to be determined in future studies. While the last decade was required for knowledge to be gained on the pro-inflammatory and anti-inflammatory pathophysiology of major surgical trauma, the research of interest for the forthcoming decade may be how to learn to compose appropriate therapeutic protocols.

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