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INTERLEUKIN 12 AND INTERFERON-γ SYNTHETIC DEFICIENCY IS ASSOCIATED WITH DENDRITIC CELL CYTOPENIA AFTER CARDIAC SURGERY

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ABSTRACT—Traumatic or inflammatory injury associates with deactivation of monocytes and impaired synthesis of proinflammatory cytokines. We conducted a prospective, observational study to test whether cardiac surgery additionally impaired dendritic and natural killer (NK) cell functions responsible for innate immune production of interleukin (IL)-12-dependent interferon (IFN)-γ in response to bacteria or toll-like receptor agonists. Blood samples were taken just before induction of anesthesia and 24 h postoperatively. LPS- and fixed Staphylococcus aureus-inducible IFN-γ synthesis in whole blood culture after surgery was reduced to 5% of preoperative values (P < 0.001). Production of IL-12 p70, a critical inducer of IFN-γ in the innate immune response, was reduced to 30% of that produced by preoperative samples (P = 0.013). Circulating CD11c+, DR+ myeloid dendritic cells (DC) that are known sources of IL-12 p70 in normal blood, declined to approximately 25% of presurgical numbers (P = 0.004). Experimental depletion of CD11c+, but not CD14+, cells from normal peripheral blood mononuclear cell (PBMC) similarly disabled Staphylococcus aureus Cowan 1 (SAC)-induced production of IL-12 p70 and IFN-γ. Consistent with SAC-induced IFN-γ expression in CD56+ NK and NK-T cells, CD56 depletion ablated IFN-γ production in normal whole blood. However, depletion of IL-12 p70, IL-18, and IL-23 in postoperative blood failed to restore presurgical levels of IFN-γ synthesis (P < 0.05). We conclude that DC cytopenia after major surgery is sufficient to explain postoperative IL-12 p70 and IFN-γ synthetic deficiency. In addition, postoperative blood became hyporesponsive to IFN-γ-inducing cytokines as a further contribution to IFN-γ insufficiency. The novel finding of DC cytopenia after major surgery may portend a lack of other immunologic functions provided by this potent accessory cell population.

KEYWORDS—Interferon-γ, interleukin-12, endotoxin, dendritic cell, monocyte deactivation

INTRODUCTION

The systemic inflammation associated with cardiac surgery with cardiopulmonary bypass is very similar to the systemic response seen in other injured populations (1), including trauma, burns, and sepsis. It is well recognized that systemic inflammation in all of these settings is frequently followed by depressed immune activation, as characterized by reduced delayed type hypersensitivity (DTH) reactivity and decreased monocyte expression of the MHC II molecule, HLA-DR (2–4). This monocyte-deactivation phenotype also associates with decreased proinflammatory cytokine synthesis and may be linked to increased susceptibility to nosocomial infection (5–7). Trauma and sepsis can also impair IFN-γ production triggered by mitogen or anti-CD3 antibody, suggesting that critical defects in T lymphocyte function also occur (4). By suppressing production of proinflammatory cytokines, these immune defects may significantly contribute to the infectious complications of trauma and other critical illnesses (8).

IFN-γ can also be generated in an antigen-independent fashion by natural killer (NK) cells and NK-T cells responding to IL-12 produced as part of the innate cellular immune response to infection (9). Dendritic cells are a critical source of bioactive IL-12 p35/p40 heterodimer (p70) in this setting (10), and this cytokine acts synergistically with IL-18 to induce innate IFN-γ synthesis by NK and NK-T cells (11, 12). IFN-γ subsequently mediates significant first-line defense against localized infection (13–18). IFN-γ and IL-12 generated during the innate response may also critically promote Th1-type T cell differentiation, further contributing to the resolution of bacterial infection (19). Therefore, the status of innate cellular immune function in injured patients may be highly relevant to understanding the clinical relationship between trauma-induced immune suppression and increased susceptibility to nosocomial bacterial infection. For instance, LPS-induced IL-12 synthesis by monocytes is reduced in patients with sepsis and after major visceral surgery and predicts an increased risk of infection (20, 21).

Although routine cardiothoracic surgery similarly disrupts monocyte expression of HLA-DR and mitogen-induced...
production of IFNγ by peripheral T lymphocytes (22), the integrity of NK cell-dependent IFNγ produced via innate cellular immune pathways has not been characterized. We hypothesized that cardiac surgery with cardiopulmonary bypass would similarly reduce bioactive IL-12 p70- and IL-12-mediated IFNγ production in response to nonviable microbial challenges represented by lipopolysaccharide- and formalin-fixed Staphylococcus aureus. Our findings confirm the presence of a profound cytokine deficiency in postsurgical patients and newly identify reduced numbers of CD11c+ dendritic cells in the peripheral blood that are sufficient to explain postoperative decreases in IL-12 and IFNγ synthesis.

MATERIALS AND METHODS

Patient selection

Participants in this study were consenting patients scheduled for elective cardiac surgery. Fifty-six patients were enrolled in pre- and postoperative studies. An additional 11 volunteers provided blood for in vitro studies. Fifteen milliliters of whole blood was collected in a sterile tube containing 100 U/mL sodium heparin (BD Vacutainer no. 366499; Becton Dickinson, Franklin Lakes, NJ) just before surgery and again 24 h later. Individuals with immunosuppressive disorders, renal insufficiency (creatinine clearance <30 mL/min), or human immunodeficiency virus infection were excluded from the study. Corticosteroids were not administered at the time of surgery. The human subjects protocol and consent forms were approved by the Institutional Review Boards of the University Hospitals of Cleveland and the Louis Stokes Cleveland Veterans Affairs Medical Center.

Flow cytometry for monocyte HLA-DR expression and numbers of leukocyte subsets

Blood anticoagulated with 5 mM EDTA (BD Vacutainer no. 366452) was processed for cell subset analysis by the clinical flow cytometry laboratory of University Hospitals of Cleveland. Peripheral blood mononuclear cells (PBMC) were stained with fluorescent antibodies specific for CD3, CD19, and CD16/CD56 (SimulSet; Becton Dickinson, Palo Alto, CA) to measure T, B, and NK lymphocyte numbers using a FACSCalibur flow cytometer (Becton Dickinson). Sample gates were selected for specific analysis of cells with the forward- and side-scattering characteristics of lymphocytes. PBMC were also stained with CD14- and pan-allelic HLA-DR on CD14+ cells with the forward- and side-scattering characteristics of monocytes. PBMC were separated from heparinized blood by density gradient centrifugation (Ficoll-Hypaque; Sigma Chemical, St. Louis, MO) commercial ELISA kits. Human IFNγ, IL-12 p40, IL-12 p70, IL-10, and IL-18 levels were measured using ELISA kits and recombinant cytokine standards from BD Pharmingen. Human IL-12 p70 was measured using medium-sensitivity (limit of detection, 15.4 pg/mL; Endogen, Woburn, MA) or high-sensitivity (limit of detection, 0.781 pg/mL; R&D Systems, Minneapolis, MN) commercial ELISA kits.

Statistical analysis

Data were tested for normality, and appropriate tests were selected. Non-normal distributions were compared using the Wilcoxon signed-rank test, and normally distributed data were compared using paired Student’s t test. Spearman’s rank correlation was used to test correlations. For the purpose of calculation, undetectable levels of cytokine were assigned values corresponding to the lower limit of detection for each assay (7.8 pg/mL for IFNγ).

RESULTS

Baseline data

Clinical characteristics of the study population are summarized in Table 1. The presence of monocyte deactivation in this population was confirmed by flow cytometry on CD14+ cells in 37 subjects. There was a uniform, 41.1% median decrease in HLA-DR mean fluorescence intensity (Fig. 1), from a median of 517.70 preoperatively (IQR of 405.36–588.85) to a median of 342.44, 24 h postoperatively (IQR of 214.12–413.71;
Innate IFNγ numbers were unchanged (Table 2). About 40% of preoperative numbers, whereas monocyte cell numbers per square millimeter declined after surgery to < 0.001. Flow cytometric analysis showed that T cell and NK P28 SHOCK cell intensity values. Analytical gates were chosen to select for CD14+ cells with expression on monocytes for one individual, including mean fluorescence each of 37 subjects. (B) A representative dot-plot analysis of HLA-DR intensity values. Analytical gates were chosen to select for CD14+ cells with expression on monocytes for one individual, including mean fluorescence each of 37 subjects. (B) A representative dot-plot analysis of HLA-DR side- and forward-scattering values characteristic of monocytes. Reduced monocyte expression of HLA-DR after cardiothoracic surgery. Data represent the mean fluorescence intensity of HLA-DR on CD14+ monocytes 24 h before cardiac surgery (preoperative) and 24 h afterward (postoperative). Each pair of data points (A) indicates findings from each of 37 subjects. (B) A representative dot-plot analysis of HLA-DR expression on monocytes for one individual, including mean fluorescence intensity values. Analytical gates were chosen to select for CD14+ cells with side- and forward-scattering values characteristic of monocytes.

P < 0.001). Flow cytometric analysis showed that T cell and NK cell numbers per square millimeter declined after surgery to about 40% of preoperative numbers, whereas monocyte numbers were unchanged (Table 2).

**Innate IFNγ production is significantly reduced after cardiac surgery**

Having established the presence of monocyte deactivation 1 day after cardiac surgery, we then examined production of cytokines critical to the integrity of innate cellular immunity. Peripheral blood was incubated with fixed SAC or LPS, both of which activate toll-like receptor functions that lead to production of IL-12 and IL-12-dependent IFNγ synthesis by NK cells in culture (9). Comparison of pre- and postoperative IFNγ levels in conditioned plasma demonstrated that IFNγ synthetic capacity 1 day after cardiac surgery was only 5% of that observed before surgery (Fig. 2). SAC was a greater stimulus for IFNγ production than was LPS, but both revealed significant decreases in production (P < 0.01; Wilcoxon signed-ranks test) in more than 95% of postoperative subjects. This synthetic defect could not be attributed wholly to the lesser decrease in NK cell or T lymphocyte populations in postoperative blood (40% of preoperative values), as there remained an additional 10-fold difference in IFNγ production. IFNγ deficiency in SAC-stimulated whole blood culture was persistent, remaining at 5% of preoperative values for at least 4 days after surgery (n = 6 subjects). Because SAC was the more potent stimulus for IFNγ production, this reagent was used in subsequent studies aimed at determining the mechanism of IFNγ underproduction after surgery.

**Cardiac surgery decreases the synthetic capacity of IL-12 p70, but not IL-12 p40**

In the innate cellular immune pathway, previous synthesis of bioactive heterodimeric IL-12 (IL-12 p70) is critically required for IFNγ production (10). To determine if postoperative IL-12 p70 deficiency might account for IFNγ underproduction, IL-12 p70 levels in 24 individuals were assayed using a commercial ELISA with a lower limit of detection of 15.4 pg/mL. Although only 10 samples contained detectable preoperative concentrations, the postoperative decline in IL-12 p70 synthetic capacity to 35% of preoperative values was significant in this subset (P = 0.004) and remained significant when all samples were included in the analysis (P = 0.01). A comparable decrease (to 30%; P = 0.013) in IL-12 p70 was subsequently confirmed in another group of nine subjects using a high-sensitivity ELISA that detected IL-12 p70 in all stimulated samples above the detection limit of 0.78 pg/mL (Fig. 2C). Consistent with a concentration-dependent induction of IFNγ by IL-12 p70, supernatant concentrations of IL-12 p70 and IFNγ in individual preoperative cultures were significantly and positively correlated (r = 0.554, P < 0.001, n = 17; Spearman rank correlation). IL-12 p70 was not detected in unstimulated cultures before or after surgery. Concentrations of IL-12 p40 levels in SAC-stimulated culture increased significantly, from 1.13 ± 0.25 ng/mL preoperatively to 1.76 ± 0.46 ng/mL.
postoperatively ($P = 0.02$, $n = 32$). Unstimulated whole blood produced less than 0.2 ng of IL-12 p40 in both groups.

**Cardiac surgery decreases numbers of circulating myeloid dendritic cells**

Although blood monocytes are capable of IL-12 p40 synthesis, isolated peripheral blood dendritic cell populations are demonstrably more potent producers of IL-12 p70 (10, 24), with myeloid dendritic cells (CD11c$^+$/CD123$^-$/HLA-DR$^+$) reportedly generating more than plasmacytoid dendritic cells (CD11c$^-$/CD123$^+$/HLA-DR$^+$) (25). We found that both subsets of circulating dendritic cells were markedly reduced in the postoperative period. In the 11 subjects studied, peripheral blood myeloid dendritic cells declined from a median of 20/mm$^3$ preoperatively (range of 6–31) to 5/mm$^3$ postoperatively (range of 1–18; $P = 0.004$; Fig. 3). Plasmacytoid dendritic cells also reduced from a median of 6/mm$^3$ preoperatively (range of 2–16) to 1/mm$^3$ postoperatively (range of 0–8; $P = 0.003$). This novel finding suggested that postoperative dendritic cell deficiency in the peripheral blood might be responsible for reduced IL-12 p70 production in response to bacterial stimuli, and that this would consequently prevent IFN$\gamma$ synthesis.

**Experimental depletion of CD11c$^+$ cells disrupts SAC-induced IFN$\gamma$ and IL-12 p70 synthesis in normal volunteer PBMC**

To test this hypothesis, we obtained PBMC from healthy volunteers and examined the effects of specific cell depletions on SAC-induced cytokines (Fig. 4). Removal of CD11c$^+$ cells, which were shown by flow cytometry to consist of CD11c$^+$/DR$^+$ myeloid dendritic cells and CD11c$^+$/CD14$^+$ monocytes, significantly reduced SAC-stimulated IFN$\gamma$ secretion to 1% of control values ($P = 0.04$) and IL-12 p70% to 33% ($P = 0.04$). In contrast, specific depletion of CD14$^+$ monocytes had no significant effect on IFN$\gamma$ or IL-12 p70 production. Magnetic removal of CD56$^+$ cells, consisting of NK and NK-T
cells by flow analysis of bead-bound cells, reduced SAC-induced IFNγ production to undetectable levels, but did not affect IL-12 p70 production. IL-12 p40 was equally reduced by CD14 or CD11c depletion. Finally, we found that CD3+ cells produced intracellular IFNγ in SAC-stimulated whole blood (Fig. 4). The majority (95% ± 7%) of IFNγ-expressing CD3+ cells expressed the NK cell marker CD56, as did 50.1% ± 6% of the IFNγ+CD3+ cells, consistent with NK and NK-T cell sources of IFNγ. An average of 13.9% ± 3.8% of CD56+/CD3− NK cells and 1.5% ± 0.6% of all CD3+ T cells stained positive for intracellular IFNγ. Taken together, these results show that a CD11c+ nonmonocyte cell population is necessary to support SAC-induced IL-12 p70 in normal PBMC and that CD56+ NK and NK-T cells are the source of IFNγ synthesis.

Recombinant IL-12 p70, IL-18, and IL-23 do not restore normal IFNγ production in postoperative whole blood culture

If postoperative IFNγ deficiency was due solely to removal of IL-12 p70, the addition of recombinant IL-12 p70 to culture should restore near-normal levels of IFNγ synthesis in response to SAC. In preoperative blood, SAC supplemented with 1.0 ng/mL IL-12 p70 significantly (P < 0.001; n = 21 subjects) increased absolute IFNγ levels compared with culture with SAC alone (Fig. 5). Intracellular staining confirmed cytokine-assisted IFNγ production was still NK and NK-T cell based (data not shown). Although recombinant IL-12 also increased absolute postoperative IFNγ levels significantly (P = 0.001), IL-12 replacement did not restore normal levels of IFNγ production after surgery. The 6% residual production of IFNγ induced by SAC in postoperative blood only increased to approximately 10% of preoperative values after the addition of IL-12 (pre- and postoperative medians of 1015.5 and 105.4 pg/mL, P = 0.002).
Increasing IL-12 concentrations up to 5 ng/mL produced only minor incremental increases in IFNγ levels without reducing the defect in postoperative IFNγ synthesis relative to preoperative function (data not shown).

We next tested whether postoperative IFNγ deficiency might be because of loss of synergistic or alternative IFNγ-inducing signals provided by IL-18, IL-15, and IL-23 (11,26). Although SAC-inducible IL-18 was detectable in preoperative and postoperative blood cultures in concentrations ranging from 0.2 to 1.0 ng/mL, these differences were not significant with regard to operative status (data not shown). The addition of up to 300 ng/mL recombinant human IL-18 to SAC- and rIL-12-stimulated whole blood culture increased preoperative IFNγ production 9-fold compared with culture without IL-18 (Fig. 5), but the maximal response of IL-12/IL-18-stimulated IFNγ in postoperative blood was still only 20% relative to preoperative cultures (P = 0.028). Similarly, the addition of 3 ng/mL rIL-15 in combination with IL-12 or with 3 ng/mL rIL-23, which induces IFNγ through a receptor distinct from IL-12R, failed to additionally increase postoperative IFNγ production even when all four cytokines were used in combination (data not shown). These findings indicate that IFNγ-inducing cytokines that were highly active in preoperative subjects were markedly less able to induce postoperative production of IFNγ in whole blood culture.

**Deficient IFNγ production after cardiac surgery is not restored by neutralization of IL-10**

We confirmed that IL-10 concentrations increased significantly in response to SAC in pre- and postoperative whole blood cultures, respectively, although the maximal induced responses were not significantly different before and after surgery (Table 3). We tested the physiologic significance of in vitro IL-10 production by measuring IFNγ responses to SAC in the absence or presence of 20 μg/mL neutralizing anti-IL-10 antibody. Although IL-10 neutralization did increase IFNγ production in preoperative and postoperative samples, postoperative SAC-inducible IFNγ levels remained only 11% relative to those in preoperative cultures.

**Down-regulation of IFNγ production is not dependent on the presence of plasma in PBMC culture**

The postoperative decreases in IFNγ and IL-12 production in whole blood culture might have reflected suppressive activities mediated by circulating factors other than IL-10 present at the time of sampling. Therefore, we measured IFNγ levels generated by Ficoll-Hypaque-purified PBMC in defined media (Fig. 6). After stimulation with 0.01% SAC, median IFNγ levels were 59.8 pg/mL preoperatively (range of 7.8–2359.3 pg/mL) and 7.8 pg/mL postoperatively (P = 0.005; n = 11 subjects). Cells cultured in media alone did not produce detectable IFNγ (<7.8 pg/mL). The addition of autologous plasma obtained from the same blood draw supported a modest increase in preoperative levels of IFNγ to 101.2 pg/mL (range of 8.0–1472.0 pg/mL) in response to SAC, but postoperative levels remained at or below the limit of detection (P = 0.028). Finally, although IL-12 supplementation increased IFNγ production overall, postoperative levels were still reduced to 17% of preoperative values compared with 13% in the absence of IL-12.

**DISCUSSION**

Because cardiothoracic surgery is a scheduled event, this population of subjects provides a readily accessible and self-controlled model for the study of mechanisms contributing to immune dysfunction in critically ill or traumatized humans. Previously, post-traumatic or sepsis-related immune deficiency was defined by decreased monocyte HLA-DR expression and proinflammatory monokine production (4,5,20,28). We confirm that the controlled trauma of cardiothoracic surgery similarly reduces HLA-DR expression on monocytes and we show that TLR-mediated production of IL-12 and IFNγ is...
markedly impaired in this specific setting. This finding complements and extends similar observations of IL-12 deficiency after major visceral surgery that was ascribed to macrophage dysfunction (7). In contrast, the central and novel observation of this report is that dendritic cell numbers in postoperative blood are significantly reduced after surgery. Furthermore, the experimental depletion of CD11c+ dendritic cells in normal PBMC culture markedly impairs SAC-induced IL-12 and IFNγ production, whereas depletion of CD14+ monocytes did not. This provides an alternative and dendritic cell-based mechanism for impaired innate immune production of IL-12 p70 and IFNγ after surgery that is distinct from macrophage deactivation. We further demonstrate that deficient postoperative IFNγ production by whole blood is not recovered by treatment with IFNγ-inducing cytokines such as IL-12, IL-18, IL-15, and IL-23. A similar IL-12 unresponsiveness occurs in humans with sepsis (20). Therefore, postoperative immune deficiency appears to be mediated by multiple mechanisms. In addition to effects mediated by macrophage deactivation and/or production of immunosuppressants (29, 30), we now conclude that dendritic cell cytopenia distinctively contributes to IL-12 p70 underproduction and that IL-12 deficiency, possibly in combination with a decreased IL-12 responsiveness by NK/NK-T cells, results in a marked loss of IFNγ synthetic capacity in postsurgical whole blood.

These studies initially focused on cytokine synthesis after activation of innate cellular immunity by TLR-active reagents, whereas many previous reports of postsurgical IFNγ deficiency used mitogens to test T cell synthetic competency. Formalin-fixed S. aureus proved to be a potent IFNγ-induced agent in whole blood culture or PBMC and is known to stimulate cytokines through innate immune mechanisms that require Myd88, TLR2, and other toll receptors (18). Because dendritic cells express TLR2 and respond to SAC with IL-12 production (31), the significant decrease in circulating dendritic cells after surgery provides a plausible mechanism for IL-12 p70 deficiency. In support of this, CD11c-depleted PBMC underproduced IL-12 p70 and IFNγ in response to SAC. Although CD11c+ depletion also removed monocytes, CD14-depleted PBMC showed little or no impairment in SAC-induced IL-12 p70 or IFNγ release. A previous report similarly described a nonessential role for CD14+ monocytes in peripheral blood production of SAC-induced IL-12 p70 (24). IL-12 p40 synthesis, which normally parallels p70 production, paradoxically increased after surgery. In contrast to effects on IL-12 p70, depletion of CD14+ or CD11c+ cells each reduced IL-12 p40 production by one-half, suggesting redundant sources of IL-12 p40 in normal blood that are distinct from myeloid dendritic cells and monocytes and that may account for preserved synthesis in postsurgical subjects.

The mechanisms responsible for dendritic cell cytopenia after surgery are not identified in this study. Cytopenia could be because of redistribution of cells from peripheral blood into other tissues or to surgery-induced apoptotic depletion of these cells. Lymphocyte and macrophage apoptosis is described in experimental or clinical models of trauma and sepsis (29), and apoptotic dendritic cell depletion occurs in mice systemically exposed to LPS or Toxoplasma gondii (32–34). More recently, depletion of follicular dendritic cells in the spleens of patients with sepsis has also been described, although these cells represent a lineage functionally and biologically distinct from circulating dendritic cells (35). Because DC are potent antigen-presenting cells and mediate critical costimulatory and regulatory functions in adaptive and innate immunity, we speculate that dendritic cell depletion may have adverse consequences on immune function extending beyond specific cytokine deficits. For instance, the loss of delayed type hypersensitivity (DTH) responsiveness after cardiac surgery (36) may be a consequence of dendritic cell depletion in tissue and blood.

The initial endpoint used in these studies was production of IFNγ by SAC- or LPS-stimulated innate immunity. SAC-induced IFNγ is IL-12 dependent and mediated by NK cells in PBMC (37, 38). Using intracellular staining techniques, we confirmed that NK and NK-T cells contribute to SAC-induced IFNγ production in whole blood. Although the numbers of NK cells declined 50% in whole blood after surgery in our study, this decrement did not account for the 95% reduction in IFNγ levels after surgery. Although loss of IL-12 p70 synthesis is sufficient to explain this defect, we also show that postoperative NK cells may become less responsive to IFNγ-stimulating cytokines. At best, using supraphysiologic amounts of IL-12 and IL-18, the postoperative deficiency in SAC-induced IFNγ synthesis was improved only from 6% to 10% of preoperative IFNγ levels. Postsurgical hyporesponsiveness also extended to IL-15 and IL-23. These data do not exclude the possibility that the partial reduction of T and NK cells after surgery was specific for a subset of cells capable of producing IFNγ. Although inhibitors of IFNγ production, such as IL-10, may be present in plasma (27, 29, 30), SAC-induced IFNγ levels in plasma-free cultures of PBMC culture were still markedly reduced relative to preoperative levels and anti-IL-10 antibody failed to restore IFNγ production in whole blood culture. Further studies are needed to determine if multiple NK cell cytokine receptors or common signal transduction pathways are disrupted as a result of surgery or if transient and previous exposure to IL-10 or other suppressant molecules persistently disables cellular function (39).

In summary, cardiothoracic surgery induces multiple defects in the innate cellular immune system that normally supports IFNγ synthesis in response to acute gram-negative and gram-positive microbial stimuli. Specifically, we show that myeloid dendritic cells are necessary for production of SAC-induced IL-12 p70 and IFNγ in PBMC and, therefore, that surgery-induced dendritic cell cytopenia is sufficient to explain postoperative IFNγ deficiency. Dendritic cell dysfunction adds to other mechanisms of postsurgical immune dysfunction due to macrophage desensitization or circulating suppressive factors (29, 30). We note similarities between postsurgical and endotoxin-induced immune defects, both of which result in macrophage deactivation, dendritic cell depletion, and combined IL-12 and IFNγ deficiency (34, 40). Because injection with TNFα reproduces these cytokine defects in mice, surgically induced production of TNFα from myocardium or other tissues (41) may mediate some of immune defects observed after cardiothoracic surgery. Separate from these mechanistic questions, the consequences of trauma- or sepsis-induced immune deficiency for the
host also need to be better understood. Although an attenuated inflammatory response may protect against death from overwhelming systemic inflammation, these same defects in toll-dependent cytokine production may increase risk of infection (17, 18). Further comparisons between animal and postsurgical models of immune deficiency may identify a rationale and a therapeutic approach for preventing dendritic cell depletion in vivo, an intervention that may restore appropriate production of important antimicrobial cytokines in injured patients.

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