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Potential Prophylactic Measures Against Postoperative Immunosuppression: Could They Reduce Recurrence Rates in Oncological Patients?

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Background: Removing the primary tumor is indispensable for eliminating the major pool of metastasizing cells, but the surgical procedure itself is suspected of promoting metastases. This adverse effect is attributed to several mechanisms acting in synergy, including mechanical release of tumor cells, enhanced angiogenesis, secretion of growth factors, and immunosuppression. Here we provide new insights into mechanisms of postoperative immunosuppression and assess the assumptions underlying the hypothesis that, by suppressing cell-mediated immunity (CMI), surgery may render the patient vulnerable to metastases that otherwise could have been controlled.

Methods: An extensive review of relevant articles in English identified by using the MEDLINE database and cross-referencing.

Results: Current literature suggests that (1) CMI can control minimal residual disease, especially if surgery is performed early; (2) major surgery transiently but markedly suppresses CMI through multiple mechanisms now better understood; (3) surgical stress promotes experimental metastasis through immunosuppression, but the clinical evidence remains indirect because of ethical limitations.

Conclusions: Minimizing postoperative immunosuppression seems feasible, may limit recurrence, and should be introduced into the broader array of considerations when planning oncological surgeries. In the short run, physicians could try to avoid immunosuppressive anesthetic approaches, inadvertent hypothermia, excessive blood transfusions, and untended postoperative pain. When feasible, minimally invasive surgery should be considered. In the long run, clinical trials should evaluate prophylactic measures, including perioperative immunostimulation and several antagonists to cytokines and hormones specified herein.

Key Words: Immunosuppression—Neuroimmunomodulation—Postoperative complications—Surgical stress—Tumor immunology—Tumor metastasis.

PROMOTION OF METASTASIS BY SURGERY: THE BROADER CONTEXT

Surgery remains the most effective treatment for solid tumors. In the long run, the tumor must be removed to eliminate the major pool of metastasizing cells, but in the short run, the surgical procedure might actually promote metastasis. The notion that surgery might promote metastasis emerged decades ago as surgeons noticed a dramatic flare-up of metastases shortly after surgery in some oncological patients.[1] Since then, the hypothesis has resurfaced repeatedly[2–8] without being widely accepted or rejected. During this period, the fields of clinical oncology, tumor biology and immunology, stress physiology, and neuroimmunomodulation have advanced impressively. We are now in a position to re-evaluate the hypothesis in light of these advances.

Several mechanisms might promote postoperative metastasis; here we focus on the unique contribution of postoperative immunosuppression. We thus discuss the ability of cell-mediated immunity (CMI) to restrict minimal residual disease, as well as the suppression of CMI

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by surgery, including the aspects of surgery and the biological pathways that lead to this suppression. We then demonstrate that immunosuppressive surgical procedures exacerbate metastasis in animals and may do so in humans. Finally, we offer initial recommendations for clinical application of this knowledge. These recommendations include prophylactic measures that, if tested clinically, would for the first time assess whether surgery promotes metastasis by suppressing CMI in patients.

Mechanisms Suggested to Promote Metastases After Surgical Removal of the Primary Tumor

Various mechanisms may promote metastasis after surgery. First, manipulating the tumor during surgery may release malignant cells into the circulation. Intrusive procedures often disrupt the tumor and may release cells from the noncohesive malignant tissue. Recently, polymerase chain reaction–based detection techniques have shown that tumor cells transiently appear in the blood of many cancer patients after surgery.[9] The clinical importance of this phenomenon is, however, unclear, because "no-touch" methods for tumor resection have failed to demonstrate conclusive clinical advantages.[9]

A second potential mechanism involves regulation of angiogenesis.[10] Animal studies show that recruitment of blood vessels, which is critical for metastatic development, is sometimes inhibited while the primary tumor is present. The most probable source of the antiangiogenic signal is enzymatic degradation of the extracellular matrix that surrounds invading tumors. Products of this degradation (e.g., angiostatin and endostatin) are claimed to inhibit angiogenesis in murine tumors. Accordingly, removing the primary tumor might eliminate a safeguard against angiogenesis and thus awaken dormant micrometastases.

A third mechanism is the local and systemic release of various growth factors and cytokines from tissues injured during surgery.[11] These factors promote inflammation and wound healing, but some (e.g., epidermal growth factor and transforming growth factor-β) also facilitate tumor proliferation. Animal studies implicate these factors in promoting tumor recurrence in the incision site, as well as in remote locations.[6]

A fourth risk factor, on which this review focuses, is the perioperative suppression of CMI. As elaborated on later, this phenomenon is clinically well established and may promote metastatic development of residual disease provided that the immune system has a role in controlling it.

Although each of these mechanisms alone may have a limited effect, the synergy between them might render the patient vulnerable to metastases that could have otherwise been controlled. For example, shedding of tumor cells into the circulation, combined with systemic suppression of CMI, might allow distant seeding of malignant cells. A decline in the levels of antiangiogenic factors, combined with the release of growth factors, may transform dormant micrometastases into proliferating macroscopic tumors.

THE CAPACITY OF CMI TO LIMIT METASTASIS

The proposal that surgery promotes metastasis by suppressing CMI hinges on the assumption that immunity can limit metastatic development. As reviewed below, tumor immunology has provided compelling evidence that both the adaptive and innate arms of CMI can recognize and eliminate malignant cells. Nevertheless, serious doubts remain whether the immune system plays a significant role in the clinical setting: immunotherapy has so far achieved limited success in treating cancer patients, spontaneous remission is scarce, and immunosuppression in transplantation patients does not affect the incidence of the most prevalent types of cancer.

Current theories in cancer immunology may finally reconcile the conflicting evidence. It is now widely acknowledged that the development of cancer is a microevolutionary process in which tumors randomly acquire mutations and undergo strict selection. The interaction between the immune system and the tumor dynamically evolves along this process[12,13] (Fig. 1). Initially, an immune response to the tumor is not mobilized because the newly transformed tissue is weakly antigenic, provokes no danger signals (e.g., inflammatory cytokines, heat shock proteins, or co-stimulatory molecules), and contacts relatively few immunocytes. Gradually, the tumor expresses more mutated antigens, emits more danger signals (because of crowding and hypoxia, which create local necrosis), and attracts more capillaries. At this stage, immune recognition and cytotoxicity often develop, and the selection pressure by the immune system builds up. This usually leads to a final stage in which tumor escape mechanisms, which were acquired through selection, render the immune system ineffective (see section below).

Elimination of Circulating Tumor Cells and Micrometastases by CMI

The relevant question for this discussion is whether the immune system can eliminate residual disease after the primary tumor is removed. Residual malignancy, if it exists, consists of pre-established micrometastases and isolated tumor cells in the circulation and lymphatics. Theoretically,

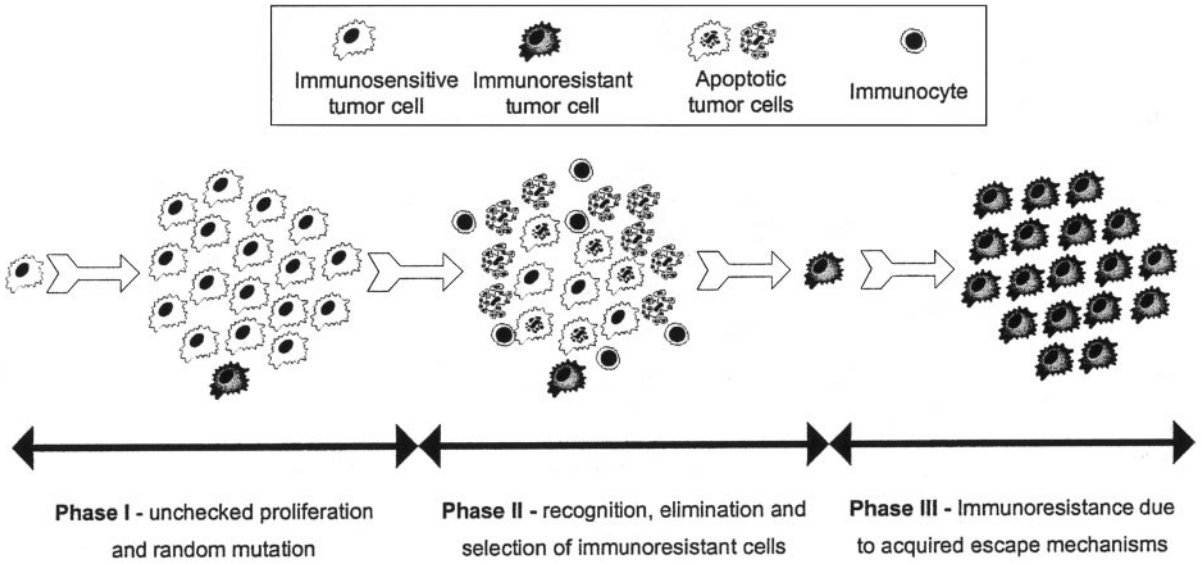

FIG. 1. The hypothetical microevolutionary process that leads to immunoresistance in tumor cells.

during migration and early colonization, tumor cells become temporarily more vulnerable to attack. Outside the protective environment of the primary tumor, the levels of tumor-derived immunosuppressive cytokines are lower,[14] and tumor cells are both greatly outnumbered by effector cells and slow to replicate.[15] Escape mechanisms established within the primary tumor (e.g., downregulation of major histocompatibility complex [MHC]-I) may prove disadvantageous within the blood or within target organs, where different populations of effector cells (e.g., natural killer [NK] cells) predominate.[16]

Therefore, although in cancer patients CMI clearly fails to eradicate the primary tumor, it may still eliminate minimal residual disease, especially if surgery is performed before insurmountable escape mechanisms develop. Indeed, immunohistochemical techniques have revealed that although a large proportion of cancer patients have residual cancer cells in target organs (e.g., bone marrow), many of them do not develop overt metastases during long follow-up.[17]

Empirical Evidence in Support of Antimetastatic Immunity

Molecular Mechanisms for Tumor Cell Recognition: In Vitro Findings Regarding Human Tumors

To suggest that CMI controls metastasis in humans, one needs to show first that its effector cells can recognize and destroy autologous tumor cells. Indeed, in many malignancies, autologous immunocytes (including cells of the innate immune system and, perhaps more importantly, cytotoxic T lymphocytes [CTLs])[18] were shown in vitro to lyse tumor cells expanded from the excised tumors.

Recent research has begun to unveil the molecular mechanisms that make antitumor immunity possible: researchers identified many long-sought-for tumor-associated antigens and discovered molecular interactions underlying tumor vulnerability to innate immunity.[19] It is important to note that some of the mechanisms used by NK cells and CTLs to recognize tumor cells are complementary. Whereas CTLs rely on tumor-associated antigens presented on MHC-I complexes, NK cells preferentially destroy tumor cells that have become MHC-I deficient,[20] supposedly because of negative selection by CTLs.

Animal Models of Metastasis

A variety of animal studies demonstrated that CMI can control metastasis, but the clinical relevance of many such models was justly questioned. In particular, models were criticized for using artificially induced hematogenous metastases, tumor lines long-maintained in vitro, implantation in incompatible organs, or biased selection of immunogenic tumors.

In response, researchers adopted syngeneic models that corroborated the antimetastatic function of CMI while boasting better clinical relevance. For example, animals were pre-exposed to a subcutaneously growing tumor before testing resistance to experimental metastasis.[21] Models of spontaneously metastasizing tumors improved as they progressed from implanted syngeneic cell

lines[22] to spontaneously occurring tumors in transgenic mice and genetically prone strains.[23] Tumors of human origin have been used to model the unique characteristics of human cancer and its interaction with innate immunity (commonly NK or macrophage activity[24]).

The methodology used to implicate immunity in such studies was diverse and included selective depletion of immune cells, knock-out mice, immunodeficient strains, and adoptive transfer of specific cell populations. Overall, this large body of research convincingly demonstrates the importance of NK cells, NK-T cells, tissue macrophages, and CTLs, guided by dendritic and T-helper (T_H) cells, for resisting metastasis, at least in the context of animal models.[19]

Correlative Clinical Studies

Several correlative clinical studies identified immunocompetence at the time of treatment as a positive prognostic factor for metastasis-free survival. It is important to note that the predictive ability of immune indices was independent of other known prognostic factors (e.g., tumor stage and grade). Positive predictors included higher NK activity[25] and the presence of $CD8^+$ T cells specific to tumor antigens.[26] Even more dramatically prognostic is the ability of the patient's circulating lymphocytes, CTLs in particular, to respond to autologous tumor cells.[26–28] For instance, Uchida et al.[27] reported that 23 of the 27 patients who exhibited high cytotoxicity against their primary localized lung cancer had complete remission at 5 years, whereas none of the 23 patients who exhibited low responses survived. Likewise, McCoy et al.[28] reported an 8-fold lower mortality rate in breast cancer patients whose peripheral blood mononuclear cells proliferated in response to cell membrane extracts from their excised tumors. Another prognostic factor is tumor infiltration by immunocytes. Metastases occur less frequently if the primary tumor is extensively infiltrated by lymphocytes, particularly NK cells and CTLs, or by dendritic cells,[29] but usually not by macrophages.[30] Overall, these studies suggest that immunity has an antimetastatic role in the natural course of human cancer.

Consequences of Immunosuppression in Transplantation Patients

Although immunosuppression in transplantation patients hardly increases the incidence of the most prevalent malignancies (breast, lung, colon, and prostate), it seems to promote the development of metastasis. Administering immunosuppressive drugs to patients long recovered from non–small-cell lung cancer occasionally reactivates dormant micrometastases.[31] Immunosuppressive therapy increases recurrence rates in patients who already have sarcomas, melanomas, myelomas, or carcinomas of the skin, bladder, or kidney.[32] Finally, when cancer appears in already immunosuppressed patients, its clinical course is usually accelerated, and more metastases appear.[33,34]

Evidence for Immunological Selection of Tumor Cells

The interaction between CMI and cancer is attested to by the eventual emergence of immunoresistant tumor cells.[35] This phenomenon most likely results from immunoselection, because tumors developing in immunodeficient mouse strains tend to be more immunogenic.[36] More directly, tumor cells isolated from metastases in immunocompetent mice consistently show genetic lesions that protect them from CTL, whereas metastatic cells in immunodeficient mice do not.[37] The plethora of identified escape mechanisms includes the disruption of every step required for antigen presentation[38] and of every known process involved in tumor destruction (both the death receptor pathway and the granzyme-perforin pathway). Also documented are secretion of cytokines that suppress CMI (notably, interleukin [IL]-10 and transforming growth factor-β), induction of immunological tolerance, and elimination of tumor-reactive lymphocytes. Some of the escape mechanisms, notably, downregulation of MHC-I, are most pronounced in metastatic lesions,[39,40] suggesting that the selection pressure is most intense in the metastatic stage.

Although these findings offer dismal prospects for antitumor immunity at the late stages of cancer, they indicate that the immune system has eliminated substantial amounts of tumor cells at earlier stages. Because these findings do not rely on questionable models of disease or on artificial clinical conditions (e.g., immunotherapy or immunosuppression), they form, in our mind, the most convincing evidence for an antitumor immune response in humans.

In summary, the evidence suggests that CMI has limited control over the emergence of cancer but can restrict the development of metastasis and may eradicate minimal residual disease. If the primary tumor is removed early, before intractable escape mechanisms develop, this capacity has clinical value. All considered, we believe that complete remission after surgery often occurs not because all the malignant foci have been removed, but because immune mechanisms have eradicated residual tumor cells.[14] Thus, maintaining immunocompetence in surgical patients may favor long-term remission.

SUPPRESSION OF CMI BY SURGERY: CHARACTERIZATION AND UNDERLYING MECHANISMS

It is clinically accepted that major surgery suppresses CMI for several days and that more invasive procedures lead to deeper and longer immunosuppression.[4] This immunosuppression can be quite profound, and many believe that it is a major factor in promoting life-threatening postoperative infections.[41] The observed perturbations are listed and referenced in Tables 1 through 6 and are briefly summarized herein.

After major surgery, there is a sharp increase in plasma levels of acute inflammatory cytokines (IL-6, IL-8, and, much less so, IL-1β and tumor necrosis factor [TNF]-α; Fig. 2A), prostaglandins (importantly, prostaglandin E_2), and stress hormones (catecholamines, corticosteroids, and pro-opiomelanocortin–derived neuropeptides; Fig. 2B). Within days, hepatic acute-phase proteins (e.g., C-reactive protein) also surge (see Fig. 2A). This response hardly affects humoral immunity. However, its net effect on CMI is a marked systemic decline, as reflected in the following four facets.

(1) Cytokine balance: monocytes and T_{H1} cells downregulate the production of cytokines that favor CMI (type 1 cytokines such as IL-2, IL-12, and interferon [IFN]-γ; see Table 4), whereas an increase occurs in plasma levels of type 2 cytokines and factors that interfere with CMI (e.g., IL-10, soluble TNF-α receptor [sTNF-αr], IL-1 receptor antagonist [IL-1rA], and sIL-2r; Fig. 2C; Table 2). (2) Cell numbers: there is a decline in the number of circulating effector cells (NKs, CTLs, and, less so, B cells) and accessory cells (dendritic cells and T_{H1} cells; see Table 1). It seems that migration of immunocytes into lymphatic tissue and the traumatized area accounts for the initial phase of this decline,[42,43] and accelerated apoptosis further diminishes cell numbers (see Table 5). (3) Ex-vivo cellular effector function: cell-mediated immune responses are suppressed, as reflected in reduced mixed lymphocyte response, reduced in vitro T-cell proliferation and blastogenesis, diminished expression of human leukocyte antigen–DR by antigen-presenting cells, and suppressed cytotoxic activity of macrophages and NK cells (see Table 5). (4) In vivo cellular immunocompetence: in vivo cell-mediated responses are disrupted, as reflected in compromised delayed-type hypersensitivity, rejection of allografts, and clearance of peritoneal bacteria (see Table 6).

The adaptive value of suppressing CMI after surgery is unclear. It could be suggested that surgery triggers a systemic anti-inflammatory response, which, among other functions, suppresses CMI. This systemic reaction is intended to restrict the inflammatory response to the surgical wound, where it is needed to promote wound healing and reduce immediate risks of bacterial infection.[44] The anti-inflammatory response may serve to reduce the risk of inflammatory damage to healthy tissue and the danger of autoimmunity against newly exposed antigens.

Immunosuppressive Aspects of Surgery

Suppression of CMI is caused by an interaction among various aspects of surgery (see Fig. 3). Each of these aspects triggers a characteristic neuroendocrine and immunological response; this is described below.

TABLE 1. *The effects of surgery on CMI and on selected plasma factors: circulating cell numbers*

Index studied	Species	Type of surgery	Effect	Extent/peak	Reference
Total lymphocytes	Human	Misc. surgery	↓	0–5 d	5, 73, 103–113
Total lymphocytes	Rat	Laparotomy	↓	3 h	72
Total lymphocytes	Rabbit	Laparotomy	↓	7 h	43
T cells (CD3)	Human	Misc. surgery	↓	1–3 d	5, 84, 110, 114–117
T_H (CD4)	Human	Misc. surgery	↓	1–4 d	5, 84, 100, 105, 110, 111, 114–119
T_{H1}	Human	Misc. surgery	↓ ↓	2 d	109, 120
T_{H2}	Human	Misc. surgery	=/↓	2 d	109, 120, 121
T_C (CD8)	Human	Misc. surgery	↓	0–2 d	5, 100, 105, 110, 111, 117–119
B cells	Human	Misc. surgery	↓	2 d	100, 110
B cells	Human	Misc. surgery	=	—	5, 111, 119
B cells	Human	Misc. surgery	↑	1–5 d	114, 116, 117
NK	Human	Misc. surgery	↓	1–3 d	5, 100, 110–112, 115, 116, 118, 119
NK	Rat	Laparotomy	↓	4 h	122
Dendritic cells	Human	Colectomy	↓	7 d	123
Granulocytes	Human	Misc. surgery	↑ ↑	1 d	103, 104, 108, 109, 113, 124–126
Monocytes	Human	Misc. surgery	↑	1 d	84, 116, 127

↑ and ↓, noticeable increase or decrease; ↑ ↑ and ↓ ↓, marked increase or decrease; =, no change; Misc., miscellaneous; CMI, cell-mediated immunity; T_H, T-helper cell; NK, natural killer cell; T_c, T cytotoxic.

TABLE 2. *The effects of surgery on CMI and on selected plasma factors: plasma levels of cytokines and their antagonists*

Index studied	Species	Type of surgery	Effect	Extent/peak	Reference
IL-6	Human	Misc. surgery	↑ ↑	6 h	61, 70, 73, 74, 83, 99, 108, 112, 116, 118, 124, 126, 128–147
TNFα	Human	Misc. surgery	↓/=/∅	—	61, 83, 89, 99, 108, 114, 130, 133, 134, 138, 144, 148–151
TNFα	Human	Ischemic surgery	↑	4 h	132, 140, 152
IL-1β	Human	Misc. surgery	↓/=/∅	1 d	61, 83, 99, 108, 114, 130, 132–134, 144, 149–151, 153–155
IL-1β	Human	Ischemic surgery	↑	1 h	133, 152, 154
IL-2	Human	Abdominal/heart	↑	1 d	156
IL-2	Human	Misc. surgery	=/∅	—	125, 149, 157
IL-8	Human	Misc. surgery	↑	3 h	99, 133, 138–140, 148, 158
IL-8	Human	Misc. surgery	∅	—	159
IL-10	Human	Misc. surgery	↑ ↑	4 h	74, 88, 89, 99, 103, 125, 137, 139–142, 160, 161
IL-1rA	Human	Misc. surgery	↑ ↑	4 h	125, 126, 130, 131, 134, 141, 148, 151, 153, 154, 158
Soluble IL-2 receptor	Human	Misc. surgery	↑	3–7 d	112, 142–144, 156, 162, 163
Soluble TNF-αr I and II	Human	Misc. surgery	↑	5 h to 5 d	125, 130, 137, 140, 148, 164

↑ and ↓, noticeable increase or decrease; ↑ ↑, marked increase; =, no change; ∅, undetectable; Misc., miscellaneous; CMI, cell-mediated immunity; IL, interleukin; IL-lrA, IL-1 receptor antagonist; TNF, tumor necrosis factor.

Tissue Damage

Trauma, whether surgical or not (e.g., severe mechanical or thermal injury) transiently suppresses CMI.[44] This observation suggests that tissue damage is a critical determinant of postoperative immunosuppression. Indeed, animal[45] and clinical[5] studies indicated that major operations were associated with greater immunosuppression than minor operations. More recently, a host of studies have demonstrated that minimally invasive surgery suppresses CMI markedly less than conventional approaches[8] and results in less postoperative infection.[46] It should be noted, though, that the benefit of these procedures might also stem from reduced bleeding, decreased pain, and reduced postoperative use of analgesics.

Blood Loss and Transfusion

Major operations frequently cause loss of blood and necessitate blood transfusion. Hypovolemic shock seems to cause immunosuppression that is correlated with the volume of lost blood.[47] Blood transfusion is also known to interfere with several aspects of CMI,[48] including cytokine levels, NK-cell activity, and T-cell blastogenesis. Indeed, it has long been noticed that patients who receive transfusions before renal transplantation have longer survival of the allografts.[48] The mechanism un-

TABLE 3. *The effects of surgery on CMI and on selected plasma factors: circulating hepatic and neuroendocrine factors*

Index studied	Species	Type of surgery	Effect	Extent/peak	Reference
C-reactive protein (CRP)	Human	Misc. surgery	↑ ↑	2–3 d	70, 74, 83, 108, 116, 126, 130, 132, 135, 136, 141, 144–147, 164–166
Immunosuppressive acidic protein	Human	Misc. surgery	↑	7 d	74, 118, 130, 167, 168
Glucocorticosteroids	Human	Misc. surgery	↑	6 h	58, 61, 70, 73, 83, 103, 104, 108, 113, 118, 130, 132, 135, 146, 151, 164–166, 169–181
Glucocorticosteroids	Rat	Laparotomy	↑	6 h	72, 182
Glucocorticosteroids	Pig	Colon resection	↑	6 h	183
Glucocorticosteroids	Rabbit	Laparotomy	↑	6 h	43
Corticotropin (ACTH)	Human	Misc. surgery	↑ ↑	0 h	83, 103, 118, 151, 169, 170, 173, 175–177
Corticotropin (ACTH)	Rat	Laparotomy/craniotomy	↑ ↑	4 h	182, 184
Corticotropin Releasing hormone (CRH)	Human	Misc. surgery	↑	0 h	169, 170
Arginin vasopressin	Human	Misc. surgery	↑ ↑	0 h	104, 151, 170, 173, 175, 185
Transcortin (CBG)	Human	Cardiac surgery	↓		186, 187
Transcortin (CBG)	Pig	Abdominal surgery	↓		188
Catecholamines	Human	Misc. surgery	↑	4 h	58, 98, 108, 113, 118, 132, 135, 146, 170–172, 174, 175, 178–180, 189, 190
β-endorphin	Human	Misc. surgery	↑	0 h	104, 175–177, 181, 191
β-endorphin	Rat	Laparotomy	↑	0 h	184
PGE2	Human	Misc. surgery	↑	6 h	185, 192, 193
PGE2	Human	Misc. surgery	=	—	194, 195
PGE2	Pig	Misc. surgery	=	—	196

↑ and ↓, noticeable increase or decrease; ↑ ↑, marked increase; =, no change; Misc., miscellaneous; CMI, cell-mediated immunity; CBG, corticosteroid-binding globulin; PGE_2, prostaglandin E_2.

TABLE 4. *The effects of surgery on CMI and on selected plasma factors: stimulated in vitro production of cytokines*

Index studied	Species	Type of surgery	Effect	Extent/peak	Reference
IL-6 (leukocytes)	Human	Misc. surgery	↓/=	5 h	134, 197, 198
TNF-α (leukocytes/monocytes/T cells)	Human	Misc. surgery	↓↓	1 h	41, 87, 89, 134, 151, 197–201
IL-1β (leukocytes)	Human	Laparoscopy	↓	2 h	134, 151, 198, 199
IFN-γ (leukocytes/PBMC/T cells)	Human	Misc. surgery	↓	2–48 h	41, 67, 109, 120, 121, 194, 198, 199, 201
IFN-γ (leukocytes/PBMC/T cells)	Rat	Laparotomy	↓	24 h	82
IL-2 (leukocytes/PBMC/monocytes/T cells)	Human	Misc. surgery	↓	1–10 d	41, 84, 109, 120, 156, 194, 198, 201
IL-12 (monocytes)	Human	Misc. surgery	=	1 d	41
IL-4 (PBMC/T cells)	Human	Misc. surgery	=/↓/↑	1 d	41, 109, 120, 121, 201
IL-10 (monocytes/T cells)	Human	Misc. surgery	↑	2 d	41, 88, 109, 201
IL-1rA (leukocytes)	Human	Misc. surgery	↑	2 h to 5 d	134, 151, 199

↑ and ↓, noticeable increase or decrease; ↓↓, marked decrease; =, no change; Misc., miscellaneous; TNF, tumor necrosis factor; IL, interleukin; IFN, interferon; PBMC, peripheral blood mononuclear cells; IL-lrA, IL-1 receptor antagonist; CMI, cell-mediated immunity.

derlying such immunosuppression remains elusive. It is suggested that cellular interactions with transfused leukocytes and, possibly, accumulation of immunosuppressive cytokines in stored blood, are key factors: autologous blood transfusion is less detrimental than allogenic transfusion, and depletion of leukocytes, especially if it is performed before the blood is stored, seems to be advantageous.[49]

Hypothermia

Intraoperative hypothermia occurs, at least to some extent, in more than 50% of surgical procedures and has been associated with increased rates of postoperative infection.[50] In rats, hypothermia was found to suppress lymphocyte proliferation,[51] macrophage phagocytosis,[51] and NK activity.[7] In humans, even mild hypothermic conditions (~35.5°C) exacerbate the immunosuppressive effects of abdominal surgery.[52] Exposure to cold is a classic stressor that stimulates vigorous sympathetic and glucocorticoid responses—both responses might mediate the effects of intraoperative hypothermia on immunity. Indeed, sympathetic blockade interfered with the promotion of NK-sensitive metastases by hypothermia.[53]

Pain, Analgesia, and Anesthesia

The neurogenic response to injury entails local activation of nociceptors, followed shortly by systemic release of endogenous opioids. The locally released neuropeptides that potentiate nociceptors (notably, substance P) seem to sensitize CMI,[54] whereas the systemically released neuropeptides that reduce pain (notably, β-endorphin) seem to downregulate CMI.[55] On top of this, perioperative anesthetics and analgesics might also suppress systemic immunity. Many of these compounds were found to suppress immunity when applied in vitro in concentrations assumed to be equivalent to those occur-

TABLE 5. *The effects of surgery on CMI and on selected plasma factors: ex vivo cellular activity and status*

Index studied	Species	Type of surgery	Effect	Extent/peak	Reference
T cell proliferation	Human	Misc. surgery	↓	1–7 d	52, 70, 84, 124, 147, 202, 203
T cell proliferation	Rat	Laparotomy	↓	1 d	45, 82, 204
B cell proliferation	Rat	Laparotomy	↓	1 d	45, 82
NK activity	Human	Mostly major surgery	↓	1 h to 7 d	111, 113, 162, 192, 194, 205, 206
NK activity	Human	Mostly minor surgery	=	1 h to 7 d	67, 162, 202, 203, 207
NK activity	Rat	Laparotomy	↓	1 h to 7 d	7, 45, 82, 85, 208, 209
NK activity	Mouse	Laparotomy	↓	1 h to 7 d	210, 211
Shift from T_{H1} to T_{H2} in differentiation	Human	Misc. surgery	↑	2 d	120, 121
Shift from T_{H1} to T_{H2} in differentiation	Human	Misc. surgery	=	—	109
PMN phagocytosis	Human	Gastric surgery	↓	1 d	112, 212
Macrophage phagocytosis	Mouse	Laparotomy	↓	1 d	213, 214
Monocyte lysis of tumor	Human	Open gastric surgery	↓	1 d	215
Monocyte lysis of tumor	Rat	Laparotomy	↓	6 h	209
HLA-DR on APC	Human	Misc. surgery	↓	1 d	41, 88, 110, 116, 124, 127, 164, 216
Autologous MLR	Human	Misc. surgery	↓	5 d	192
PBL apoptosis	Rat	Laparotomy	↑	3 h	72
PBL apoptosis	Human	Misc. surgery	↑	1 d	106, 136
T cell apoptosis	Human	Misc. surgery	↑	1–5 d	107, 217

↑ and ↓, noticeable increase or decrease; =, no change; Misc., miscellaneous; CMI, cell-mediated immunity; T_H, T-helper cell; NK, natural killer cell; HLA, human leukocyte antigen; MLR, mixed lymphocyte response; PBL, peripheral blood lymphocytes.

TABLE 6. *The effects of surgery on CMI and on selected plasma factors: in vivo function of cellular immunity*

Index studied	Species	Type of surgery	Effect	Extent/peak	Reference
Skin DTH response	Human	Misc. surgery	↓	1–3 d	84, 112, 124, 218–220
Skin DTH response	Mouse	Laparotomy	↓	1–3 d	221
Skin DTH response	Rat	Laparotomy	↓	1–3 d	222, 223
Skin DTH response	Pig	Colectomy	↓	1–3 d	183
Skin graft rejection	Rat	Colectomy	↓	1–7 d	224
Skin graft rejection	Mouse	Laparotomy	↓	1–7 d	225
Resisting peritonitis	Rat	Laparotomy	↓	7 d	226
Resisting peritonitis	Mouse	Laparotomy	↓	1–3 d	227, 228
Resisting metastasis	Rat			See Tables 7–10	
Resisting metastasis	Mouse			See Tables 7–10	

↓, noticeable decrease; CMI, cell-mediated immunity; DTH, delayed-type hypersensitivity.

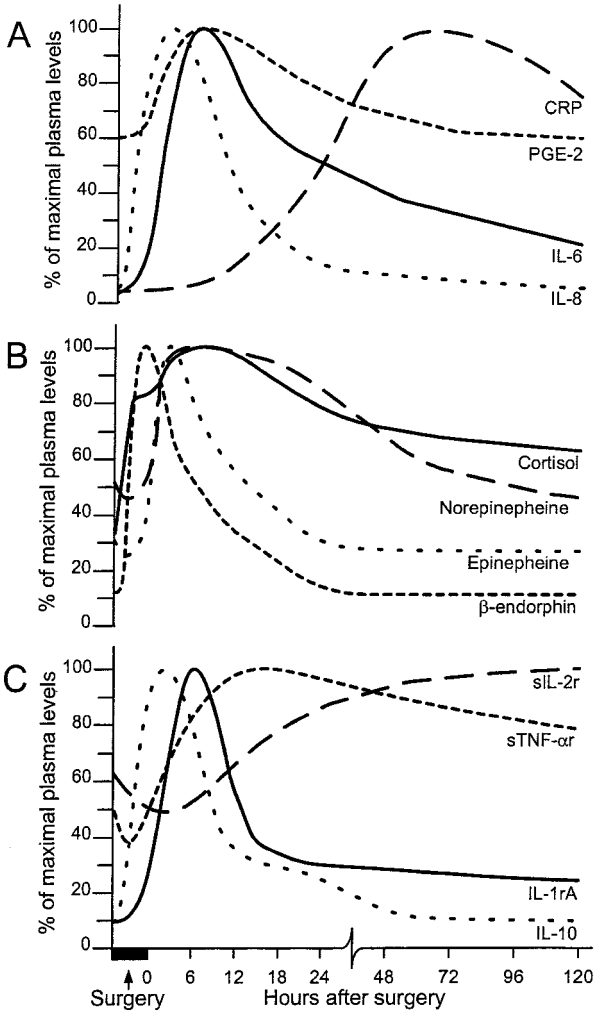

FIG. 2. A schematic representation of postoperative plasma levels of (**A**) acute inflammatory cytokines, (**B**) neuroendocrine hormones, and (**C**) anti-inflammatory mediators. The y-axis denotes the concentration of each factor as a percentage of its peak (100%) postoperative concentration. The exact magnitude and duration of each response vary among different operations (sources are listed in Tables 2 and 3). IL, interleukin; PGE_2, prostaglandin E_2; TNF, tumor necrosis factor; sr, soluble receptors; IL-1rA, IL-1 receptor antagonist; CRP, C-reactive protein.

ring in surgery.[56] More clinically relevant are ex-vivo clinical studies, which indicate that general anesthesia and opiate analgesia are somewhat immunosuppressive.[56] However, untreated pain has been suggested to suppress CMI and, consequently, promote metastasis.[57] Thus, to preserve immunocompetence, clinicians must

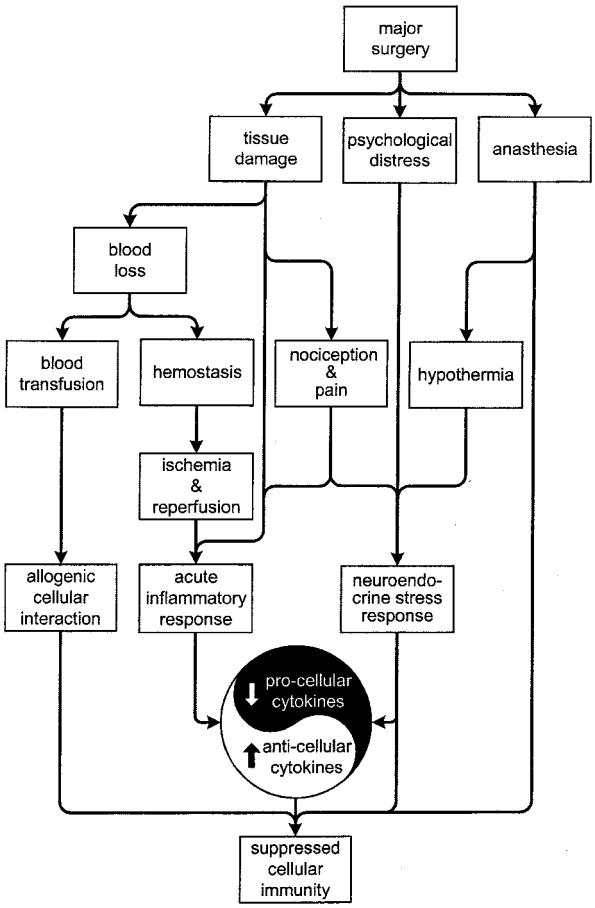

FIG. 3. The hierarchy of immunosuppressive aspects of surgery and the putative mechanisms they trigger.

tread a thin line between excessive pain and excessive use of analgesics.

A consistent finding is that local or regional anesthesia is less immunosuppressive than general anesthesia.[56] Additionally, regional blockade, when used alone or to supplement general anesthesia, often attenuates suppression of CMI by surgery[58,59] and reduces the incidence of postoperative infections (e.g., pneumonia).[60] These benefits can be attributed to the lower doses of drugs used for regional anesthesia and to the blockade of both ascending and descending pathways, which blunts the hypothalamo-pituitary-adrenal (HPA), sympathetic, and opioid stress responses to nociception and inflammation.[58,61]

Preoperative Anxiety

Before surgery, most patients experience emotional distress that stems from loss of control and from fear of anesthesia, pain, disfigurement, disability, or death. In cancer patients, this distress exacerbates the anxiety associated with the progression of the disease and with chemotherapy or radiotherapy. Psychological stress, especially when chronic, is associated with depressed CMI and increased susceptibility to infectious disease.[62] Animal studies have provided causal evidence that stress suppresses immunity[63] and consequently increases susceptibility to metastasis.[7,64] Correspondingly, anxiolytic drugs reduce postoperative suppression of CMI in mice.[65] Studies in cancer patients maintain that the level of stress experienced is associated (although weakly) with the extent of immunosuppression after surgery[66] and that psychological intervention can somewhat attenuate such effects.[67] Although perioperative psychological factors may affect neuroendocrine responses less profoundly than intraoperative physiological stressors, they probably last longer.

Specific Mechanisms Mediating Postoperative Immunosuppression

The acute response to surgery consists of an intricate interplay between the neuroendocrine and immune systems, which eventually leads to immunosuppression. Given the complexity of the response, the critical determinants of immunosuppression are hard to pinpoint. Nevertheless, several factors emerge as key players; many of them put the central nervous system at the crux of this immunoregulation.[68]

The HPA Axis

Surgery activates the HPA axis through a neural pathway, which can be efficiently blocked by regional anesthesia,[61] and through a humoral pathway. The latter involves the peripheral release of IL-1 and IL-6,[69] which elicit central release of corticotropin releasing hormone, followed by hypophysial release of vasopressin and adrenocorticotropic hormone (see Table 3). Glucocorticoids, which are established immunosuppressants, remain increased for days after major surgery, and their levels are usually well correlated with the extent of tissue damage and with the degree of immunosuppression.[61,70] Thus, glucocorticoids are excellent candidates for mediating stress- and surgery-induced immunosuppression. Indeed, animal studies indicate that inhibition of glucocorticoid synthesis reduces NK-cell suppression, T-cell apoptosis, and tumor metastasis after surgery.[71,72] In humans, inhibiting glucocorticoid synthesis improves postoperative immune function by reducing lymphopenia and by intensifying the release of the proinflammatory cytokine IL-6.[73] Conversely, preoperative administration of synthetic glucocorticoids increases the levels of the anti-inflammatory cytokine IL-10, suppresses the levels of IL-6, and paralyzes the delayed-type hypersensitivity response.[74,75]

Notwithstanding, glucocorticoids are no longer considered to be the sole mediators of immunosuppression. For instance, whereas minimally invasive operations often trigger HPA responses that are similar to those observed in corresponding open procedures, they cause less immunosuppression.[8]

The Sympathetic Nervous System

Less acknowledged, but not necessarily less significant, is the involvement of the sympathetic nervous system in immunosuppression.[76] Both norepinephrine and epinephrine are secreted abundantly in the perioperative period (Table 3), all lymphoid organs are richly innervated by sympathetic terminals,[77] and most leukocytes constitutively express β-adrenergic receptors.[78] Stimulating these receptors influences patterns of cytokine release, controls proliferation and effector functions, and radically affects cell distribution.[76] Risking overgeneralization, it can be stated that excessive catecholamine release inhibits CMI[76]: in vitro studies indicate that catecholamines can directly suppress the activity of NK cells and CTLs through cyclic adenosine monophosphate–dependent β-adrenoceptor activation. Catecholamines also act indirectly by influencing macrophages and T_H cytokine production, reducing type 1 cytokines (e.g., IL-12, TNF-α, and IFN-γ), and stimulating the release of the immunosuppressive cytokine IL-10.[68,79]

With respect to surgery, three groups have demonstrated that β-adrenergic antagonists can block various aspects of immunosuppression in rats. In our studies,[80]

nadolol attenuated the NK-suppressive and metastasis-promoting effects of laparotomy; Nelson and Lysle[45] reduced the suppression of lymphocyte proliferation after abdominal surgery; and Woiciechowsky et al.[81] prevented the increase in IL-10 plasma levels after brain surgery.

Endogenous Opioids

In response to pain and stress, the pituitary and the adrenal medulla secrete opioids into the circulation. β-endorphin, whose levels increase sharply after surgery (Table 3; Fig. 2B), is the opioid most characterized for its immunosuppressive effects. β-endorphin has been shown to suppress CMI in vitro and in vivo.[55] Recently, Nelson et al.[82] demonstrated that the opiate antagonist naltrexone markedly attenuates the suppression of immunity after laparotomy in rats, as expressed in levels of NK cytotoxicity, lymphocyte proliferation, and IFN-γ production.

Prostaglandins

Important local mediators of CMI dysfunction are prostaglandins, in particular, prostaglandin E_2. This substance is a potent immunosuppressant that is quickly synthesized in damaged tissue by macrophages and other cells, and it has been reported to increase systemically after surgery (Table 3; Fig. 2A). The administration of cyclooxygenase inhibitors to surgical patients results in blunted cytokine responses[83] and less suppression of CMI.[84] In rats, the same intervention reduced postoperative metastasis as well.[80,85,86]

Cytokines and Their Endogenous Antagonists

After surgery, local and systemic signals (e.g., lysates from damaged cells and stress hormones) stimulate monocytes and other cells to release cytokines.[44] As can be expected, in the vicinity of the wound, the cytokine response is primarily proinflammatory.[44,87] However, in the periphery, where the fate of metastases is determined, the predominant cytokines suppress inflammation and inhibit CMI.[44] Specifically, after major surgery, plasma levels of proinflammatory cytokines (TNF-α and IL-1, but not IL-6) remain relatively low (see Table 2 and Fig. 2A). Conversely, there is an immediate surge in plasma levels of IL-10 and IL-1rA, followed by increases in sIL-2r, sTNF-αr, and immunosuppressive acidic protein (Table 2 and Fig. 2C)—all known to downregulate CMI. In vitro, stimulated cytokine release by leukocytes shows a similar picture: after surgery, the production of TNF-α, IL-1β, IFN-γ, and IL-2 is arrested, whereas the production of IL-10 and IL-1rA is augmented (Table 4). The relative importance of each cytokine in suppressing CMI after surgery is still unclear, but in vitro neutralization of IL-10 can reduce the suppression of both human leukocyte antigen–DR expression[88] and lipopolysaccharide-induced TNF secretion.[89]

Overall, the suppression of peripheral CMI by surgery is unmistakable. Various aspects of surgery contribute to this adverse effect, which is mediated by a complex interaction among local factors, cytokines, neurotransmitters, hormones, and drugs.

DOES SURGERY FACILITATE THE DEVELOPMENT OF METASTASES, AND CAN SUPPRESSION OF CMI BE IMPLICATED?

If major surgery suppresses CMI and CMI limits metastasis, it would be tempting to conclude that surgery promotes metastasis. However, metastases are often refractory to immune surveillance by the time the tumor is removed, and the extent of immunosuppression clearly varies among surgical procedures. Furthermore, because other mechanisms may promote metastasis after surgery, the relative contribution of immunosuppression is unclear.

With regard to other sequelae of surgery, immunosuppression is clearly detrimental: it is thought to trigger life-threatening infections, such as pneumonia and sepsis, that are commonly observed after surgery.[90] Unlike postoperative infections, metastases typically develop for many months before detection, so the postoperative period of immunosuppression might be too brief to affect prognosis. We believe, however, that the effect of the immediate postoperative period on the fate of residual cancer cells is disproportionately large. On the one hand, surgery favors metastatic development by releasing tumor cells, reducing antiangiogenic factors, and inducing growth factors (see Mechanisms Suggested to Promote Metastases After Surgical Removal of the Primary Tumor, discussed previously). On the other hand, it obliterates the major source of metastasizing cells and drastically reduces the odds for the emergence of mutated immunoresistant cells. Surgery thus opens a narrow window of opportunity for CMI to eradicate residual malignant cells. This window starts closing as circulating tumor cells colonize target organs and permanently closes when metastases grow beyond a critical size,[91] establishing a microenvironment that is hostile to CMI. We therefore believe that shortly after surgery, even transitory immune dysfunction might permit neoplasms to enter the next stage of development and eventually form sizable metastases.

The prospect that postoperative immunosuppression promotes metastasis is alarming. Although these consid-

erations show that this hypothesis is feasible, it needs support from sound preclinical and clinical studies before it is seriously considered in cancer treatment.

Empirical Evidence From Animal Studies

Using a wide range of tumors and laboratory animals, many research groups have demonstrated that surgery can promote metastasis (see Tables 7 through 10 for summaries and references). They have also shown that the more invasive the surgery, the greater the effect (Table 7). Although most studies recorded colonization of target organs only after intravenous tumor inoculation, some simulated the clinical setting more accurately by operating on animals with primary tumors and assessing the formation of spontaneous metastasis.

A major question concerning these results is whether suppression of CMI accounts for these adverse effects of surgery. Addressing this question, several groups reported that surgery compromised both resistance to metastasis and immune functions such as NK and macrophage activity; two studies showed that minimally invasive surgery, which affected immunity mildly, promoted metastasis less. We reported that the period of immunosuppression coincides with the period of compromised resistance to metastasis.[7] These results, however, are merely correlative. Other studies indicated that immunostimulation before surgery can reduce metastasis (Table 8). These findings, although clinically important, also fall short of implicating immunosuppression because immunostimulation may have acted by merely compensating for the promotion of metastasis by nonimmune mechanisms. More indicative is a single study in which surgery increased metastasis in immunocompetent animals, but not in athymic ones. Finally, we and others succeeded in reducing metastasis by blocking the physiological responses to surgery that are known to suppress CMI (Table 9). In our study, laparotomy promoted the development of MADB106 metastases in the lungs and suppressed the cytotoxicity of pulmonary NK cells against this syngeneic tumor. A combination of a cyclooxygenase inhibitor and a β-adrener-

TABLE 7. *Promotion of metastasis by surgery: experiments demonstrating the role of the extent of tissue damage*

Tumor type and challenge mode	Genetic relation and species used	Oncological outcome	Immunological outcome	Type of surgery and comparison group	Ref
Sato lung cancer cells IV and IP	Syngeneic to Donryu rats	Mortality and lung metastases: ↑, ↑		Thoracotomy versus laparotomy versus control	229
AH 60C hepatocellular carcinoma into portal vein	Donryu rats	Liver metastases: ↑		Thoraco-laparotomy, versus laparotomy	230
B16 melanoma SC in flank	Syngeneic to C57BL/6 mice	Spontaneous metastasis: ↑, ↑ Tumor growth: ↑	NK activity: ↓, ↓ LAK activity: ↓	Laparotomy versus laparoscopy versus anesthesia	211, 231
BSp73ASML pancreatic adenocarcinoma SC in foot	Syngeneic to BDX rats	Spontaneous metastasis: ↑, ↑ Primary tumor: = Survival: =	IL-1β, IL-6, neopterin: ↑, ↑	Colectomy in laparotomy versus laparoscopy versus anesthesia	232
Line 26 colon adenocarcinoma IV	BALB/c mice	Lung metastases: ↑	IL-6 and TNF-α: ↑	Laparotomy versus laparoscopy or control	233
CC-531 colon adenocarcinoma IP solid or suspension	Syngeneic to WAG rats	Incidence and size of tumor: ↑		Laparotomy versus laparoscopy	234
CC-531 colon adenocarcinoma IP or into kidney	Syngeneic to WAG rats	IP growth: ↑, ↑ Renal growth: ↑		Laparotomy versus laparoscopy versus anesthesia	235
Ductal pancreatic carcinoma intra-pancreatic	Lewis rats	Local growth and spontaneous metastasis: = But if tumor is manipulated: ↑		Laparotomy versus laparoscopy ± tumor manipulation	236
MC2 mammary carcinoma intradermal on back	Syngeneic to C3H/He mice	Incidence and size of tumor: ↑, ↑		Cecal resection laparotomy versus laparoscopy versus anesthesia	237
MC2 mammary carcinoma intradermal on back	C3H/He mice or athymic mice	Size of tumor: ↑, ↑ in C3H/He: = in athymic: ↑		Laparotomy versus laparoscopy versus anesthesia	238

↑, ↑, increase in both comparisons listed under Type of Surgery and Comparison Group (e.g., laparotomy versus laparoscopy and laparoscopy versus anesthesia); ↑ and ↓, noticeable increase or decrease; =, no change; IV, intravenous; IP, intraperitoneal; SC, subcutaneous; NK, natural killer; LAK, lymphokine-activated killer; IL, interleukin; TNF, tumor necrosis factor.

TABLE 8. *Promotion of metastasis by surgery: experiments using immunostimulation*

Tumor type and challenge mode	Genetic relation and species used	Oncological outcome	Immunological outcome	Type of surgery and comparison group	Ameliorating intervention	Ref
Fibrosarcoma IV	Syngeneic to C57BL/6 mice	Lung metastases: ↑	MLR ↓ DTH ↓ NK activity: ↓	Amputation versus anesthesia or control	Thiabendazole	239
RCA colon adenocarcinoma IV	Syngeneic to F344 rats	Incidence and burden of liver metastasis: ↑	NK activity: ↓	Control versus laparotomy	Ketorolac (PG synthesis inhibitor) IL-2	85
MADB106 mammary adenocarcinoma IV	Syngeneic to F344 rats	Lung tumor retention: ↑	NK activity in Spleen: ↓ Blood: ↓ Lung: ↓	Laparotomy versus control	Poly I:C	102
MRMT-1 mammary carcinoma SC in flank	Female SD rats	Spontaneous pulmonary metastasis: ↑	PHA-induced blastogeneiss: ↓	Laparotomy versus control	OK-432	240
BSp73ASML pancreatic adenocarcinoma SC in foot	Syngeneic to BDX rats	Spontaneous metastasis: ↑	NK activity: ↓ ↑ Mϕ activity: ↓	Laparotomy versus control	Corynebacterium parvum	209
Line 26 Colon adenocarcinoma into hepatic vein	BALB/c or SCID mice	Liver metastases: ↑		Laparotomy only	IFN-gamma	241
Colon adenocarcinoma into hepatic portal vein	Syngeneic to F344 rats	Incidence of hepatic metastases: ↑		Celiotomy only	IL-12	242
Colon adenocarcinoma into hepatic portal vein	Syngeneic to F344 rats	Number of hepatic metastases, liver weight: ↑		Laparotomy only	Levamisole	243
Colon adenocarcinoma into hepatic portal vein	Syngeneic to F344 rats	Incidence of hepatic metastases, liver weight, morbidity: ↑		Laparotomy only	MVE-2	244

↑ and ↓, noticeable increase or decrease; IV, intravenous; SC, subcutaneous; NK, natural killer; IL, interleukin; SD, Sprague-Dawley; MLR, mixed lymphocyte response; DTH, delayed-type hypersensitivity; PHA, phytohemagglutinin; PG, prostaglandin; IFN, interferon; poly I-C, polyribonosinic acid-polyribocytidylic acid.

gic blocker efficiently ameliorated both adverse effects to surgery.[80]

Although well controlled and consistent in their findings, animal studies often inadequately model the human disease (see Empirical Evidence in Support of Antimetastatic Immunity, discussed previously). On top of this concern, they typically synchronize postoperative immunosuppression with the high-risk period of dissemination and probably suffer from "file drawer" publication bias. Thus, the results of such studies can be instructive only if they are corroborated by clinical studies.

Empirical Evidence From Human Studies

To the best of our knowledge, no clinical study has directly tested the hypothesis that surgery promotes metastatic development. This neglect is understandable in view of the tremendous ethical and methodological constraints. First, in most cases, patients with an operable primary tumor cannot be denied surgery. Thus, a nonoperated control group is not available for direct comparison. Second, oncological surgery not only exerts surgical stress, but also eliminates the primary tumor. These two opposing influences on metastatic disease are practically inseparable in humans. Finally, the latency between surgery and the detection of metastases is long and variable, making it hard to establish a temporal association between the two.

Nevertheless, clinical support for the hypothesis does exist, although in an indirect form. Although surgery itself is unavoidable, some of its immunosuppressive aspects are avoidable. These changes in clinical practice sometimes alleviate immunosuppression and reduce metastatic recurrence. Conversely, more immunosuppressive conditions often increase long-term recurrence rates. When examined in light of controlled experiments in animals, these observations clearly provide further support for the hypothesis, as indicated below.

First, as reviewed previously in Immunosuppressive Aspects of Surgery, general anesthesia have been shown in clinical studies to suppress CMI,[56] and animal models have indicated that they promote metastasis as well.[92,93] Regional anesthesia, however, often blocks immunosuppression.[58,59] In melanoma patients, a large-scale study[94]

TABLE 9. *Promotion of metastasis by surgery: experiments implicating certain mechanisms of action*

Tumor type and challenge mode	Genetic relation and species used	Oncological outcome	Immunological outcome	Type of surgery and comparison group	Ameliorating intervention	Ref
RCA colon adenocarcinoma IV	Syngeneic to F344 rats	Incidence and burden of liver metastasis: ↑	NK activity: ↓	Control versus laparotomy	Ketorolac (PG synthesis inhibitor) IL-2	85
AH 60C hepatocellular carcinoma into portal vein	Donryu rats	Liver metastases: ↑		Thoraco-laparotomy, versus laparotomy	EPC-K1 (radical scavenger)	230
MRMT-1 mammary carcinoma IV	Female SD rats	Lung metastases: ↑	Peripheral lymphocytes: ↓ Thymocyte apoptosis: ↑	Laparotomy versus anesthesia or control	Adrenalectomy, metyrapone	72
MADB106 mammary adenocarcinoma IV	Syngeneic to F344 rats	Lung metastases: ↑ Lung tumor retention: ↑	NK activity in blood: ↓	Laparotomy versus anesthesia or control	Spinal block, systemic morphine	95
MADB106 mammary adenocarcinoma IV	Syngeneic to F344 rats	Lung metastasis: ↑ Lung tumor retention: ↑	NK activity in blood: ↓	Laparotomy versus anesthesia or control	Fentanil (analgesic) Spinal block	57
MADB106 mammary adenocarcinoma IV	Syngeneic to F344 rats	Lung metastasis: ↑ Lung tumor retention: ↑	NK activity in blood: ↓	Laparotomy versus control	Morphine	245
MADB106 mammary adenocarcinoma IV	Syngeneic to F344 rats	Lung tumor retention: ↑	NK activity in: Spleen: ↓ Blood: ↓ Lung: ↓	Laparotomy versus control	Nadolol (β-blocker), indomethacin (PG synthesis inhibitor)	80

↑ and ↓, noticeable increase or decrease; IV, intravenous; NK, natural killer; PG, prostaglandin; SD, Sprague-Dawley.

recently identified local anesthesia (instead of general anesthesia) as an independent favorable prognostic factor that resulted in less distant recurrence. Correspondingly, animal studies indicated that epidural block supplementing general anesthesia reduces the promotion of metastasis by surgery.[57,95]

Second, blood transfusion during surgery is immunosuppressive.[48] The consequences of this immunosuppres-

TABLE 10. *Promotion of metastasis by surgery: other experiments*

Tumor type and challenge mode	Genetic relation and species used	Oncological outcome	Immunological outcome	Type of surgery and comparison group	Ref
MADB106 mammary adenocarcinoma IV	Syngeneic to F344 rats	Lung tumor retention: ↑	NK activity in Spleen: ↓ Blood: ↓	Laparotomy versus control	7
Colon adenocarcinoma IP or SC	Syngeneic to F344 rats	Incidence and size of tumor: ↑		Laparotomy versus control	3
MRMT-1 mammary carcinoma into portal vein	Female SD rats	Size and number of liver metastases: ↑	NK activity in liver: ↓ PBMCs: =	Laparotomy + intestine resection versus control	246
MCA-105 sarcoma IP	Syngeneic to C57BL mice	Tumor growth: ↑		Laparotomy versus back skin incision or control	6, 247
3LL Lewis lung carcinoma into footpad	Syngeneic to BALB/c mice	Spontaneous metastases: ↑	NK activity: ↓	Amputation versus control	248, 249
MtLn3 adenocarcinoma IP	Syngeneic to F344 rats	Peritoneal nodules: ↑		Laparoscopy versus control	250
Walker 256 carcinoma IV	Holtzman rats	Lung and hepatic tumor retention: ↑	Macrophage phagocytosis and opsonin levels: ↓	Laparotomy versus anesthesia	251
YAC-1 lymphoma and melanoma IV	BALB/c mice	Lung tumor retention: ↑	NK activity: ↓	Laparotomy versus anesthesia	210
T241 sarcoma SC in foot	Syngeneic to C57BL/6 mice	Spontaneous pulmonary metastasis: ↑		Amputation versus control	252

↑ and ↓, noticeable increase or decrease; =, no change; IV, intravenous; SC, subcutaneous; IP, intraperitoneal; SD, Sprague-Dawley; NK, natural killer; PBMC, peripheral blood mononuclear cell.

sion for cancer patients might be grim. Transfusion is clearly associated with higher recurrence rates. However, it has long been disputed whether the transfusion itself promotes metastasis or whether it is only the circumstances requiring it. More than 60 retrospective studies and 3 clinical trials have been conducted in different malignancies; most concluded that transfusion was an independent risk factor for recurrence.[48] Animal studies suggest that allogenic blood transfusion per se can indeed promote metastasis by suppressing immunity.[49]

Third, in cancer patients who have large bowl obstructions, surgeons occasionally resorted to a staged procedure: first a colostomy to relieve the obstruction and then a colectomy to excise the tumor. This double insult resulted in a higher metastatic recurrence.[2] Later studies corroborated these results in animal models.[3]

Finally, minimally invasive surgeries are markedly less immunosuppressive than standard oncological operations.[8] Animal models additionally showed that laparoscopy results in less metastasis than does comparable laparotomy, presumably through less disruption of CMI (see Tables 7–10).

Because the minimally invasive approach has some disadvantages in surgical oncology (e.g., suboptimal inspection and isolation of the tumor and a risk of porthole metastases), its introduction into clinical practice has been hesitant. However, initial data suggest that it might be beneficial if it replaces highly immunosuppressive operations. Although minimally invasive techniques have yet to show dramatic long-term benefits over conventional abdominal surgery,[8] they seem to reduce recurrence when substituting for highly invasive thoracic surgery. Retrospective data from several centers suggest that using video-assisted thoracoscopic lobectomy may have increased the survival rates of patients with stage I lung carcinoma from the historical records of approximately 70% to an estimated 90% (at 5 years).[96] A recent randomized trial[97] reported a corresponding decrease (from 14% to 4%) in the incidence of metastasis at 5 years. Regrettably, these studies are too small to be conclusive. As for the mechanisms involved, video-assisted thoracoscopic lobectomy elicits milder sympathetic[98] and cytokine[99] responses and less lymphopenia[100] but fails to prevent the release of tumor cells into the circulation.[101] Reduced immunosuppression may therefore underlie its emerging advantages.

INTEGRATION AND CLINICAL IMPLICATIONS

After critically reviewing the literature, we believe that the following conclusions can be drawn safely: the immune system can and does react to cancer, although its efficacy in limiting postoperative metastasis varies with the type and the stage of the tumor. Major surgical procedures transiently but unequivocally suppress CMI and do so through multiple pathways. Findings in animals repeatedly demonstrate that surgical stress can promote experimental metastasis, particularly by suppressing CMI, but evidence in humans is still indirect.

All considered, the hypothesis that surgery and immunosuppression promote metastasis has gained substantial support. It seems that practitioners should now incorporate this factor into the broader array of medical considerations when planning cancer treatment. We believe that immunological status will become increasingly important as techniques for early detection bring more patients to surgery before their tumors become immunoresistant.

We now sufficiently understand the critical aspects of surgery and the mechanisms of immunosuppression to evaluate specific prophylactic measures. These are listed below and justified theoretically and empirically in the preceding sections.

Adopting Clinical and Surgical Procedures That Are Less Immunosuppressive

Most of the following recommendations can be readily adopted because they are considered good practice in general and have proven advantages in reducing other adverse effects of surgery. Thus, caregivers should offer the patients attentive medical consultation and psychological support to minimize perioperative psychological distress. Anesthesiologists should prevent inadvertent hypothermia and can consult current literature (e.g., Galley et al.[56]) to select less immunosuppressive analgesics and anesthetics. In certain circumstances, general anesthesia can be replaced or supplemented by spinal block. Blood loss should be minimized, and blood transfusion should be used only when necessary. On further clinical justification, autologous or leukodepleted blood can be used. Still debated, but potentially beneficial, is the use of minimally invasive surgery in early stages of cancer. Currently this approach should be attempted only within clinical trials.

Blocking Physiological Responses That Mediate Immunosuppression

The physiological and psychological stress response to surgery can be blunted by using specific blockers of the sympathetic nervous system, the HPA axis, or the endogenous opioid system. Anxiolytic drugs may also be considered. Complete perioperative pain management, preferably through neuroaxial block with local anesthetics, should be considered to reduce immunosuppressive

neuroendocrine responses. Inhibition of prostaglandin synthesis and neutralization of IL-10 also hold promise. All of these measures were suggested by animal studies to reduce the suppression of immunity or the promotion of metastasis after surgery, but most demand further preclinical studies before they are taken into randomized trials.

Counteracting Immunosuppression Through Perioperative Immunotherapy

It is still unknown whether enhancement of CMI would reduce the perioperative risk of metastases if applied before or during surgery. The wide range of potential strategies includes nonspecific immunostimulation (e.g., bacille Calmette-Guérin or poly I-C [polyriboinosinic acid-polyribocytidylic acid]), cytokine therapy (e.g., IFN-γ, IL-2, and IL-12), adoptive immunotherapy (e.g., lymphokine-activated killer or tumor-infiltrating lymphocyte), and various methods of vaccination (e.g. peptides, DNA, or dendritic cells). Although antitumor immunotherapy is a very active field of clinical research, very few studies have been conducted in the perioperative context. In our experience, even very low doses of poly I-C used perioperatively in rats can dramatically restrict metastatic development by preserving critical immune functions.[102]

Suggested Guidelines for Relevant Clinical Trials

We believe that a number of principles should guide investigators as they try to improve the prognosis of surgical cancer patients: (1) Randomized clinical trials should initially concentrate on malignancies that are curable by resection but still have a substantial recurrence rate, and on highly invasive surgical procedures known to be more immunosuppressive (e.g., thoracic surgery). (2) Prophylactic measures should ideally start well before the operation and terminate after complete recovery from surgery. (3) Clinical records of blood transfusions, surgical and anesthetic techniques, and body temperature should be preserved. (4) Immunological investigation should focus on responses to the autologous tumor, such as lymphocyte cytotoxicity against it or lymphocyte proliferation and delayed-type hypersensitivity responses to its antigens. The available literature, although limited, suggests that these criteria are more prognostic than others. (5) Trials should assess not only perioperative immunocompetence, but also long-term patterns of tumor recurrence. Shorter-term predictors of recurrence (e.g., polymerase chain reaction–based diagnosis of residual disease) can be used as interim readouts, facilitating larger clinical trials that require long follow-up.

It is our belief that adopting these recommendations holds promise for improving the prognosis of cancer patients. Evaluating possible prophylactic measures in clinical trials would, for the first time, indicate whether the adverse effects of immunosuppressive surgery that are evident in animal models hold true in cancer patients.

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