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Fundamental Principles of Cancer Biology: Does It Have Relevance to the Perioperative Period?

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Abstract Malignant tumors are characterized by their ability to metastasize, which is the main cause of cancer-related mortality. Besides intrinsic alternations in cancer cells, the tumor microenvironment plays a pivotal role in tumor growth and metastasis. Ample evidence suggests that the perioperative period and the excision of the primary tumor can promote the development of metastases and can influence long-term cancer patient outcomes. The role of cancer biology and its impact on the perioperative period are of increasing interest. This review will present evidence regarding fundamental principles of cancer biology, especially tumor microenvironment, and discuss new therapeutic opportunities in the perioperative timeframe. We will also discuss the regulatory signaling that could be relevant to various aspects of surgery and surgical responses, which could facilitate the metastatic process by directly or indirectly affecting malignant tissues and the tumor microenvironment. We address the influences of surgery-related stress, anesthetic and analgesic agents, blood transfusion, hypothermia, and β-adrenergic blockade administration on tumor growth and metastasis. Through an improved understanding of these processes, we will provide suggestions for potential new perioperative approaches aimed at improving treatment outcomes of cancer patients.

Keywords Perioperative · Cancer biology · Therapeutics

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Introduction

Cancer is known to be highly complex and characterized several hallmarks including unrelenting proliferation, avoidance of growth suppressive signals, apoptotic resistance, neovascularization, and acquired capabilities for invasion and metastasis. Conceptual advances over the past several years have resulted in the addition of two additional hallmarks which include reprogramming of cellular energy metabolism and immune escape [1, 2••]. The "normal" neighboring cells (e.g., fibroblasts, endothelial, nerve, and immune cells) comprise the tumor microenvironment, which contribute to the acquisition of hallmarks of cancer [1]. Among each of these, the two felt to be most significant in the perioperative period, include induction of angiogenesis and immune escape, both of which are mediated by the surgical stress response. The influence of the non-malignant, stromal cells of tumor microenvironment is now widely appreciated, with these cells becoming increasingly recognized as major determinants of cancer biology. The critical cell lineages in this context are tumor-associated macrophages (TAM), fibroblasts, and inflammatory cells, all which commonly interact with the tumor cells through a variety of secreted factors. In addition to their impact on tumor growth, the tumor microenvironment has also been shown to affect tumor initiation, metastasis,

and tumor therapy [3]. Decades of research has suggested that the perioperative period and surgical excision of the primary tumor can have an impact on the metastatic process and even on patient survival [4••]. Here, we review contemporary knowledge of the tumor microenvironment and how the events during perioperative care can influence the microenvironment. On the basis of recent discoveries, we will also discuss new opportunities for therapeutic applications in the perioperative timeframe.

Tumor Microenvironment

Characteristics of the Tumor Microenvironment

The interplay between cancer cells and their local environment is crucial for regulating the malignant features of cancer cells. The tumor microenvironment is composed of tumor, immune, endothelial, fibroblast, nerve, and other cells, which collectively orchestrate tumor growth, invasion, and metastasis. We will first briefly describe the contributions of some of these cell types in the tumor microenvironment to malignant biology and also discuss the regulatory signaling that controls their individual and collective functions.

Tumor-Associated Macrophages (TAMs)

Macrophages are among the more prevalent cell types in the tumor microenvironment. Macrophages arise from peripheral blood monocytes, which are derived from bone marrow progenitors and then enter circulation. Macrophages have several subtypes and their phenotype can vary depending on the microenvironment. Two states for polarized macrophages have been described including M1 (type I or classically activated) and M2 (type II or alternatively activated) subsets [5]; these are likely part of a continuum rather than absolute discreet classifications. In general, TAMs have properties of M2-activated cells through the influence of multiple cytokines (interleukin-4, interleukin-10, etc.) in the tumor microenvironment. Given that there is likely a continuum of activation, newer classification refers to macrophages as pro-inflammatory or pro-angiogenic [6]. Macrophages have been shown to play key roles in solid tumor development via a vast array of cytokines, chemokines, and inflammatory mediators that can directly influence the behavior of tumor cells [7]. Although there are few reported exceptions, it should be recognized that the clinical and experimental data largely support the hypothesis that macrophages promote malignancy. Clinical studies make a strong case that increased macrophage density in tumor stroma correlates with poor clinical outcomes in different types of solid tumors [8–10]. Moreover, recent studies have revealed that TAMs promote malignant progression based on their capacity to enhance angiogenic, invasive, and metastatic programming of neoplastic tissues [11–15].

Tumor-Infiltrating Lymphocytes

Tumor-infiltrating lymphocytes (TILs) in tumor microenvironment were described about 30 years ago. As a tumor develops, the body elicits an immune response where lymphocytes migrate to the tumor in an attempt to fight the cancer. Studies with large cohorts of human tumors have established that TILs are found in tumors with varying frequency, and TILs are strongly associated with disease free and overall survival for many cancer types, which suggests that TILs likely play biologically critical roles in restricting tumor growth [1, 16–19]. It is important to distinguish that there are different types of T lymphocytes, which have different functions in the tumor microenvironment. T cells are fully differentiated immune cells presented in tumor stroma. Among them

- CD8+ cytotoxic T lymphocytes (CTLs) are directly capable of killing tumor cells [20],
- CD4+ T helper lymphocytes (Th) are a heterogeneous cytokine-secreting class of T lymphocytes: T helper type 1 lymphocytes (Th1) have a crucial role in activating CTLs and T helper type 2 lymphocytes (Th2) stimulate humoral immunity.
- Natural killer (NK) cells have a critical role in tumor cell destruction and in the restriction of tumor growth, and reduced NK cell activity has been shown to be associated with higher cancer mortality in patients with cancer [21].

Tumor infiltration by Th1 and CTL cells, together with the presence of cytokines such as IFN-γ and tumor necrosis factor-α (TNF-α), has been associated with improved prognosis of patients with many different cancers [22].

In addition to the effector immune cells, multiple cell types are known to contribute to tumor-mediated immune suppression, including regulatory T cells (Treg), type 2 NK T cells, TAMs, and myeloid-derived suppressor cells (MDSCs). In cancer patients and animal tumor models, these suppressor cells (e.g., Tregs and MDSCs) accumulate in the tumor microenvironment and suppress innate and adaptive anticancer immunity, which foster disease development and metastasis [8]. CD4+CD25+FoxP3+ Tregs are a subpopulation of T cells characterized by the expression of FoxP3, which is essential for their development and function. Tregs control immune responses by suppressing conventional effector T lymphocytes, NK cells, dendritic cells (DCs), or macrophages [23]. Tregs are

also critical for the maintenance of self-tolerance. Evidence shows that Tregs play a central role in immune tolerance by inhibiting effector cytotoxic T cell lymphocytes. In the tumor microenvironment, a large number of Tregs accumulate by several possible mechanisms, including recruitment of naive FoxP3+ Tregs and induction of CD4+ T helper cells to Tregs [24, 25]. MDSCs are a variety of partially differentiated myeloid progenitors that have been identified in tumors, which have been shown to antagonize tumor senescence and suppress CTL activity [26, 27]. Tumor- and host-secreted factors can induce and promote the accumulation of MDSCs that down-regulate immune surveillance and antitumor immunity, thereby facilitating tumor growth [28].

Endothelial Cells

Tumor vascularization is a critical step for tumor growth and progression. Endothelial cells (ECs) are a major component of the angiogenic process and modulate a diverse spectrum of pathophysiologic processes in normal and hyperplastic tissues. Tumor-associated ECs form angiogenic vessels to provide nutritional support to the growing tumor [29, 30]. Tumor-associated ECs play a central role in controlling leukocyte recruitment, tumor cell behavior, and metastasis formation because they are the interface for circulating blood cells, tumor cells, and the extracellular matrix. In the tumor microenvironment, tumor cells produce a variety of pro-angiogenic factors, including VEGF, to promote tumor angiogenesis, tumor cell motility, and metastasis.

Cancer-Associated Fibroblasts

Fibroblasts are the most abundant cell type in connective tissues and they form the structural framework by secreting extracellular matrix components [31]. Cancer-associated fibroblasts (CAFs) are abundant in the stroma of many tumors, and serve as one of the most crucial components of the tumor microenvironment. CAFs are mainly responsible for the production of extracellular matrix proteins and retain a major role in extracellular matrix remodeling. CAFs secrete growth factors and cytokines that produce oncogenic signals. Compared to normal fibroblasts, CAFs promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion [32]. An understanding of this mutual relationship would enable us to treat cancer patients by targeting CAFs.

The ability to modify the environment is an important property of cancer cells that likely allows acquisition of some of the hallmarks required for tumor growth and metastasis. A better understanding of these processes should lead to innovative strategies for disrupting the complex crosstalk between the cancer cells and host cells.

Factors Influencing Loco-Regional and Distant Metastatic Disease

Metastasis is the dominant cause of morbidity and death in cancer patients. Increased evidence from animal and human studies has showed that surgery and other perioperative processes can promote metastasis. Recently, researchers have increasingly identified several underlying perioperative factors that play a pivotal role in influencing loco-regional and distant site metastatic disease.

Surgical Aspects Affecting Metastasis

While surgery is a major component of cancer care, the perioperative period is also a time of intense stress that could actually lead to undesired tumor growth and progression. Such concerns have prompted investigation of underlying mechanisms and for innovative therapeutic opportunities to maximize patient benefit. Here, we will summarize the potential impact of various aspects of perioperative care.

Anesthetic Approaches

Studies indicate that the anesthetic and/or analgesic approach used during surgery and the perioperative period may influence cancer recurrence [33, 34]. Certain perioperative anesthetics and analgesics have the potential to impact cancer outcomes [35–38]. Anesthetic agents such as ketamine, thiopental, and halothane have been shown to suppress NK cell activity, increasing the likelihood of tumor metastases [39]. Both nitrous oxide and halothane can accelerate postoperative progression of spontaneous lung metastases in pre-clinical lung and melanoma models [40]. The mechanism of action for tumor growth has been postulated to be both direct and indirect effects of the anesthetic agents themselves. The indirect effects include impact on the neuroendocrine pathways and modulators of cell-mediated immunity. In contrast, direct effects include upregulation of hypoxia-inducible factor-1 (HIF-1) gene expression by inhalational anesthetics. Both pathways contribute to cancer recurrence [41].

In many surgical settings, regional and general anesthesia are used jointly. Using a combined modality approach would be expected to reduce the requirement for inhaled general anesthetics. Regional anesthesia dampens the neuroendocrine stress response and decreases perioperative immune suppression by impacting NK cell activity [38]. Pre-clinical studies indicate that regional anesthesia

in combination with optimal postoperative analgesia yields reduced metastatic burden post-operatively. Retrospective clinical studies confirm that regional analgesia may reduce recurrence risk after cancer surgery [42]. Meta-analyses demonstrate that inhalation anesthetics such as ketamine, thiopental, and halothane might influence tumor progression by promoting cancer cell proliferation and angiogenesis [35].

Surgical Approach

During the perioperative period, different surgical techniques may influence the oncological results, especially the laparoscopic versus open approaches. Surgical trauma at the time of cancer resection elicits an acute phase response [43]. The acute phase response is a transient reaction to surgery that accompanies a period of release of tumor cells, increased angiogenesis, an imbalance of growth stimulatory and inhibitory factors, and suppression of the host cell-mediated immunity [44]. Collectively, this response to surgery can leave the host vulnerable to the propagation of metastases. The extent of the acute phase response is directly proportional to the degree of surgical trauma [45, 46].

Surgical oncologic delivery of care has been revolutionized with the introduction of minimally invasive surgical techniques. Minimally invasive surgery is known to reduce the degree of surgical trauma that occurs during the postoperative period. For example, colorectal resection via conventional laparotomy or mini-laparotomy approach was compared for potential impact on host immune function [47]. Longitudinal blood collections pre- and post-operatively were obtained to evaluate for differences in immune mediators and inflammatory cytokines. Lymphocyte counts remained lower in the conventional and mini-laparotomy groups but had returned to baseline in the laparoscopy group 5 days post-operatively. Furthermore, postoperative inflammatory cytokines serum concentrations were significantly lower in the laparoscopic compared to conventional patients. The down-stream impact of a singular perioperative event on risk of disease metastases and recurrences remains to be fully elucidated clinically; however, pre-clinical data point to a biologically meaningful impact. Tai et al. utilized an animal model of spontaneously metastasizing tumors and surgical stress to demonstrate the potential impact of surgical stress on tumor growth. In this model, 4T1 breast cancer cells were inoculated into the mammary fat pad of mice. Fourteen days post-tumor implantation, complete resection of the primary tumor was performed and a subset of mice were exposed to abdominal nephrectomy. Numbers of lung nodules were then quantified. When oncolytic virus immune stimulation is administered pre-operatively, prevention of lung metastases was noted suggesting a correlation between immune suppression and tumor growth and metastases in the perioperative period [48]. Direct clinical translation remains to be determined. Surgery has been shown to promote the formation of fibrin and platelet clots, thereby impairing NK cell-mediated tumor cell clearance, with a resultant increase in metastases [49]. Work done in our own laboratory has demonstrated the impact of surgery on tumor growth in an orthotopic model of ovarian cancer. Mice inoculated with tumor cells and then exposed to mastectomy or laparotomy had significantly increased tumor growth compared to those treated with anesthesia alone with a mechanism of action found to be mediated via adrenergic receptors and increased angiogenesis [37]. However, clinical evidence for an improved endocrine and immune profile following laparoscopy has been less convincing in several large randomized clinical trials. Although these studies have demonstrated lower levels of IL-6, the alterations in other key cytokines, number of circulating NK cells, and the hormonal stress response are less clear and may be related to the complex nature of advanced laparoscopic procedures in oncology [4••, 50–52].

The Surgical Stress Response

The stress response is defined by the hormonal and metabolic changes that follow surgery including activation of the sympathetic nervous system, the endocrine "stress response," and the subsequent immunological and hematological changes [53]. Collectively, this response after surgery can augment the healing process, but over-activity or under-activity of host defense mechanisms may lead to unintended consequences [21]. Numerous studies indicate that stress is considered a contributor to cancer development [54]. Levels of stress biomarkers, primarily epinephrine and norepinephrine, are elevated in the perioperative period [55]. In the perioperative period, the persistent activation of the hypothalamic–pituitary–adrenal axis can contribute to the progression of cancer [54]. The surgical stress response may provide the optimal milieu for persistence of minimal residual disease post-operatively. Furthermore, surgery has been suggested to accelerate the growth of preexisting micro-metastases and to promote the establishment of new metastases [56]. Both pre-clinical and clinical studies have shown that surgery induces suppression of anti-metastatic cell-mediated immunity at a critical period, which may lead to immune escape of micrometastatic disease [57]. The release of catecholamines and pro-inflammatory cytokines as a result of surgical stress is believed to promote cancer progression [58]. The depression of the immune system occurs within hours of surgery, lasts for several days, and is proportional to the extent of surgical trauma [59]. The underlying mechanisms of postoperative immune suppression have not been completely established. The surgical stress response with

associated immune shifts towards NK suppression, as well as Th2 and TAM dominance, may provide optimal conditions for the persistence of residual disease and recurrence [36]. However, there is limited understanding of the longer-term impact of perioperative immune alterations on patients' cancer and survival outcomes.

Perioperative Factors that Influence Tumor Growth

Other factors such as blood transfusion, pain, and hypothermia are also potentially important perioperative factors to consider when evaluating the impact of surgery on tumor growth and metastases [21, 60, 61]. Retrospective studies implicate neuroendocrine mediators, such as catecholamines and prostaglandins. Many different malignancies express receptors for catecholamines [62] and prostaglandins [63] exerting a direct tumoral effect, which includes promotion of tumor cell proliferation [64], adhesion [65], migration [66] and invasion [64], resistance to apoptosis and anoikis [67, 68], as well as secretion of pro-angiogenic factors such as vascular endothelial growth factor [69]. Again the indirect mechanism of suppression of perioperative anti-metastatic immunity exists [44]. Perioperative pain management may also have an effect on patient outcomes due to its interplay with this component of perioperative tumor growth in that pain and nociception are associated with catecholamine secretion [70].

A meta-analysis aimed at evaluating the role of perioperative blood transfusion on colorectal cancer recurrence demonstrated that perioperative blood transfusions have a detrimental effect on curable colorectal cancers [60, 71]. Direct causal relationships are difficult to draw due to differences in disease site and stages of disease included in this analysis. Nevertheless, it is important to carefully consider the indications for perioperative blood transfusions.

Surgery commonly results in mild perioperative hypothermia, which has immunosuppressive effects, and has been shown to delay healing and predispose patients to wound infections [72]. Hypothermia also causes increased blood loss and predisposes patients to transfusion of blood products [73]. Additionally, hypothermia in combination with surgery and general anesthesia has been shown to lead to a reduction in NK cell activity, and an increase in lung tumor retention and metastasis [74]. Therefore, maintaining normothermia is important for perioperative care of cancer patients.

Interventions Directed at Improving Perioperative Outcomes

As noted above, excess catecholamine and prostaglandin release in the perioperative period results in significant impairment of immune responses. Blockade of catecholamines and prostaglandins could be an effective therapeutic approach targeted at improving patient outcomes. Preclinically, the use of nonselective β-adrenergic blockers and selective COX2-inhibitors has resulted in reduced endocrine and angiogenic perturbations, improved immune profiles, and an attenuated surgical stress response [4••]. Furthermore, some studies suggest that regional anesthesia can reduce the sympathetic response and improve oncologic outcomes.

Statins are commonly used as lipid-lowering drugs. Several of these drugs function by inhibiting the enzyme HMG-CoA, which plays a role in cholesterol formation in the liver. Omega-3 fatty acids may have cancer chemo-preventative and anti-inflammatory properties. Both of these drugs, in some studies, are associated with reduced cancer-related mortality, reduced postoperative immune suppression and infection (omega 3-fatty acids), and decreased tumor proliferation and increased apoptotic markers (statins) [75].

Given the noted benefits regarding modifications in the delivery of post-surgical care, results from numerous studies have been integrated into enhanced recovery after surgery (ERAS) guidelines in various surgical subspecialties [76]. ERAS is an evidenced-based multidisciplinary approach to perioperative care delivery aimed at improving early recovery of patients undergoing major surgery. Components of ERAS programs include multimodal analgesia and anesthesia in the perioperative period, early feeding and ambulation, goal-directed fluid therapy, as well as avoidance of routine drain or nasogastric tube placement. Although the oncologic benefits of such a program remain to be realized, initial studies have demonstrated a 50 % reduction in postoperative complications and a 30 % reduction in hospital length of stay [4••]. This per se helps keep patients on their cancer journey with timely return to intended adjuvant therapies, and may thereby indirectly improve cancer outcomes by this mechanism.

Conclusions

Growing evidence suggests that events and care in the perioperative period can influence tumor biology and the microenvironment. As such, long-term oncological outcomes may be impacted. Therapies directed at the perioperative period (e.g., β-adrenergic blockade and/or COX2 inhibitors) may represent opportunities to reduce the risk of metastasis and/or growth of minimal residual disease. Furthermore, perioperative interventions that work towards mediating the immune and neuro-hormonal milieu of the perioperative period should be the focus of perioperative care teams. These include careful selection of anesthetic agents, avoidance of hypothermia, restrictive blood

management policies, and adequate pain management. The possibility that perioperative management may alter the rate or incidence of cancer recurrence represents another important component of care during the entire cancer continuum.

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Compliance with Ethics Guidelines

Conflict of Interest Li Jiang, Alpa M. Nick, and Anil K. Sood declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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