Review Article
The effects of anesthetics on tumor progression

Lifang Mao[1], Suizhen Lin[2], Jun Lin[1]

[1]Department of Anesthesiology, SUNY Downstate Medical Center, 450 Clarkson Avenue, Box 6, Brooklyn, New York 11203-2098, USA; [2]Guangzhou Cellproteck Pharmaceutical CO., Ltd, 3 Lanyue Road, Science City, Guangzhou 510663, P.R China

Abstract: More and more cancer patients receive surgery and chronic pain control. Cell-mediated immunosuppression from surgical stress renders perioperative period a vulnerable period for tumor metastasis. Retrospective studies suggest that regional anesthesia reduces the risk of tumor metastasis and recurrence. This benefit may be due to the attenuation of immunosuppression by regional anesthesia. On the other hand, accumulating evidence points to a direct role of anesthetics in tumor progression. A variety of malignancies exhibit increased activity of voltage-gated sodium channels. Blockade of these channels by local anesthetics may help inhibit tumor progression. Opioids promote angiogenesis, cancer cell proliferation and metastasis. It will be interesting to examine the therapeutic potential of peripheral opioid antagonists against malignancy. Volatile anesthetics are organ-protective against hypoxia, however; this very protective mechanism may lead to tumor growth and poor prognosis. In this review, we examine the direct effects of anesthetics in tumor progression in hope that a thorough understanding will help to select the optimal anesthetic regimens for better outcomes in cancer patients.

Keywords: Metastasis, recurrence, regional anesthesia, local anesthetics, voltage-gated sodium channels, opioids, volatile anesthetics

Introduction

Anesthesiologists treat cancer patients in two main areas: perioperative anesthesia/analgesia for surgical tumor removal and management of chronic cancer pain. As more and more cancer patients receive surgery and cancer pain control, a comprehensive understanding of potential implication of anesthetics in tumor biology will significantly impact the long term well-being of cancer patients.

Surgery is the most effective treatment for solid tumors; however, surgery poses significant risks for tumor spreading. While invisible at macro-level, micrometastases may have already existed at the time of surgery. Tumor manipulation during surgery will lead to the release of tumor cells into vascular and lymphatic circulations [1-3]. Positive perioperative circulating tumor cells are an independent risk factor for poor prognosis [3-5]. Surgical stress, together with subsequent neuroendocrine,

metabolic, inflammatory responses, results in significant suppression of cell-mediated immunity [6]. The combination of compromised host immune defense and tumor seeding renders the perioperative period particularly susceptible to tumor metastasis.

Retrospective studies suggest a beneficial role of regional anesthesia in reducing tumor recurrence in various cancers [7, 8]. If these observations are true, it is important to clarify whether the anesthetic techniques per se, anesthetic agents, pain control regimens, or all of them contribute to this favorable outcome.

The purpose of this review is 1) to summarize the current body of evidence for the relationship between anesthesia and oncological outcome; 2) to examine the direct roles of anesthetics in tumor invasion and metastasis with emphasis on molecular and cellular biology; 3) to identify appropriate direction for future research and clinical management.

Clinical outcome

A number of retrospective studies suggest that regional anesthesia reduces tumor metastasis and recurrence. A chart review of 129 patients with breast cancer undergoing mastectomy and lymph node clearance shows that paravertebral block reduces cancer recurrence by a factor of 4 compared to systemic morphine for postoperative analgesia [9]. Similar observations are made from patients with prostate cancer undergoing prostatectomy and from patients undergoing colon cancer surgery [10, 11]. However, several follow-up retrospective studies do not find apparent benefit of epidural analgesia compared to systemic opioid administration for tumor recurrence [6]. A randomized clinical trial examines the effect of epidural block on a variety of abdominal cancer surgeries and finds no difference in the duration of disease-free survival with epidural block [12]. In a more recent study, patients with colorectal carcinoma either receive epidural/spinal analgesia or morphine patient-controlled analgesia for postoperative pain after abdominal laparoscopic surgeries; no overall survival benefit is observed in the regional analgesia group [13].

Possible explanations for this discrepancy are different tumor types, patient demographics, variable anesthesia protocols such as the usage of supplemental opioids with regional anesthesia, and small sample sizes. As a matter of fact, for the above-mentioned colon cancer patients, the beneficial effect of survival is only observed in the first 1.5 years in patients without macro-metastasis at the time of surgery [11]. Gottschalk *et al.* have detected a favorable tendency of epidural analgesia in elderly patients with colorectal carcinoma recurrence, although the result is not statistically significant [14]. With a larger patient sample, the difference of recurrence may be significant.

Studies to examine whether different approaches of chronic pain management affect tumor progression are very limited. Optimal pain control significantly improves the quality of life for the terminally ill cancer patients. Patients with unresectable pancreatic cancer, when receiving alcohol splanchnicectomy, achieve a marked improvement in survival [15]. A randomized trial of 100 patients with pancreatic cancer shows a better tendency of survival for patients who receive neurolytic celiac block than these treated with systemic analgesia [16]. In patient with refractory oncological pain, intrathecal pain therapy with implantable delivery system provides better six-month survival than comprehensive medical management [17]. Do these results give a hint that chronic regional pain regimen is better than systemic approach to curb tumor progression? The situation is very complicated: the improved survival may be due to better pain control and less pain-induced immunosuppression, less drug toxicity due to decreased systemic opioid usage, and improved nutrition.

Anesthetic techniques on cell-mediated immunity

The interaction among anesthesia, malignancy, and the immune system has been extensively discussed [7, 18] and is beyond the scope of this review. A leading theory for the beneficial effect of regional anesthesia on tumor progression is that regional block attenuates perioperative immunosuppression. During a major surgery, there is a measurable decrease of cytokines for cell-mediated immunity such as IL-2, IL-12, and IFN-γ. The number of circulating natural killer (NK) cells, cytotoxic T lymphocytes, and the ratio of T-helper 1 (Th1) to T-helper 2 (Th2) are also significantly reduced [7]. Regional anesthesia blocks the afferent sensory transmission, efferent sympathetic activation, and the associated endocrine and metabolic responses. Intraoperative use of regional anesthesia lowers the plasma levels of cortisol [19] and catecholamines [20]. Under spinal analgesia, the function of NK cells and the balance of Th1/Th2 are better preserved [21]. In addition, most intravenous and volatile anesthetics are immunosuppressors [22]; regional anesthesia decreases systemic opioid use and the amount of general anesthetics required. All these aspects of regional anesthesia help to maintain NK function and cell-mediated immunity, the first line and the most important defense against malignancy.

Anesthetics and cancer cell biology

The effect of anesthetics on tumor progression is two-folded: most anesthetics are immunosuppressive and this renders patients more liable to tumor progression [23]; recently, accumulating evidence points to a direct role of

Table 1. Anesthesia Factors and Tumor Progression

Anesthetic factors	Potential effects on tumors	Cell-mediate Immunity [7, 18]	Proposed Mechanisms
Regional anesthesia	Inhibition	Attenuate immuno-suppression	Decrease perioperative stress responses Decrease systemic opioid use Decrease the use of volatile agents
Local anesthetics	Inhibition	Attenuate immuno-suppression	Act through VGSC to inhibit metastasis [24-26] Inhibit cell proliferation [27] Inhibit motor machinery of cancer cells [28] Inhibit Src signaling and cancer cell migration [29]
Opioids	Activation	Immuno-suppression	Promote angiogenesis [30] Co-activate with EGFR [31] Act through NET1 pathway for cell migration [32]
Volatile agents	Activation	Immuno-suppression	Activate HIF-1α [8, 33] Inhibit TNF-induced apoptosis [34] Inhibit antiapoptotic Bcl-2 down-regulation [35]
Propofol	Inhibition	None	Decrease MMP expression [36] Modulate RhoA and stress fiber for cell migration [37]

anesthetics in malignant growth and invasion (**Table 1**).

Local anesthetics and voltage-gated sodium channels

Local anesthetics mainly block voltage-gated sodium channels (VGSC) in excitable cells. VGSCs are transmembrane proteins composed of one pore-forming α-unit and one or more auxiliary β-units. Tumor cells have been found to express an array of ion channels that their terminally differentiated counterparts don't [38]. One of the major players is VGSC. VGSC are highly expressed in a variety of carcinomas *in vitro* and *in vivo*, including breast cancer, prostate cancer, cervical cancer, colon cancer, melanoma, mesothelioma, neuroblastoma, ovarian cancer, non-small cell lung cancer, small-cell lung cancer, glioma, lymphoma, and leukemia cells [24, 25, 39].

An important aspect of VGSC expression in cancer cells is that these VGSCs are often embryonic/neonatal splice variants [24]. There are nine subtypes of VGSC α-units. Most of the tumor cells express Nav1.5 and Nav1.7 [24]. Nav 1.5 is a neonatal variant of VGSC [39] . Neonatal VGSCs are found to be more sensitive to lidocaine and phenytoin than the adult forms [40, 41]. The level of VGSC α-unit correlates highly with the metastatic potential of the tumors [25, 26]. VGSC in tumor cells tend to be constitutively active. Cancer cells have high concentration of intracellular sodium and are usually more depolarized than the terminally differentiated cells. The activity of VGSC

α-subunits is regulated by positive feedback; blockade of the channel activity by local anesthetics may have exponential benefit to curb VGSC-dependent metastatic behaviors [42]. The regulating β-subunits are structurally similar to cell adhesion molecules of immunoglobin family. They appear to regulate the expression of α-subunits, cell adhesion, and cell migration [43].

Evidence of local anesthetics to curb tumor progression through VGSC is very limited. However, inhibition of VGSC with non-local anesthetic blockers does affect tumor metastasis. The highly selective VGSC blocker, tetrodotoxin (TTX), inhibits the metastatic behavior in breast, prostate, and lung cancer cells [24-26, 44, 45]. Anticonvulsant phenytoin at therapeutic concentrations suppresses Na^+ current and the metastatic behaviors of breast cancer cells [46]. Phenytoin also inhibits the production of interleukin-6 and the migration of prostate cancer cells [47]. Down-regulation of VGSC gene expression suppresses the migration and invasion for multiple tumor cells, while overexpression of tumor-prone VGSC Nav1.5 converts a weakly invasive prostate cancer cell line into a highly invasively one [39]. In small-cell lung cancer cells, lidocaine and phenytoin inhibit VGSC-dependent enhancement of cell endocytic membrane activities, an important feature of metastatic cell behaviors [48]. In human umbilical vein endothelial cells, VGSC regulates angiogenic properties of endothelial cells, including vascular endothelial growth factor (VEGF)-induced proliferation, tubular differentiation and adhesion [49]. VEGF is one of the

most important signaling pathways for tumor progression.

Besides tumor metastasis, local anesthetics also affect cell proliferation. Lidocaine and ropivacaine impair proliferation, differentiation, and are cytotoxic to mesenchymal stem cells *in vitro*. Mesenchymal stem cells are key players of tumor growth and metastatic formation [27]. *In vitro* exposure of human fibroblasts to several amide local anesthetics impairs cell growth [50].

Local anesthetics also act through a VGSC-independent pathway. Lidocaine and tetracaine are inhibitors of kinesin motor machinery and their application to breast cancer cells leads to the collapse of microtubule protrusions. These dynamic protrusions are very important for circulating tumor cells to attach to blood vessel walls in the distant tissues [28]. Amide-linked local anesthetics inhibit inflammatory Src signaling and the migration of lung adenocarcinoma cells; however, this effect is not abolished by TTX [29]. Lidocaine infiltration protects against tumor cell invasion at concentrations used in surgical operation. The blockade of VGSC does not attenuate this protection [51]. It seems that the anti-proliferative effect of local anesthetics is largely VGSC independent. While VGSC activation promotes invasive changes in prostate and breast cancer cells, no significant proliferation is observed [25, 52]. Local anesthetics not only block VGSC, but also block potassium channels and calcium channels. It is possible that some of the VGSC-insensitive effects act through potassium or calcium channels.

Opioids

The interest in opioids' roles to directly promote tumor progression is largely sparked by the ability of opioids to stimulate angiogenesis. Opioid receptors, particularly μ opioid receptors (MOR) are found in vascular endothelial cells [53]. Activation of these opioid receptors leads to VEGF- dependent angiogenesis [53, 54].

Several lines of evidence support a pro-tumorigenic role of opioids. In an early study, breast cancer xenoplant is transplanted into model animals. When stimulated by morphine at clinically relevant concentrations, these trans-plants grow larger sizes and exhibit increased tumor neovasculation [30]. In a later laboratory study, methylnaltrexone, a peripheral opioid antagonist, when infused into model animals, attenuates tumor growth and lung metastasis. When lung cancer cells are introduced into animals with no MOR, these animals do not develop significant tumors compared to their wild type counterparts [55]. There is substantially increased expression of opioid receptors in non-small cell lung cancer cells; these MORs co-activate epidermal growth factor receptor (EGFR) and promote tumor cell proliferation and survival [31].

In addition to angiogenesis, morphine is found to act on cytoskeleton system in a line of breast adenocarcinoma cells. The addition of morphine into the tumor cells leads to the up-regulation of NET1 and increased cell migration. NET1 is a key organizer of cytoskeleton and mediates cancer cell migration. Silencing of NET1 expression reverses this effect of morphine on migration [32]. In contrast, in colon cancer cells, morphine inhibits adhesion, invasion and pulmonary metastasis of colon tumor cell line. This effect is mediated by regulating matrix metalloproteinase (MMP), an extracellular matrix peptidase that promotes cell migration by dissolving extracellular matrix and adhesion complexes [56].

Besides the studies in cell-based systems and animal models, a recent human study examines the genetic polymorphism of MOR in breast cancer patients. The authors identify several MOR variants in this group. The most common one, A118G, is associated with a reduced binding affinity to μ-opioids. Patients harboring this polymorphism, when in pain, require high opioids. The most interesting part is that patients with one or more copies of this G allele have decreased breast cancer-specific mortality [57].

Despite that regional anesthesia decreases the use of systemic opioids, systemic opioid administration is still inevitable. One approach to minimize their pro-tumor effect is to co-administer a peripheral opioid inhibitor. Regular opioid receptor blockers such as naloxone act both peripherally and centrally. Its use can lead to severe side effects such as pain aggravation and withdrawal. Peripheral opioid inhibitors, on the other hand, do not cross blood-brain barrier

and presumably have minimal central side effects. There is evidence that endogenous opioids may also promote tumor progression [58]. It will be interesting to explore the therapeutic potential of peripheral opioid blockers in countering the tumorigenic effect of both exogenous and endogenous opioids.

Others anesthetics

Except propofol, volatile anesthetics and intravenous anesthetics are known to depress all aspects of immunity system. This depression augments the surgically-induced immunosuppression [8]. However, most of the studies concerning the direct effect of anesthetics on tumor progression are focused on opioids and VGSC. Such studies on volatile anesthetics and intravenous induction agents are scarce. Isoflurane is found to protect colon cancer cells from tumor necrosis factor (TNF)-induced apoptosis [34]. In neuroblastoma cells, isoflurane attenuates neurotoxicity imposed by opioid peptide [35]. Animal studies suggest that halogenated volatile anesthetics are organ-protective against ischemia [59]. Unfortunately, this very effect may be detrimental in the context of cancer. Under hypoxic conditions, halogenated volatile anesthetics up-regulate the expression of hypoxia-inducible factor 1α (HIF-1α) in the heart and brain [33, 60]. HIF-1α is regarded as a master mediator for ischemic protection [33]. Interestingly, HIF-1α is over-expressed in a variety of carcinomas and their metastases [61]. The level of HIF-1α protein in the primary tumor correlates with early relapse of breast cancer [62]. On the other hand, several studies show the opposite results. Sevoflurane and desflurane inhibit MMP-9 release and subsequent migration of colorectal cancer cells in *vitro* [63]. In a cell-based system, sevoflurane reduces the invasion and migration of lung cancer cells by down-regulating MMP-2 and MMP-9 [64].

For nitrous oxide, a very early study in mice shows it is associated with accelerated development of post-surgical metastasis in the lung and liver [65]. However, a recent randomized follow-up study finds no increased risk of recurrence in 4-8 years after colorectal cancer surgery in patients who have received nitrous oxide anesthesia during the operations [66].

Propofol may have anti-tumor effect. Propofol promotes cytotoxic T lymphocyte activities and

inhibits lymphoma growth [67]. Propofol also decreases the expression of extracelluar matrix protein and the invasiveness of colon cancer cells [36]. Similar anti-invasive phenomena are observed in a few other cancer cells at clinically relevant concentrations [37]. For benzodiazepines, despite that early epidemiological studies suggest their use is associated with increased occurrence of tumors [68, 69], large scale analysis, adjusted with confounders, finds no association between benzodiazepine use and cancer risk [70, 71]. Among all intravenous anesthetics, ketamine is the most potent agent for lung cancer metastasis in animal models. This effect is mediated mainly by strong immunosuppression from ketamine [22].

Discussions

The likelihood of tumor metastasis depends on the balance between human anti-malignant defense and the ability of tumor to grow and spread. The former mainly relies on NK and cell-mediated immunity. For the latter, the main determinant is the innate aggressiveness of the tumors. Exogenous factors can act as facilitators or suppressors.

Surgery creates a profound perioperative stress that manifests in neural, endocrine, metabolic, inflammatory, and immunological changes. These changes result in significant immunosuppression. Meanwhile, tumor cells are released into circulation during surgery. This double punch makes perioperative period highly conducive to tumor metastasis. General anesthesia suppresses cerebral and thalamus functions while preserving the function of low brain and spinal circuits [72]. In contrast, regional anesthesia, due to direct nerve block, attenuates or abolishes the reflex circuit between noxious afferents and sympathetic efferents at the surgical level and thus attenuates the surgical stress and immunosuppression. Blockade of sympathetic activity can produce a similar effect. In fact, ketamine-induced lung cancer cell invasion is markedly reduced by the pretreatment of nadolol, a β-adrenergic antagonist [22].

Retrospective human studies suggest that regional anesthesia is an independent beneficial factor for tumor recurrence [6, 9]. The main problem of these studies is that perioperative

anesthesia is multimodal and it is difficult to lineate the contributions of each individual factor. No standardization of anesthetic applications is available. A variety of general anesthesia methods can be used for induction and maintenance; the protocols of regional anesthesia can also be very different. In addition, no follow-up is possible to assess the long-term outcome. Randomized clinical trials with more specific stratifications and long-term follow-up are needed for further clarification.

Anesthetics act on neoplasms both directly and indirectly. Past studies have been focused more on the indirect aspect, the immune suppression [73]. Recently, growing evidence demonstrates that anesthetics directly regulate tumor molecular and cell biology. First of all, there is a positive correlation between VGSC and tumor metastasis [24, 25]. This provides excellent theoretical rationale to further investigate the role of local anesthetics in tumor inhibition. One interesting finding is that often tumors express a neonatal form of VSGC [39]. A specific blocker against this VGSC subtype may provide better targeting and less systemic toxicity. For opioids, one of the theories that regional anesthesia has better outcome is because less systemic opioids are used under regional anesthesia. Tumor cells are equipped with opioid-responsive molecular machinery to promote angiogenesis and invasion. This opioid sensitivity provides a therapeutic opportunity for peripheral opioid blockers. Alvimopan, a peripheral opioid receptor blocker, has been approved in clinical use to mitigate opioid side effects such as ileus [74]. Further investigations are warranted to evaluate the efficacy of similar blockers in oncotherapy. Finally, tumors are exposed to the lowest oxygen environments [75]; halogenated volatile agents are able to activate hypoxic mediators for ischemic protection and tumor progression [62]. It may be advisable to reduce volatile agent use in favor of propofol anesthesia in cancer patients.

In spite of the growing evidence, the significance of these studies is still very limited. Most of them are cell-based or simple animal model studies. A better approach is to test the theories in animal models closely mimicking human pathology. Ultimately, controlled clinical trials are needed to demonstrate whether there is a significant effect of each individual anesthetic on tumor progression. For now, scientific evidence is not sufficient to compile a definite strategy for optimal anesthesia management in cancer patients. Fortunately, most procedures can accommodate multiple anesthetic choices. A good approach is to avoid regimens that are potentially harmful and favor these potentially beneficial. The former includes volatile anesthetics, systemic opioids, and ketamine; while the latter includes regional block, local anesthetics, and propofol. In addition, multidisciplinary strategies need to be implemented to reduce perioperative stress.

In summary, regional anesthesia is a beneficial technique in cancer patients. Basic science studies indicate an encouraging role of local anesthetics in attenuating tumor recurrence; while systemic opioids are more likely to be pro-tumorigenic. A shared mechanism of volatile anesthetics may exist between ischemic organ-protection and tumor progression. Further studies at different levels are urgently needed for a better clinical guide.

Address correspondence to: Dr. Jun Lin, Department of Anesthesiology Downstate Medical Center, 450 Clarkson Avenue, Box 6, Brooklyn, New York 11203-2098, USA. E-mail: jun.lin@downstate.edu

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