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The influence of immunology and anesthesia on cancer

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Abstract. Oncogenesis, characterized by abnormal cell proliferation, poses a global concern due to its high morbidity and mortality rates. Surgical interventions, often involving anesthetics, are common in cancer patients. Understanding their effects can lead to breakthroughs in cancer treatment, especially in the context of immunotherapy. Researchers have identified how the immune system and anesthetics affect the recurrence and metastasis of cancer. Immunotherapy, which utilizes the immune system to target tumors, has shown promise in clinical trials. In the adaptive immune system, T cells and B cells play significant roles in tumor detection and elimination. The immune system consists of innate and adaptive systems that help fight infections and diseases. Pattern recognition receptors (PRRs) trigger non-specific inflammatory responses in the innate immune system. Anesthesia is commonly administered to cancer patients, but different methods and groups of anesthesia exert divergent effects on oncological progression. Some studies have suggested a potential correlation between specific inhalation anesthetics and the modulation of tumor cell proliferation and apoptosis. Considering the interaction between the immune system and anesthetics, different combinations have the potential to either promote or inhibit cancer metastasis. Further exploration of these interactions is crucial for optimizing the administration of anesthesia in cancer patients and maximizing the efficacy of immunotherapy. This review sheds light on the complex interplay between immunotherapy, anesthesia, and cancer progression, providing valuable insights for future advancements in cancer treatment strategies.

Keywords: immune system, immunotherapy, anesthesia, anesthetics, cancer.

1. Introduction

The immune system comprises innate and adaptive systems with different cells that aid the body in fighting inflammation, infections, and other illnesses. The innate immune system generates rapid, non-specific inflammatory responses when it receives pattern recognition receptors (PRR) signals. Receptors are integrated protein channels locked into the cell membrane, with specific shapes for particular binding ligands in the extracellular environment, such as signaling molecules, antigens, or cytokines. This binding of ligand trigger transduction inside the cell and a response such as committing suicide and causing abnormal cell death to initiate adaptive immunity. In this case, PRRs detect viral components and activate intracellular transduction cascades to perform a response.

Anesthesia is an essential technology designed to keep patients painless or unconscious during an unendurable procedure, such as surgery. Depending on the patient's approach, they will receive different kinds of anesthesia, including local, regional, neuraxial, or general. volatile, intravenous, and

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perioperative adjuvant medications are the most frequently used anesthetic agents. Specifically, volatile liquids produce unconscious effects when administered intravenously or inhalational. Local anesthetics cause sensory and motor paralysis by affecting part of the nervous system.

Oncogenesis originates from aberrant cell proliferation, characterized by the evasion of regulatory checkpoints. The immune system is able to detect and minimize tumor cells with increased protein and lipid turnover, higher mutation rates, and heightened stress signaling. However, tumor cells employ various evasion tactics, such as inducing systemic immune suppression and facilitating metastatic outgrowth. Cancer incidence remains a significant global concern, with substantial morbidity and mortality rates. In 2022, there were approximately 1.9 million new cases of cancer and 609,360 deaths in the United States alone [1]. Additionally, close to 10 million people died from cancer in 2020, according to statistics from the WHO, making it the one of the largest causes of death worldwide. It is noteworthy that over 80% of cancer patients necessitate surgical or palliative interventions, often involving anesthetics [2].

Researchers have extensively acknowledged the potential impact of the immune system and anesthetics on long-term cancer recurrence and metastasis. Innate and adaptive immunity may be impacted by every type of anesthetic and postoperative treatment. The immune system is complex, and anesthetic agents and perioperative medication can have various impacts on many organ systems, making it difficult to fully understand how the immune system and the anesthetic medications interact. Global concepts like "immunosuppression" or "immune activation" must make way for more precise and situational descriptors. T Biologists noticed the neural activity of the central nervous system could encourage cancer development. Surgical removal induces unpleasant stimulation, and anesthetic agents elicit immunosuppression, stimulating the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis. These approaches produce immunosuppressive cytokines and inhibit cell-mediated immunity, which induces the metastasis of tumors.

In conclusion, the immune system and anesthesia exert distinct effects on the field of oncology. An in-depth exploration of the latest advancements in cancer treatment, such as immunotherapy, coupled with the potential utilization of anesthetics for cancer therapy, holds the potential for pioneering breakthroughs. Additionally, comprehending the impact of diverse anesthesia modalities on the immune system and unraveling the intricate interplay between these two systems could offer insights into cancer recurrence while paving the way for drug development and improved treatment strategies. In this review, given the intersecting roles of the immune system and anesthetics in cancer, we systematically introduce their interaction and potential therapeutic implications.

2. Influence of immunotherapy on cancer

Innate and adaptive systems are parts of the immune system. NK cells, neutrophils, mast cells, and macrophages are examples of innate immune system cells that protect the host when they detect invading pathogens or infections. Macrophage plays a role in tissue homeostasis or repair and response to infections. It contributes to cancer progression and metastasis since it promotes cancer cell survival and proliferation, Neutrophils, the most abundant leukocytes, are recruited to damaged tissues, eliminating pathogens, and adjusting inflammation by phagocytosis. However, they also secrete chemicals like PGE2 that stimulate cancer cell proliferation, migration, and intravasation. Without priming or activation, natural killer cells are lymphocytes that kill cancers and virally infected cells; NK cells would not kill healthy cells because they recognize them as self. The mechanism is that the MHC molecule on the healthy cell binds to the inhibitory receptor on the NK Cell, causing NK cell inhibition. In addition, they are considered critical contributors to the immune control of cancer cells by regulating the production of cytokines and chemokines. Therefore, their dysfunction could be causing cancer metastasis.

In the adaptive immune system, B cells and T cells are responsible for slow responses. B lymphocytes secrete antibodies and form multipotent hematopoietic stem cells. The antibodies differentiate into plasma cells that secrete more antibodies and memory B cells that mediate immunity against pathogens. B lymphocytes have the capacity to engage in two significant mechanisms involving the interaction with

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T cells and tumor-associated antigens. Firstly, B cells possess the ability to present tumor-associated antigens to T cells directly. Alternatively, B cells can secrete antibodies that augment the process of antigen presentation to T cells, thereby heightening their efficiency in recognizing and eliminating tumor cells. Compared to B cells, Due to their high frequency of discovery in human cancers, T cells are increasingly commonly examined in a variety of cancer forms. Even though T cells are particularly effective at destroying cancerous cell, their effectiveness depends on the response that the tumor antigen induces and the signals that restrict the T cell's ability to function. Therefore, Cancerous cells evade being destroyed because the immune response contributes to tumorigenesis and stimulates cancer cell proliferation.

2.1. Advancement and breakthrough

Emerging research has postulated the engagement of the immune system within the realm of biologically based therapies, particularly those that directly focus on the tumor microenvironment (TME). Notably, significant progress has been made in the management of malignant tumors through the utilization of immune cells, with a particular emphasis on T cells, which possess a fundamental role in facilitating cell-mediated immunity. These advancements have consequently yielded favorable outcomes in various clinical trials. Recent scientific investigations have placed significant emphasis on elucidating the capacity of T cells to facilitate the advancement of cancer treatments encompassing cancer vaccine, CAR T cell therapy, and monoclonal antibody-based immunotherapy.

Cancer vaccines elicit an immunostimulatory response, thereby enhancing the host's immune system's capacity to initiate a targeted attack on malignant cells. Cancer immunotherapy has emerged as an essential facet of cancer management through its specific targeting of tumor-associated antigens (TAAs). This therapeutic approach has demonstrated numerous clinical advantages while exhibiting a favorable absence of undesirable off-target effects. For example, Ipilimumab (Yervoy), which suppress the immune system by aiming the cytotoxic T lymphocyte antigen 4 (CTLA-4) protein receptor, has the status of FDA-approved for treating melanoma and renal cell carcinoma. Vaccines must meet the requirements of generating heightened immune responses while avoiding autoimmune-associated toxicities. Consequently, it is imperative to explore novel methodologies that can advance cancer therapy by achieving improved effectiveness and extended survival rates.

Besides, CAR T cell therapy represents a potent immunotherapeutic approach that leverages the patient's innate immune system to eradicate cancer. This therapeutic strategy entails the manipulation of T cells by introducing a chimeric antigen receptor (CAR) gene, enabling transformed T cells to recognize TAAs specifically. However, the emergence of tumor resistance against CAR constructs targeting a singular antigen poses a significant challenge to the effectiveness of the therapy. Despite this, recent large-scale clinical trials have shown that CAR T cell therapy is better to traditional therapies for patients with relapsed non-Hodgkin lymphoma subsequent to initial chemotherapy (known as first-line treatment). As a consequence, some experts have postulated that CAR T cell therapy could potentially supplant chemotherapy as the standard second-line treatment for this specific patient population.

Furthermore, monoclonal antibody (mAb)-based immunotherapy is widely recognized as a fundamental constituent of cancer treatment owing to its superior efficacy and reduced toxicity compared to conventional chemotherapy. In recent times, a novel strategy has emerged, wherein the focus has shifted from directly targeting tumor antigens to the stimulation of T cell-mediated anti-tumor immune responses. This approach involves the utilization of bispecific T Cell Engager (BiTE) antibodies, which are designed to specifically bind to a tumor antigen present in T cells. Notably, this represents the initial mAb modality capable of augmenting the anti-tumor capabilities of T cells. As a testament to its efficacy, the FDA has granted approval for the clinical use of CD19-CD3 BiTE, known as blinatumomab, as a therapeutic intervention for patients diagnosed with acute lymphoblastic leukemia [3].

Other potential includes subduing Indoleamine 2,3-dioxygenase 1 (IDO1) activity which holds the potential to elicit robust antitumor immune responses in murine neoplasm models. Despite the arduous progress in the development of IDO1 inhibitors and the setbacks observed in specific clinical trials, the

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immunomodulatory efficacy of IDO1 inhibitors has been confirmed, signifying the enduring prospects for their advancement [4].

2.2. Limitations and adverse effects

The growing application of cancer immunotherapy focused on TAAs promotes the advancement of personalized recombinant vaccines with enhanced efficacy and reduced adverse effects. Remarkably, an elevated prevalence of mutational load is observed across various tumor classifications. A positive association has been established between heightened mutational occurrences within tumors and enhanced immunogenicity, as well as improved post-treatment survival outcomes following checkpoint blockade interventions. Conversely, cancer types with lower mutational burdens exhibit limited responsivity to immunotherapeutic interventions. Consequently, it becomes imperative to pursue multifarious advancements in the realm of immunotherapy to gain a comprehensive comprehension of the underlying mechanisms governing antitumoral immune responses [3].

The promising outcomes observed in numerous clinical trials pertaining to cancer immunotherapy may potentially signify favorable clinical prospects. Nonetheless, several obstacles persist in the extensive implementation of immunotherapy. These obstacles encompass the limited efficacy of immunotherapy against all tumor types alongside the manifestation of significant adverse effects, notably encompassing nonspecific inflammation and autoimmunity inflammation. In patients subjected to ipilimumab treatment, the proactive implementation of CD177 and CEACAM1 may serve as proactive measures to mitigate the adverse impact stemming from immune-related colitis. Moreover, numerous prospective biomarkers exhibit notable utility in prognosticating both the side effects and therapeutic efficacy. Illustratively, the deficiency in mismatch repair (MMR), the mRNA profile associated with interferon-γ (IFN-γ), and the ratio between T-cell invigoration and tumor burden present as potential candidates. Precision medicine and immune checkpoint blockade treatment will develop significantly because of the validation of these biomarkers in a larger patient cohort. Although there are formidable obstacles encountered in achieving optimal therapeutic efficacy stemming from the deleterious consequences, inadequate immunological reactions, and the immunosuppressive environment of tumors, researchers are finding numerous ways, such as finding reliable biomarkers, to reduce the toxic effects [5].

3. Influence of anesthetics on cancer

The utilization of anesthesia during the perioperative phase holds significance within the realm of routine clinical procedures conducted on surgical patients. Particularly in the context of cancer surgery, the perioperative period assumes a crucial role in shaping the subsequent course of the disease. What causes this phenomenon is that the tumor cells that are discharged from the original tumor travel through the patient's bloodstream, and potentially give rise to novel micro-metastases, irrespective of the complete excision of the tumor itself. Many studies have been conducted to investigate the potential benefits of various anesthetic procedures on the outcomes, including overall or recurrence-free survival, of patients with cancer receiving surgery. The main types of anesthetics used in tumor surgery encompass general anesthesia, local anesthesia, and regional anesthesia, each exhibiting diverse impacts on the immunological response and ability of the host to eradicate any remaining tumor cells (Figure 1). An extensive review of the evidence from human research, in vitro experiments, and animal models indicates that due to possible immunoprotected qualities over general anesthetic, regional anesthesia may be more preferred [6].

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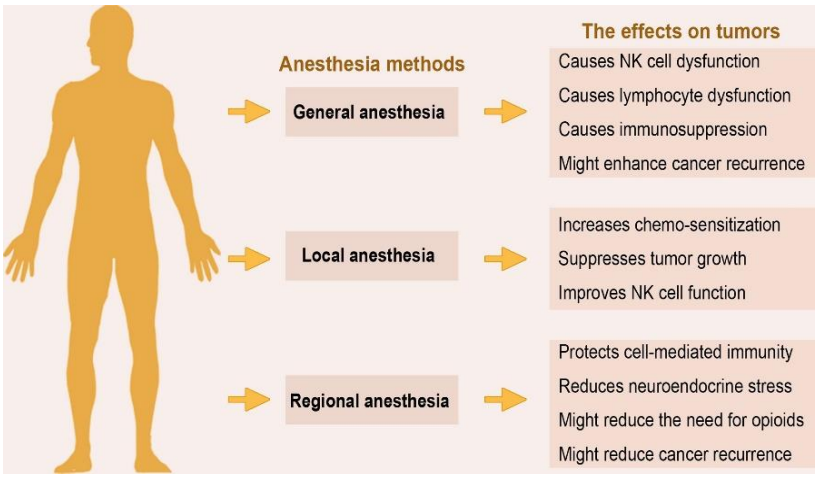

Figure 1. Different methods of anesthesia and their effect on tumors.

3.1. Inhalation and general anesthetics

In the clinical setting, inhalation anesthesia is extensively employed due to its potential therapeutic efficacy and notable level of manageability. Nevertheless, the impact of inhalation anesthetics on tumor progression remains a contentious matter. A mounting body of evidence substantiates that inhalation anesthetics possess the capacity to influence immunological response, regulation of genes, and tumor biological dynamics, consequently exerting an interventionist role in cancers' regional recurrence and distant metastasis. A growing amount of evidence has emerged in recent years that has demonstrated a potential association between inhalation anesthesia and the control of tumor cell death and growth. Therefore, there are impact of inhalation anesthetics on cancer patients' prognosis, as shown in Table 1.

Table 1. The impact of inhalation anesthetic on cancer patients' prognostic outcomes.

Cancer Forms	Groups	Inhalation anesthetic dosage	Methods	Results
Breast cancer	Sevoflurane versus propofol	Not explicitly expressed	Retrospective	Propofol demonstrates a superior advantage of survival
Colorectal cancer	Inhalation versus intravenous anesthesia	Not explicitly expressed	Retrospective	The application of inhalation anesthetic was linked to an increased incidence of recurrence
Colon cancer	Desflurane versus propofol	8-12%	Retrospective	Propofol is more effective than other drugs at increasing patient survival.

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Hypoxia-inducible factor 1 (HIF-1) is a prominent transcription factor that responds to low oxygen conditions and governs the production of vascular endothelial growth factor (VEGF). Previous investigations have demonstrated that sevoflurane, in a time- and concentration-dependent way, can elicit the upregulation of HIF-1α and VEGF following in vitro treatment of glioma stem cells, thereby fostering the advancement of tumors. An experimental observation has indicated that the administration of isoflurane leads to the upregulation of VEGF and angiopoietin-1 expression within ovarian cancer cells, thereby facilitating the process of tumor angiogenesis and augmenting tumor aggressiveness. However, additional investigations have corroborated that isoflurane does not influence the expression of genes linked to essential features of cancer. As a result, isoflurane has an inhibiting effect on tumor angiogenesis necessitates validation across diverse tumor types [7].

3.2. Local anesthetics

Researchers discovered that local anesthetics could influence the growth, invasion, and metastasis of various tumor cell types using multiple mechanisms of action. Additionally, their different administration techniques could affect the tumor's prognosis, recurrence, and metastasis after surgery. For instance, research using a 10 nm concentration of procaine, an ester local anesthetic, inhibited A549 proliferation. After administering procaine for three weeks, the mice with lung cancer have significantly lowered tumor volume. Besides, procaine prevented the growth of breast cancer cells and demethylated tumor suppressor genes, proving its excellent application potential in patients resistant to targeted drugs. Moreover, procaine inhibited the growth of liver cancer cells. It efficiently regulated DNA methylation in stomach cancer, suggesting it could be a candidate drug for cancers [8]. The non-nucleoside compounds present in local anesthetics function as inhibitors of DNA methyltransferase (DNMT) activity, thereby influencing the expression of micro-RNAs and suppressing histone acetylation. Consequently, these mechanisms induce cytotoxicity in malignant cells. Furthermore, the epigenetic consequences of these effects could potentially contribute to the utilization of local anesthetics as therapeutic agents against cancer. Local anesthetics exhibit dual functionality within cancer cells, encompassing the facilitation of DNA demethylation and subsequent reinstatement of tumor suppressor gene expression while concurrently regulating non-coding RNAs. Following primary tumor excision with local anesthetic as opposed to merely general anesthesia, several retrospective clinical investigations have shown a significant improvement in overall survival and a decrease in recurrence rates. The observed epidemiological data lends support to the hypothesis that local anesthesia may possess anticancer properties [9].

4. Anesthesia and the immune system’s impact on cancer

The convergence of anesthesiology and immunology has emerged as a captivating area of exploration, capturing growing attention within the clinical sphere. Based on prior investigations, it has been observed that the immune system is influenced by general anesthesia. So, enhancing anesthesia administration protocols involves evaluating these immune system impacts.

One research found that numerous perioperative factors contribute the immune system's dysregulation or suppression, potentially influencing cancer cell proliferation and the emergence of new metastases. These elements can directly inhibit the immune system while also stimulating the sympathetic nervous system and hypothalamic-pituitary-adrenal axis, which further impairs immunity. The innate and adaptive immune system, the inflammatory system, and angiogenesis may be modulated by the anesthetics and painkillers used during the perioperative period, potentially impacting cancer recurrence and long-term outcomes. Despite the existence of contradictory and conflicting current data, it is imperative to raise awareness of this issue among medical practitioners to enable more thoughtful and careful choice of anesthetic methods [10].

However, other researchers studied the prolonged administration of general anesthesia drugs, as a consequence of their impact on cytokines, which has the potential to contribute to the progression of disease in individuals with compromised immune systems. Given the disparate outcomes reported across multiple studies and the escalating population of immune-deficient patients, selecting suitable general

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anesthesia agents becomes crucial for optimizing cytokine function to promote favorable clinical outcomes. The impact of general anesthesia on the immune system in individuals with good health and during surgeries of short duration appears negligible, while alterations in the immune system are primarily associated with the physiological stress induced by surgical trauma, specifically in cases of major surgery [11].

The perturbing notion of whether the perioperative and intraoperative anesthetic method for patients undergoing cancer surgical procedures can exert a substantive impact on tumor recurrence has become a matter of significant concern [6].

Given the associations of both the immune system and anesthetics with cancer, it is imperative for researchers to conduct further investigations into the potential interaction between these systems as a means to advance cancer treatment. Since inhalation anesthetics have fluorinated ethers, it can affect the receptors on the central nervous system and receptors (such as Calcium/Magnesium channel protein, TLRs, Rap 1) on the exterior of the immune cells. This process caused the cells to lose their granules and secrete their preformed mediator through degranulation. For example, the NK cells and macrophages experience a reduction in their killing capability and inhibit anti-tumor effects. According to research, fluothane and isoflurane decrease the immune cell's cytostatic activity and may also increase apoptosis of adaptive immune cells. On the other hand, sevoflurane and desflurane impede the colon cancer cells proliferation. Furthermore, the vitro experiments showed that inhalation anesthetics could control immune cells' ability to identify antigens, recruit inflammatory cells, and influence immunological responses carried out by cells. However, due to the dose-dependent effect, sevoflurane and desflurane caused suicide of adaptive immune cells, causing immune suppression [8].

Patients with colorectal cancer have disrupted immunity due to the stress of having surgery, which increases the dissemination and metastasis of cancer. One effective way to control the stress response is by applying anesthesia. Anesthesia affects the secretion of proinflammatory cytokines, especially tumor necrosis factor-a, interleukin (IL-1), IL-6, and IL-8. Also, it increases the anti-inflammatory factors—IL-10, interferon 7, and interleukin two receptors–to reduce inflammation and promote healing. Research shows that tramadol, propofol, and selective nonsteroidal anti-inflammatory analgesics benefit the body's immune system and can lessen tumor recurrence and metastasis. Hence, selecting an appropriate narcotic medication for the patients would be crucial [12].

The key elements encompassed within one study comprise surgical procedures and their associated postoperative pain, the neuroendocrine stress response, and anesthetics such opioid medications. Among the immune cells under scrutiny, the primary focus lies on natural killer (NK) cells, which are subject to the influence of both anesthesia and surgery. Empirical evidence has indicated that the administration of ketamine, thiopental, volatile anesthetics, fentanyl, and morphine while excluding propofol, remifentanil, and tramadol, leads to a decrease in the circulating population of NK cells and its cytotoxicity. Notably, the cytotoxicity amount of NK cells exhibits an inverse relationship with the stage and metastasis of cancer. In light of this, the potential advantageous effects of regional anesthesia on perioperative immunological reactions and long-term outcomes subsequent to breast cancer surgery have been considered as another option to general anesthesia [13].

5. Conclusions

In summary, the immune system and anesthesia have discrete influences on the field of oncology. A comprehensive examination of recent progressions in cancer therapy, including immunotherapy, alongside the possible application of anesthetics in cancer treatment, presents an opportunity for groundbreaking advancements. Numerous auspicious prospects lie ahead for the progressive advancement of cancer immunotherapy. Subsequent investigations aim to explore the combinatorial approach involving IDO1 inhibitors and other antitumor agents, thereby offering significant implications for the triumph of clinical development. While numerous small-molecule medications aimed at modulating the extracellular or intracellular pathways governing adaptive and innate immunity have been devised, the majority of these compounds are presently undergoing preliminary clinical evaluations. Further, comprehensive investigations encompassing fundamental experiments and clinical

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trials are imperative to fully unravel their underlying mechanisms, ascertain their clinical effectiveness, and thoroughly evaluate their pharmacokinetic profiles. Small-molecule inhibitors possess promising potential as viable alternatives and adjuncts to mAb, substantiating their continued significance within tumor immunotherapy. These inhibitors are poised to assume a crucial role in the future landscape of therapeutic interventions. Aside from improving the small molecule drug, advancement should also be made in checkpoint blockade techniques, cancer vaccines, CAR T cell therapy, and personalized recombinant vaccines. Applying anesthetic and the types of anesthetic drugs affects the operation of the immune cells, consequently promoting or inhibiting the spreading of cancer cells. Sevoflurane and desflurane are inhalation anesthetics; procaine, a local anesthetic; tramadol, propofol, and selective nonsteroidal anti-inflammatory analgesics promising candidate anesthetic medication for application in the surgery for patients with malignant cancer cells. Furthermore, understanding the impact of various anesthesia modalities on the immune system and elucidating the complex interaction between these two systems may yield insights into cancer recurrence, facilitating drug development and enhancing treatment strategies.

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