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The Impact of Sevoflurane on NKG2D-Mediated Cancer Immunosurveillance and its Implications for Future Research

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Description

Surgical resection remains the primary curative treatment option for solid tumors [1]. Recently, improvements in diagnostic methods and the expansion of health screenings have led to an increased number of patients who can receive curative surgery by diagnosing cancer at an early stage. Furthermore, advancements in understanding pathogenesis and surgical techniques have improved the survival rates of solid tumor patients. Nevertheless, cancer recurrence and metastasis remain the leading causes of death in patients with solid tumors after surgery [2].

Changes in a patient's metabolism, hormone levels and hemodynamics due to surgery and anesthesia can alter the tumor microenvironment, affecting the presence of residual cancer cells [2,3]. Therefore, despite successful surgical removal, various perioperative factors may contribute to cancer cell metastasis, growth and resistance to postoperative chemotherapy. Clinicians face a critical task in identifying the impact of anesthetics on cancer progression and selecting the appropriate anesthetic method, given the difficulty of controlling surgery-related stress.

By the 2000s, it was suggested that anesthetics and anesthesia methods used during cancer surgery could potentially influence cancer metastasis and progression [4]. Recent meta-analyses have also indicated that the type and administration method of anesthetics used during surgery may impact recurrence-free survival and overall survival in cancer patients [5]. However, a clear conclusion has not yet been reached regarding the effects of anesthetics on the prognosis of individual cancers, nor have the mechanisms been clearly explained [5]. As previously mentioned, it is difficult to adjust or alter the surgical techniques. Therefore, understanding the impact of anesthetics on the course of cancer and selecting the optimal anesthetic method accordingly is a critical task for clinicians.

Natural Killer (NK) cells play an important role in the immune surveillance of tumors not only by directly inhibiting the occurrence, proliferation and metastasis of cancer cells but also by eliminating circulating tumor cells and cancer stem cells, which are responsible for cancer recurrence [6]. NK cells recognize ligands specifically expressed on abnormal cells [7]. NKG2D (Natural Killer Group 2, Member D) ligands, which are primarily expressed on the surface of cancer cells, bind to NK cell activation receptors and transmit activation signals that allow NK cells to recognize and eliminate cancer cells [7]. To evade NK cell-mediated tumor immunosurveillance, cancer cells secrete Matrix Metallo Proteinases (MMPs) that alter the tumor microenvironment and shed NKG2D ligands from the cancer cell surface [8]. Additionally, MMPs break down and remodel the extracellular matrix, creating a tumor microenvironment favorable for cancer growth and metastasis [8]. To date, research on how anesthetics affect the tumor microenvironment, particularly in relation to tumor immunosurveillance, remains limited.

Thus, we conducted a series of *in vitro* studies on the effects of the widely used inhalation anesthetic sevoflurane on non-small cell lung cancer and breast cancer cell lines [9,10]. In the non-small cell lung cancer cell line (NCI-H23), a clinical dose of sevoflurane weakened the expression of *NKG2D* ligands and increased the expression of MMP-1, -2 and -9. This led to decreased NK cell-mediated cytotoxicity and increased cell migration [10]. In the breast cancer cell line, sevoflurane inhibited *NKG2D* ligand expression in a dose-dependent manner, resulting in decreased NK cell-mediated cytotoxicity. However, the breast cancer cell line did not show any changes in MMP expression due to sevoflurane [9].

Due to the limitations of our preliminary *in vitro* study, it is difficult to directly apply the results to patients in clinical settings. Additionally, the study does not elucidate the molecular mechanisms through which sevoflurane affects the expression of NKG2D ligands and MMPs. Additionally, whether our findings apply to anesthetics in general or only to sevoflurane remains unclear. Nonetheless, the results from our study emphasize the importance of considering the impact of anesthetics on cancer immunosurveillance and suggest the alteration of immune-regulatory capabilities *via* NKG2D ligands upon anesthetics exposure as a plausible hypothesis. Therefore, future research should focus on exploring the effects of various anesthetics on the molecular mechanisms related to cancer immunosurveillance, including clinical studies. Such studies will contribute to a deeper understanding of the immunomodulatory effects of anesthetics and provide critical guidance in the selection of anesthetics for tumor surgery.

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Conflict of Interest

The authors declare no competing interests.

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