The Effects of Sevoflurane in the Progression of Solid Tumors Based on the Evidence of Preclinical Studies

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Abstract: Sevoflurane is a widely used volatile anesthetic in clinical treatment. Recently, the effect of sevoflurane on tumor cell signaling pathways has attracted the attention of many researchers in the field. However, the underlying mechanism behind the effect of sevoflurane on tumor cell signaling pathways still remains unclear. Based on the evidence of in vitro experiments, this paper reviews the recent research results on the sevoflurane-mediated regulation on solid tumors and presents its potential molecular mechanisms that can provide references for clinical practices.

Keywords: Sevoflurane, Anesthetics, Solid tumors, Apoptosis

1. Introduction

The incidence of cancer has been showing an increasing trend in recent years. Despite the development of radiotherapy, chemotherapy, and immunotherapy, resection is still the mainstay of treatment for most solid tumors at present, and the spread of tumor cells during surgery is still one of the main causative factors for post-operative metastasis. Many studies have found that the use of anesthetics in surgical operation has an effect on the prognosis of cancer[1-4]. However, there are currently no guidelines in the selection of the best anesthesia for tumor surgery as the mechanism of anesthetics affecting the prognosis of cancer patients remains to be clarified.

Sevoflurane is a widely used volatile anesthetic in the tumor surgery. Several studies have confirmed that sevoflurane has anti-cancer properties. Through the analysis of the key anesthetic effects at the cellular level as well as the involved signal transduction mechanism, this paper presents a review of the effects of sevoflurane on different solid tumor based on the findings of in vitro experiment.

2. Lung cancer

The bronchi and alveoli have to be exposed to sevoflurane during the lung cancer surgery. Liang et al. investigated the effects of sevoflurane on the invasion and migration of lung cancer cells using A549 human lung tumor cell line, and demonstrated that sevoflurane inhibited the proliferation of A549 cells, induced apoptosis, and blocked cell cycle progression[5]. Moreover, this study showed that the anti-proliferative and pro-apoptotic effects of sevoflurane were related to the decreased expression of X-linked inhibitor of
apoptosis (XIAP) and surviving as well as the activation of caspase-3. The researchers also found that because of sevoflurane, phosphorylation of P38 MAPK was reduced. In addition, the downregulation of matrix metalloproteinase (MMP)-2, MMP-9, fascin, and ezrin was also related to sevoflurane, and sevoflurane could inhibit the invasion and migration of A549 cells[6]. Studies have shown that hypoxic microenvironment can promote the proliferation and metastasis of A549 human lung cancer cells[7]. This hypoxia-related growth and metastasis could be inhibited by sevoflurane, which was possibly associated with the suppression of hypoxia-inducible factor-1 alpha (HIF-1α) expression. Besides, they also revealed that the downstream genes of HIF-1α might be XIAP, survivin, fascin, and heparanase (HPA), and the mechanism of sevoflurane inhibiting the expression of HIF-1α was probably related to the reduction of the activity of p38 MAPK signaling pathway (Figure 1). Another study by Liang et al. found that sevoflurane or cisplatin alone suppressed the growth of A549 human lung cancer cells, with greater inhibition when the two anesthetics were combined[8]. Based on other studies related to lung cancer, it was found that sevoflurane had an inhibitory effect on the proliferation and invasion of lung cancer cells, but it had a promoting effect on their apoptosis through Wnt/β-catenin signaling pathway by affecting the lncRNA PCAT6/miR-326 axis[9]. Kim et al. studied the regulation of sevoflurane on Lewis lung cancer (LLC) cell growth and outcome in vivo and in vitro, and showed that the survival of LLC xenograft mouse models and tumor growth in their bodies was not related to sevoflurane exposure but sevoflurane significantly increased the proliferation rate of LLC cells in vitro, suggesting that the results of in vitro studies on sevoflurane’s effects on cancer cells may not be applicable to in vivo or clinical studies[10]. The different results from in vitro studies may be due to the selection of different types of lung cancer cells.

3. Breast cancer

Breast cancer is the most common malignant tumor in women around the world[11]. Deegan et al. investigated the effects of different anesthesia techniques on the proliferation and migration of breast cancer cells in vitro, and found that the serum of breast cancer patients undergoing propofol and paravertebral anesthesia could inhibit the growth of ER-MDA-MB-231 cells more than that of those undergoing sevoflurane and opioids[12]. The beneficial effect may be attributed to the change of a few cytokines that regulate the perioperative tumor immunity, such as interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor-alpha (TNF-α), and MMPs (including MMP-9), as well as the anti-tumor and anti-metastasis activities of propofol/paravertebral anesthesia in enhancing the lysis of tumor cells by natural killer (NK) cells[13,14]. In addition, sevoflurane can influence or regulate the gene expression in tumor cells[15]. Similarly, another study showed that the serum from patients treated with sevoflurane and opioids during the surgical operation on primary breast cancer showed more significant effect in the reduction of apoptosis of estrogen receptor (ER)-negative breast cancer cells than that from those treated with paravertebral anesthesia[16], indicating that the anesthesia alters the molecular environment of the serum and may affect the function of breast cancer cells.

Some studies have shown that volatile anesthetics, including sevoflurane, regulate gene expression in cultured breast cancer cells in a time-dependent manner. For example, the expression of 5-hydroxytryptamine receptor 4 (5-HT4), which is a serotonin receptor, was upregulated after 10 min of exposure to sevoflurane, but downregulated 20 min later[17]. Sevoflurane can influence the gene expression and regulate intracellular Ca2+ homeostasis to influence the survival of breast cancer cells[18]. Sevoflurane has inhibitory effects on the migration and invasion of breast cancer cells and epithelial-mesenchymal transition through miR-139-5p/ARF6 axis, especially in high concentrations (4%)[18].

In the in vitro experiments, however, sevoflurane had different effects on ER-positive and ER-negative MCF7 cells. In particular, the growth, migration, and invasion of ER-positive MCF7 cells were increased, while for the ER-negative MCF7 cells, only the proliferation and migration were increased. Nevertheless, the degree of influence observed was small and did not depend on the dosage[19]. ER-negative breast cancer is generally associated with a poorer prognosis. Since sevoflurane reduces the invasion of ER-negative MCF7 cells, theoretically, it
can reduce their malignant potentials, but further clinical studies are needed to confirm these results. Another study also demonstrated the effects of sevoflurane on the proliferation, differentiation, and invasion of breast cancer cell[17]. In a variety of malignant tumors, the isoforms of AKT are often amplified which is thought to be involved in the survival growth and invasion of malignant cells. Their activation has been shown to reduce the survival of cancer patients. Sevoflurane exposure during surgical operation may promote the recurrence of cancer through AKT3-induced epithelial mesenchymal transition and three AKT isoforms promoted the survival and growth of cancer cells.[20]

4. Colorectal cancer (CRC)

Highly metastatic CRC is one of the most common malignant tumors in the world[21]. MMP-9 promotes tumor invasion and migration by degrading neutrophils in the extracellular matrix. During ischemia-reperfusion injury, the secretion of IL-8 is increased, thereby stimulating the release of neutrophils protein kinase C (PKC), increasing the expression of MMP-9, and promoting tumor cell invasion. Sevoflurane preconditioning has been shown to reduce ischemia-reperfusion injury and stimulate IL-8-invasion. Sevoflurane preconditioning has been shown to reduce ischemia-reperfusion injury and stimulate IL-8-mediated MMP-9 secretion, thereby reducing the migration of mouse CRC cells in the simulated extracellular matrix in vitro[21,22].

There is no doubt that sevoflurane can inhibit the migration and invasion of CRC and induce apoptosis, which may be related to epigenetic pathways, including regulation of ERK/MMP-9 pathway through miR-203/Robo1[23], miR-34a/ADAM10 axis[24], and miR-637/WNT1 pathway[25]. In addition, the in vitro treatment of sevoflurane exerts an inhibitory effect on tumor growth by modulating hsa_circ_000231[26]. The results are instrumental to the development of appropriate anesthesia regimen for CRC patients undergoing surgical operation (Figure 2).

5. Glioma

Sevoflurane exposure has an inhibitory effect on the migration and invasion of glioma cells. The mechanism involves epigenetic pathways and MMP[26]. Sevoflurane has a promoting effect on the proliferation of human glioma stem cells (GSCs) through HIFs based on findings from in vitro experiments[27]. The other study found that sevoflurane inhibited glioma tumorigenesis and regulated tumor stem cell-like properties and mitochondrial membrane potentials by activating the Ca2+-dependent CaMKII/JNK cascade[28].

Hurmath et al. showed that both sevoflurane and thiopental inhibited the migration and MMP-2 activity of malignant glioma cells after treating the cells with U87MG for 90 min with 2.5% sevoflurane[29]. Similarly, sevoflurane exerted an inhibitory effect on cell migration and invasion by regulating miR-146b-5p and MMP16 in gliomas, which provided a new theoretical basis for the usage of anesthetic agents such as sevoflurane in glioma[30]. Inhibition of AKT1 expression could inhibit the migration and invasion of glioma cells, and the inhibition of sevoflurane might be mediated by the upregulation of miRNA-637, which could inhibit the expression and activity of AKT1.[31]. Sevoflurane in glioma was accompanied with downregulated expression of KCNQ1OT1 and STC1, but with an upregulated expression of miR-146b-5p.[22]. Sevoflurane mediated the progression of glioma by regulating the circ_0012129/miR-761/TGF2 axis[33], circ_0002755/miR-628-5p/MAGT1 axis[34], miR-124-3p/ROCK1 axis[35], ANRIL/let-7b-5p axis[36], HMMR-AS1/miR-7/CDK4 axis[37], circ_0000215/miR-1290/RORA axis[38], miR-27b/VEGF axis[39], miR-335/HIF-1/MMP-9 axis[40], circRELN-mediated miR-1290/RORA axis[41], and miR-218-5p/DEK/β-Catenin axis[42]. Besides, the circ_0079593/miR-633/ROCK1 axis dominated the beneficial effects of sevoflurane on glioma cell tumorigenesis. In addition, the beneficial effect of sevoflurane on glioma cell tumorigenesis is also related to the regulation of the cirC_0079593/miR-633/ROCK1 axis, which provides a new theoretical basis for the usage of sevoflurane in the treatment of glioma[43] (Table 1).

Sevoflurane inhibits the expression of insulin-like growth factor 1 (IGF-1) protein in glioma, thereby promoting the expression of related proteins downstream of apoptosis, and inhibiting the PI3K/AKT signaling pathway in glioma cells[44].

6. Hepatocellular carcinoma (HCC)

Diabetes is associated with the onset and progression of HCC[45]. Fu et al. studied the influence of sevoflurane}
on the growth of human HCC cell line (HepG2) under the condition of high glucose and insulin\cite{46}. The results showed that sevoflurane might affect the proliferation of HepG2 under a physiological state similar to diabetes.

Song et al. attempted to clarify the effective mechanism related to miR-29a/DNA methyltransferase 3 alpha (Dnmt3α) in HCC cells\cite{39}. They found that sevoflurane could enhance the apoptosis of HuH7 and HepG2 cells and inhibit cell migration and invasion, which might be related to the increased expression of PTEN and inhibition of PI3K and AKT. The anti-tumor properties of sevoflurane in HCC cells are evidenced by its abilities to restore the downregulation of miR-29a in HCC tissues and cells, and target the downregulation of Dnmt3a transcription. The study by Cao et al. found that sevoflurane suppressed the proliferation of both HCCLM3 and Huh7 cells\cite{43}. Besides, the invasiveness of both cells decreased with exposure to increasing sevoflurane concentration. Particularly, sevoflurane’s anti-tumor effects on HCC cells could be partially explained by its suppression on the miR-25-3p/PTEN/ Akt/GSK-3β/β catenin signaling pathway. The miR-29a-3p/CBX3 axis was also related to the anti-tumor effect of sevoflurane\cite{42}.

<table>
<thead>
<tr>
<th>Study</th>
<th>Cell line</th>
<th>Exposure</th>
<th>Signaling pathway</th>
<th>Major outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yi et al.\cite{31}</td>
<td>U251</td>
<td>1.7%, 3.4%, and 5.1% 6 h</td>
<td>miR-637↑/AKT1↓</td>
<td>Inhibited glioma cell migration and invasion</td>
</tr>
<tr>
<td>Zhang et al.\cite{30}</td>
<td>U87-MG, U251</td>
<td>1.7%, 3.4%, and 5.1% 6 h</td>
<td>miR-146b-5p↑/MMP-16↓</td>
<td>Impeded glioma cell migration and invasion</td>
</tr>
<tr>
<td>Wen et al.\cite{32}</td>
<td>A172 and U251</td>
<td>1.7%, 3.4%, and 5.1% 6 h</td>
<td>miR-146b-5p↑/STC1↓</td>
<td>Enhanced apoptotic rate, inhibited cell viability, migration, and invasion abilities</td>
</tr>
<tr>
<td>Zhao et al.\cite{26}</td>
<td>LN229 and U251</td>
<td>1.2%, 2.4%, and 4.8% 6 h</td>
<td>miR-34a-5p↑/MMP-2↓</td>
<td>Repressed cell migration and invasion</td>
</tr>
<tr>
<td>Xu et al.\cite{33}</td>
<td>T98G and LN229</td>
<td>1.7%, 3.4%, and 5.1% 6 h</td>
<td>circ_0012129↑/miR-761↑/TGIF2↓</td>
<td>Suppressed growth, colony formation, cell cycle, migration and invasion, and promoted apoptosis</td>
</tr>
<tr>
<td>Li et al.\cite{34}</td>
<td>A-172 and SHG-44</td>
<td>1.7%, 3.4%, and 5.1% 6 h</td>
<td>Circ_0002755↓/miR-628-5p↑/MAGT1↓</td>
<td>Suppressed cell viability, migration and invasion, and accelerated cell apoptosis</td>
</tr>
<tr>
<td>Gao et al.\cite{35}</td>
<td>U251 and U87</td>
<td>4.1% 4 h</td>
<td>miR-124-3p↑/ROCK1↓</td>
<td>Inhibited glioma cells growth, migration and invasion</td>
</tr>
<tr>
<td>Gao et al.\cite{36}</td>
<td>U251 and LN229</td>
<td>1%, 2%, or 4% 6 h</td>
<td>ANRIL↓/miR-let-7b-5p↑/JAK2/STAT3↓</td>
<td>Suppressed growth and migration of glioma cells</td>
</tr>
<tr>
<td>Cheng et al.\cite{41}</td>
<td>T98G and LN-229</td>
<td>1.7%, 3.4%, and 5.1% 6 h</td>
<td>circ_0079593↓/miR-633c/ROCK1↓</td>
<td>Inhibited glioma cell proliferation and metastasis, and induced apoptosis</td>
</tr>
<tr>
<td>Bao et al.\cite{37}</td>
<td>LN229, T98, and A172</td>
<td>1.7%, 3.4%, and 5.1% 6 h</td>
<td>HMMR-AS1↓/miR-7↑/CDK4↓</td>
<td>Inhibited cell proliferation and repressed glioma cell progression</td>
</tr>
<tr>
<td>Zhao et al.\cite{38}</td>
<td>A172 and U251</td>
<td>1.7%, 3.4%, and 5.1% 6 h</td>
<td>circ_0000215↑/miR-1200↓/NCR3LG1↑</td>
<td>Inhibited glioma cell growth and metastasis, accelerated apoptosis, and prevented tumor growth</td>
</tr>
<tr>
<td>Zhan et al.\cite{29}</td>
<td>HEB, U251, and U87</td>
<td>3.4% 6 h</td>
<td>miR-27b-5p↑/VEGF↓/MMP-2, MMP-9↓</td>
<td>Inhibited the growth and migration of glioma cells</td>
</tr>
<tr>
<td>Ishikawa et al.\cite{40}</td>
<td>H4 cell</td>
<td>3.6% 2 h</td>
<td>miR-138-210 and -335↑/HIF-1α, MMP-9↓</td>
<td>Inhibited glioma cell malignancy</td>
</tr>
<tr>
<td>Kang et al.\cite{41}</td>
<td>A172, T98G, N18, and LN229</td>
<td>1.7%, 3.4%, and 5.1% 6 h</td>
<td>circRELI↓/miR-1290↑/RORA↓</td>
<td>Suppressed glioma cell growth, migration and invasion, and accelerated apoptosis and cell cycle block</td>
</tr>
<tr>
<td>Qi et al.\cite{42}</td>
<td>U251 and U343</td>
<td>1%, 2%, or 4% 6 h</td>
<td>miR-218-5p↑/DEK↓/β catenin↓</td>
<td>Suppressed survival, migration, invasion</td>
</tr>
</tbody>
</table>
7. Conclusion and prospects
Sevoflurane is a volatile anesthetic widely used in tumor surgeries. Increasing evidence suggests that the use of sevoflurane in tumor surgery may affect the apoptotic invasion and migration of tumor cells. However, exposure to sevoflurane does not guarantee the manifestation of completely identical biological effect, especially for tumor cells of different entity. For instance, sevoflurane does not show anti-cancer properties in all solid tumors. Sevoflurane has attracted increasing attention because of its potential to inhibit cancer progression. Sevoflurane can effectively regulate epigenetic pathways of miRNA, lncRNA, and circRNA, and regulate signaling pathways, such as hypoxia-activated PI3K/AKT, MAPK, and MMP. In addition, sevoflurane can also influence the immune function of patients.

As noted above, preclinical studies have been conducted to determine the relationship between sevoflurane and tumor cells. Due to the diversity of tumor types and patient status, it is difficult to reach a uniform conclusion about the relationship between sevoflurane and tumor development; therefore, further clinical trials are needed.

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Author contributions
J.O. and H.W. conceived the idea of this review and wrote the paper. Q.N. and Y.C. completed the figures and tables. C.L., J.Y., and H.W. reviewed and edited drafts of the paper. All authors have read and agree to the published version of the manuscript.

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