Review Article
How does the anesthetic agent propofol affect tumors?

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Abstract: Propofol is one of the most popular intravenous agents used for induction and maintenance of anesthesia. Numerous studies have intended to explore whether or how propofol affects tumor metastasis and invasion but the results are conflicting. Propofol can influence cancer progression through indirectly affecting the function of immune cells such as T cells, NK cells or macrophages and directly interfering with cancer cell biology. The anti-inflammation property of propofol may be beneficial in certain cancer surgeries. In this review, we will discuss the current understanding about the postulated mechanisms underlying the effect of propofol on tumors and the present research progress in this field.

Keywords: Propofol, cancer, immune cells, GABA_A, inflammation

Introduction
The occurrence and development of cancer are caused by a series of factors interacting with each other. Hanahan and colleagues [1] described the hallmarks of cancer in detail. A variety of biological characteristics facilitate tumorigenesis or promote tumor progression. Surgery is of paramount importance in the management of solid tumors as definitive resection can be curative. However, cancer recurrence and metastasis after primary resections remain the main causes for high morbidity and mortality. Surgery is likely to evoke strong stress and dissemination of cancer cells [2-4], and meanwhile the body is under relative immunosuppression [5, 6]. In addition, certain perioperative agents could give rise to body’s metabolic disturbance and immunosuppression [7], and hence, the perioperative period is a window for cancer metastasis and postoperative recurrence.

Increased numbers of studies have focused on the impact of perioperative factors on cancer recurrence, including the pathophysiological effects of anesthesia techniques and anesthetics on tumor metastasis [8-12]. Propofol (2,6-diisopropylphenol) is a potent intravenous anesthetic characterized by fast onset, rapid recovery and stable hemodynamics and the chemical properties of propofol have been reviewed in detail by Fan et al. [13]. The mechanism underlying the hypnotic action of propofol is complex with interactions at different neurotransmitter receptors on the central nervous system (CNS), particularly gamma-aminobutyric acid A (GABA_A) receptors [14]. It is extensively used for the induction and maintenance of clinical anesthesia and sedation for critically ill patients in the intensive care units (ICUs) [15]. Propofol exerts both anti-oxidative stress activity and immunoregulation properties [16]. Furthermore, some studies [17] reported that the propofol concentration commonly used in clinical practice could induce apoptosis and inhibit the invasion of human cancer cells, but others argued that [18, 19] propofol potentiated cancer cell proliferation and metastasis. The present review summarizes the progress in the research of the propofol effect on tumors and possible underlying mechanisms with respect to the impact of propofol on immune cells, its direct effect on cancer cells and its potential anti-inflammatory property, hoping that the result could provide some useful references for
future research and clinical selection of anesthetic agents.

**Indirect effects of propofol on tumors through immune cells**

CD8+ T and CD4+ T cells are of paramount importance to immune surveillance against tumorigenesis [20]. Among these, CD8+ cytotoxic T lymphocytes (CTLs) work as the main effector cells in the specific immune response to the identification and eradication of tumor cells. CD4+ T cells can directly exterminate MHC-II molecule-positive tumor cells and indirectly kill MHC-II molecule-negative cancer cells in some way [21]. CD4+ T cells are classified into four subtypes: Th1, Th2, Th17 and T regulatory cells (Tregs). IL-12 and IFN-γ can promote differentiation of CD4+ T cells into Th1 and cement CTL anti-tumor immune activity or activate macrophages to kill tumor cells. Accordingly, IL-4 promotes Th2 differentiation and inhibits Th1 differentiation. T cell-mediated immunity also plays a critical role during the perioperative period. Change in T lymphocytes in peripheral circulation may depend on the stress degree and the duration of surgery. Ji et al. [22] demonstrated that propofol anesthesia promoted Th1 cell differentiation in patients receiving laparoscopic cholecystectomy. In patients undergoing pulmonary lobectomy for non-small cell lung cancer (NSCLC), both the IFNγ/IL-4 ratio and the percentage of CD4+CD28+ T cells in peripheral blood were significantly higher in propofol anesthesia group than that in isoflurane group [23]. In addition, propofol was demonstrated to enhance in vitro anticancer cell activity of CTLs [24], probably due to the contribution of propofol to high cytokine ratio of IFN-γ/IL-4 [25], which is prone to induce Th1 cell differentiation as a consequence of the reinforced CTL-killing capacity [26, 27].

NK cells are the major lymphocyte subpopulation that secrete immunity mediators and dissolve cancerous cells directly by cytotoxicity [28]. NK cells play pivotal roles in immune surveillance and killing tumor cells [29]. However, the number and activity of NK cells are both affected by surgical stress and medications. Clinical studies [30] showed when NK cells from healthy individuals were cultured with sera from patients who received breast cancer resection under anesthesia of either propofol-paravertebral block or isoflurane with morphine, the in vitro anti-tumor activity of NK cells was increased in propofol group and decreased in isoflurane-morphine group. Rivka Melamed et al. [10] inoculated MADB106 cancer cells into rats via the tail vein and found that NK cytotoxicity was suppressed markedly and lung tumor retention within 1 h was increased in either ketamine group or thiopentone group but not in propofol group. However, the mechanism by which propofol affects NK activity or counts in peripheral blood is unknown.

Solid tumors are composed of a group of heterogeneous cells including malignant tumor cells and stromal cells such as macrophages, NK cells, neutrophils, fibroblasts and endothelia [31, 32], among which tumor-associated macrophages (TAM) were reported to be closely related to tumor angiogenesis, cancer cell metastasis and prognosis [33-35]. TAMs were supposed to be evolved from monocytes in the peripheral circulation recruited by the release of chemotactic cytokines to the tumor microenvironment, where they were further modified to secrete growth cytokines such as EGF [36], TNF-α [37], VEGF and bFGF [35] to promote tumor growth. In vitro overdose propofol 140 μM (25 μg/ml) induced macrophage RAW264.7 apoptosis by inhibiting Akt and activating GSK-3β [38]. In contrast, low dose propofol 56 μM (10 μg/ml) suppressed neutrophils or acute promyelocytic leukemia HL60 cell apoptosis by activating PI3K/Akt and inhibiting GSK-3β activity [39]. Therefore, the cytotoxicity and cytoprotection of propofol may associate with heterogeneous cells and varied dose because 150 μM propofol could induce significant apoptosis of HL60 cells [40]. GSK-3β is an intracellular serine/threonine protein kinase that acts as downstream signal of PI3K/Akt and is inhibited by phosphorylation. Blocking PI3K or over-expressing GSK-3β was reported to promote cell apoptosis [41]. Interestingly, a recent study [42] reported that GSK-3β inhibition enhanced dendritic cell-based cancer vaccine potency.

Additionally, Zhang et al. [43] conducted a study with propofol for in vivo anti-hepatocellular carcinoma and demonstrated that propofol could repress cancer cell proliferation and metastasis by stimulating macrophages to overexpress miR-142-3p which was transferred into hepatic carcinoma Hepal-6 cells and downregulated...
RAC1 protein expression by targeting its target gene. However, miR-142-3p could not be upregulated when Hepal-6 cells were directly treated with propofol. MicroRNAs (miR) are small non-coding RNAs that regulate gene expression primarily through pairing to sites located within the 3’ untranslated regions (UTR) of the target mRNA [44]. It was reported [45] that enforcing miR-142-3p expression could prevent tumor-induced medullary cells to differentiate into immunosuppressive macrophages, also known as tumor-associated macrophages (TAM). TAM modified the tumor microenvironment in vivo and favored antitumor immunity. Targeting miR or TAM may create a new strategy for improving tumor immunotherapy [46]. Nonetheless, whether or how propofol affects the tumor microenvironment needs to be clarified.

Tumor immunity is acknowledged as a complex process. Innate immune and adaptive immune cells collectively mediate immune surveillance for tumorigenesis and cancer cell killing (Table 1). Immune function could be affected by various factors during the perioperative period. Immune cells act collaboratively in the antitumor process. For example, NK cells and antigen presenting cells DCs induce T cell antitumor immunity synergistically [47-49]. Postoperative cancer recurrence and metastasis may hinge upon, to some extent, perioperative immunocyte function, which will affect immune surveillance against tumors or tumor metastasis. Surprisingly, dendritic cell-based vaccines treated with propofol enhanced antitumor immunity in mice [50]. Still, the effect of propofol on immune function requires further study, embracing the interactions among diverse immunocytes and the variations in heterogeneous cancer cells and different patients.

The direct effect of propofol on tumor cells

Studies have suggested several mechanisms by which propofol affected the proliferation and metastasis of tumors. Tadanori et al. [17] showed 1-5 ug/ml propofol decreased the invasiveness ability of human cancer cells dose dependently through suppressing β1 integrin clustering and actin stress fiber formation mainly by modulating RhoA. Rho protein is known as a member of the p21 Ras subfamily of small GTPases and regulates tumor progress [51, 52], which was reported to facilitate cancer cell invasion after activation [53].

In the process of tumor growth, hypoxia induces significant biological effects, among which induced angiogenesis has been well documented, and promotes tumor proliferation and metastasis. Hypoxia inducible factor HIF-1α acts as a key regulator therein [54]. In vitro HIF-1α protein synthesis and its mediated genes including LDHA, VEGF, PHD-3 and FIH-1 were inhibited by 100 uM propofol in an oxygen concentration-dependent manner [55]. Volatile anesthetic isoflurane induced HIF-1α expression and exerted activity that favored tumor growth [56, 57]. However, propofol was reported to antagonize isoflurane-induced expression of HIF-1α and VEGF, proliferation and metastasis of tumor cells and reverse isoflurane-induced resistance of prostate cancer PC3 cells to chemotherapy drug docetaxel.

Studies [57] reported that both inhibition of PI3K/Akt/mTOR and MAPK/ERK pathways were involved in propofol anti-tumor activity. Besides, propofol attenuated the activity of MAPK/ERK/MMP-9 signal pathway in esophageal squamous carcinoma Eca-109 cells and colon cancer LoVo cells, there by impairing cancer cell proliferation and invasion and tumor angiogenesis [58, 59]. Propofol also inhibited invasion and increased apoptosis of osteosarcoma cell in vitro via downregulation of transforming growth factor-β1 (TGF-β1) expression [60]. EGFR/Ras/Raf/MAPK/ERK pathways controlled normal cell proliferation, survival and differentiation and EGFR activation correlated with HIF-1α induced angiogenesis [54]. Plenty of human cancer cells go with R as mutation resulting inaberrant activation of Ras/Raf/MAPK/ERK pathway, consequently bringing about persistent proliferation and metastasis of cancer cells and insensitivity to EGFR blockers [61]. However, lung cancer A549 cell lines with K-ras gene mutation at codon12 treated by propofol showed declined levels of ERK1/2 phosphorylation, upregulation of Caspase-3 and BAX proteins and were inclined to apoptosis [62]. Clinical target therapy is preferred to lung cancer patients with K-ras mutation. We therefore speculate whether propofol could improve the chemotherapeutic effect of target drugs, which of course needs to be verified by in vitro experiments in the first place.

Other than the above-mentioned mechanisms, there are also other mechanisms underlying the suppressive effect of propofol on tumor
Table 1. Indirect effects of propofol on tumors through immune cells

<table>
<thead>
<tr>
<th>Immune cells</th>
<th>Publications</th>
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<tr>
<td>T cells</td>
<td>Promote CD4+ T cells differentiating into Th1 and cement in vitro anti-cancer cell activity of CTLs [22-25]</td>
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<tr>
<td>NK cells</td>
<td>Increase in vitro anti-tumor activity and cytotoxicity of NK cells [10, 30]</td>
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<tr>
<td>Macrophage</td>
<td>Induce macrophage apoptosis; stimulate miR-142-3p overexpression in macrophage and miR-142-3p induce TAM differentiation [38-40, 43]</td>
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Table 2. Propofol effect on cancer cells

<table>
<thead>
<tr>
<th>Effect</th>
<th>Reported underlying mechanisms</th>
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<tr>
<td>Inhibiting</td>
<td>Decrease the invasiveness ability of human cancer cells by modulating RhoA protein [17]</td>
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<tr>
<td></td>
<td>Inhibit HIF-1α protein synthesis and its mediated genes [55-57]</td>
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<tr>
<td></td>
<td>Inhibit PI3K/Akt/mTOR or MAPK/ERK pathway [57-59, 62]; downregulate TGF β1 expression [60]</td>
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<td></td>
<td>Repress the NF-κB activity of pancreatic cancer cells and enhance in vitro gemcitabine chemotherapeutic effect [63]</td>
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<td></td>
<td>Trigger HL-60 cell apoptosis through activating death receptors-caspase signal pathway and mitochondrial apoptotic pathway [40]</td>
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<td></td>
<td>Cripple cancer cell proliferation by upregulating miR-199a expression within liver cancer cells HepG2 [64]</td>
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<tr>
<td></td>
<td>Attenuate the invasive and migratory abilities of colon cancer cells by activating GABAₐ receptors [59]</td>
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<tr>
<td></td>
<td>Attenuate inflammation and oxidative stress [72-76]</td>
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<tr>
<td>Promoting</td>
<td>Accelerate gallbladder carcinoma GBC-SD cell proliferation by promoting Nrf2 nucleus translocation [18]</td>
</tr>
<tr>
<td></td>
<td>Trigger migration of breast cancer MDA-MB-468 cells via incrementing calcium influx and reconstituting troponin after activating GABAₐ receptors [19]</td>
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cells. Propofol was found to repress the NF-κB activity of pancreatic cancer cells and enhance the in vitro chemotherapeutic effect of gemcitabine [63]. Additionally, 150 uM propofol was proved to trigger HL-60 cell apoptosis through activating death receptors-caspase signal pathway on the cell surface and mitochondrial apoptotic pathway [40]. Propofol upregulated miR-199a expression within liver cancer cells HepG2 to cripple cancer cell proliferation [64]. MiR-199a is documented as a highly conserved microRNA and it is down-regulated universally in Hepatocarcinoma cells, whose overexpression both in vivo and in vitro could suppress cancer cell proliferation [65]. A recent study [66] reported that the level of miR-199a-5p expression correlated with the malignancy and prognosis of cancers, and HIF-1α was shown to inhibit its expression. As propofol was demonstrated to inhibit HIF-1α protein synthesis [55, 57], there possibly exists a link between propofol, HIF-1α and miR-199a.

Although numerous studies have demonstrated the suppressive effect of propofol on tumor cells, there are conflicting reports in the literature. A published study [18] reported that propofol treatment regulated downstream target gene transcription in gallbladder carcinoma GBC-SD cells by promoting transit of activated Nrf2 from the cytoplasm to the nucleus, thus increasing the level of ERK1/2 phosphorylation and ultimately accelerating cancer cell proliferation. Nrf2 is a critical transcriptional regulatory factor that regulates the expression of antioxidases and detoxifying enzymes, of which hemeoxygenase HO-1 is a typical one [67]. Stimulating HO-1 expression by propofol protected neuroblastoma cells SH-SY5Y against oxidative stress-induced cell death through activating ERK signal pathway [68]. Garib V et al. [19] discovered that propofol triggered migration of breast cancer MDA-MB-468 cells via incrementing calcium influx and reconstituting troponin. An overview is seen below (Table 2). Different cancer cells respond to propofol in different ways due to various reasons including the propofol concentration, the diversity of cancer cells, gene mutations [62], heterogeneity of phenotypes and functions of cancer cells [69] or variation of surface receptors on tumor cells. Therefore, more in vivo and in vitro experiments are needed to confirm the relevant underlying mechanisms.

The anti-inflammatory effect of propofol on tumors

Innate immune and adaptive immune cells as well as non-hematopoietic cells collaborate with each other to regulate immunity, inflammation, tissue repair, and tumor occurrence and development [70]. Cancer-related inflammation is recognized as the 7th hallmark of cancer [1]. Inflammation promotes angiogenesis, proliferation and invasion of tumor cells, eventually accelerating tumor evolvement [71]. Existing studies indicate that propofol can attenuate inflammation and oxidative stress [72-76], and therefore it seems reasonable to postulate that these properties of propofol may account for its antitumor effect.

Propofol-GABA$_A$ receptors and tumors

GABA (γ-Amino butyric acid) receptors comprise ionotropic receptors GABA$_A$$_1$ and GABA$_A$$_2$ and metabotropic receptor GABA$_A$$_3$. The endogenous ligand GABA for GABA$_A$ receptor is a kind of inhibitory neurotransmitter. GABAergic signaling is not only limited to the nervous system; rather it extensively exists in peripheral organs and various cancer cells [77]. Additionally, GABAergic signaling is involved in the control over cell proliferation, differentiation and migration, including cancer cells [78].

Propofol has been found to exert different effects following triggering GABA$_A$$_1$ receptors on different cancer cells. For instance, propofol attenuated the invasive and migratory abilities of colon cancer cells [59] but promoted the metastasis of breast cancer MDA-MB-468 cells [19] after activating GABA$_A$$_1$ receptors. GABA$_A$$_1$ receptors/ERK1/2/keratin signaling was reported to be possibly involved in the metastasis and dissemination of cancer cells [79]. However, Satoshi et al. [55] found that HIF-1α protein expression was also suppressed by 2,4-diisopropylphenol almost commensurate with 2,6-diisopropylphenol in Hep3 cells under the condition of 20% aloxygen. As 2,4-diisopropylphenol does not possess GABA$_A$$_1$ receptor-binding capacity, the propofol effect could not be totally explained by GABA$_A$$_1$ receptor binding. These research findings are discrepant, but what contributes to the discrepancy may be attributed to the differences in GABA$_A$ergic-mediated cellular signaling in different cancer cells and the variations of GABA$_A$$_1$ receptor binding.
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expression or their structural mutations on the surface of cancer cells. Nonetheless, studies suggest that GABA\textsubscript{A} receptors may be involved in the inhibitory or promoting effect of propofol on cancer cells. As few studies have focused on the correlation between propofol-GABA\textsubscript{A}ergic signaling and tumor development, more studies are required to illuminate why propofol-GABA\textsubscript{A}ergic signaling facilitates the migration and invasion of some tumor cells while suppresses others.

Conclusion

Studies have demonstrated that propofol has positive effect on the anti-tumor immune cells and properties against the proliferation and metastasis of cancer cells. Probably the above effect or properties correlate with GABA\textsubscript{A}ergic signaling, though discrepancies exist. These discrepancies maybe because of the heterogeneity of cancer cells. Besides, many factors such as surgery stress, inflammation, pain, immunocompromise, and other anesthetic agents including morphine, inhalation gas or analgesics could affect immunity in the perioperative period. Clinical prospective randomized studies are expected to confirm the effect of propofol anesthesia on immune function and postoperative prognosis of cancer patients. Therefore, consensus guidelines for the selection of clinical anesthetics for cancer surgeries are required with respect to their immunologic properties, methods of their use, and their direct or potential effects on cancer cell biology. Clinical anesthesiologists should be prudent in the selection of anesthetic agents and related techniques.

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Disclosure of conflict of interest

None.

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