Int J Clin Exp Med 2017;10(4):5995-6003
www.ijcem.com /ISSN:1940-5901/IJCEM0046882

Review Article

How does the anesthetic agent propofol affect tumors?

Juan Wei[1,3], Jing Luo[3,4], Xin Lv[1,2,3,4]

[1]Department of Anesthesiology, Shanghai Pulmonary Hospital, Soochow University, Suzhou, China; [2]Department of Anesthesiology, First Affiliated Hospital of Anhui Medical University, Anhui, China; [3]Department of Anesthesiology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China; [4]Jiangsu Province Key Laboratory of Anesthesiology, Xuzhou Medical College, Xuzhou, China

Received December 19, 2016; Accepted December 30, 2016; Epub April 15, 2017; Published April 30, 2017

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 propofolis 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 propofolon 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 overexpressing 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 noncoding 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 variationsin 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

Immune cells	Publications
T cells	Promote $CD4^+$ T cells differentiating into Th1 and cement *in vitro* anti-cancer cell activity of CTLs [22-25]
NK cells	Increase *in vitro* anti-tumor activity and cytotoxicity of NK cells [10, 30]
Macrophage	Induce macrophage apoptosis; stimulate miR-142-3p overexpression in macrophage and miR-142-3p induce TAM differentiation [38-40, 43]

Table 2. Propofol effect on cancer cells

Effect	Reported underlying mechanisms
Inhibiting	Decrease the invasiveness ability of human cancer cells by modulting RhoA protein [17]
	Inhibit HIF-1α protein synthesis and its mediated genes [55-57]
	Inhibit PI3K/Akt/mTOR or MAPK/ERK pathway [57-59, 62]; downregulate TGF β1 expression [60]
	Repress the NF-κB activity of pancreatic cancer cells and enhance *in vitro* gemcitabine chemotherapeutic effect [63]
	Trigger HL-60 cell apoptosis through activating death receptors-caspase signal pathway and mitochondrial apoptotic pathway [40]
	Cripple cancer cell proliferation by upregulating miR-199a expression within liver cancer cells HepG2 [64]
	Attenuate the invasive and migratory abilities of colon cancer cells by activating $GABA_A$ receptors [59]
	Attenuate inflammation and oxidative stress [72-76]
Promoting	Accelerate gallbladder carcinoma GBC-SD cell proliferation by promoting Nrf2 nucleus translocation [18]
	Trigger migration of breast cancer MDA-MB-468 cells via incrementing calcium influx and reconstituting troponin after activating $GABA_A$ receptors [19]

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 $GABA_A$ and $GABA_C$ and metabotropic receptor $GABA_B$. 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 $GABA_A$ 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 $GABA_A$ receptors. $GABA_A$ 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 $GABA_A$ receptor-binding capacity, the propofol effect could not be totally explained by $GABA_A$ 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 $GABA_A$ receptor

expression or their structural mutations on the surface of cancer cells. Nonetheless, studies suggest that $GABA_A$ receptors may be involved in the inhibitory or promoting effect of propofol on cancer cells. As few studies have directly focused on the correlation between propofol-$GABA_A$ ergic signaling and tumor development, more studies are required toto illuminate why propofol-$GABA_A$ ergic signaling facilitates the migration and invasion of some tumor cells [19] while suppresses others [59].

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 $GABA_A$ 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.

Acknowledgements

This work is supported in full by grant from the National Natural Science Foundation of China (NO. 81272142 and 81671947).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xin Lv, Department of Anesthesiology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, #507 Zhengmin Road, Shanghai 200433, China. Tel: +86-21-65115006; Fax: +86-021-65115006; E-mail: xinlvg@126.com

References

[1] Hanahan D and Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144: 646-674.

[2] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.

[3] Eschwege P, Dumas F, Blanchet P, Le Maire V, Benoit G, Jardin A, Lacour B and Loric S. Haematogenous dissemination of prostatic epithelial cells during radical prostatectomy. Lancet 1995; 346: 1528-1530.

[4] Tsuchiya Y, Sawada S, Yoshioka I, Ohashi Y, Matsuo M, Harimaya Y, Tsukada K and Saiki I. Increased surgical stress promotes tumor metastasis. Surgery 2003; 133: 547-555.

[5] Angele MK and Faist E. Clinical review: immunodepression in the surgical patient and increased susceptibility to infection. Crit Care 2002; 6: 298-305.

[6] Lennard TW, Shenton BK, Borzotta A, Donnelly PK, White M, Gerrie LM, Proud G and Taylor RM. The influence of surgical operations on components of the human immune system. Br J Surg 1985; 72: 771-776.

[7] Cassinello F, Prieto I, del Olmo M, Rivas S and Strichartz GR. Cancer surgery: how may anesthesia influence outcome? J Clin Anesth 2015; 27: 262-272.

[8] Wada H, Seki S, Takahashi T, Kawarabayashi N, Higuchi H, Habu Y, Sugahara S and Kazama T. Combined spinal and general anesthesia attenuates liver metastasis by preserving TH1/TH2 cytokine balance. Anesthesiology 2007; 106: 499-506.

[9] Snyder GL and Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. Br J Anaesth 2010; 105: 106-115.

[10] Melamed R, Bar-Yosef S, Shakhar G, Shakhar K and Ben-Eliyahu S. Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane, but not by propofol: mediating mechanisms and prophylactic measures. Anesth Analg 2003; 97: 1331-1339.

[11] Kurosawa S and Kato M. Anesthetics, immune cells, and immune responses. J Anesth 2008; 22: 263-277.

[12] Niwa H, Rowbotham DJ, Lambert DG and Buggy DJ. Can anesthetic techniques or drugs affect cancer recurrence in patients undergoing cancer surgery? J Anesth 2013; 27: 731-741.

[13] Fan W, Zhu X, Wu L, Wu Z, Li D, Huang F and He H. Propofol: an anesthetic possessing neuroprotective effects. Eur Rev Med Pharmacol Sci 2015; 19: 1520-1529.

[14] Trapani G, Altomare C, Sanna E, Biggio G and Liso G. Propofol in anesthesia. mechanism of action, structure-activity relationships, and drug delivery. Curr Med Chem 2000; 7: 249-271.
[15] Fulton B and Sorkin EM. Propofol. An overview of its pharmacology and a review of its clinical efficacy in intensive care sedation. Drugs 1995; 50: 636-657.
[16] Marik PE. Propofol: an immunomodulating agent. Pharmacotherapy 2005; 25: 28s-33s.
[17] Mammoto T, Mukai M, Mammoto A, Yamanaka Y, Hayashi Y, Mashimo T, Kishi Y and Nakamura H. Intravenous anesthetic, propofol inhibits invasion of cancer cells. Cancer Lett 2002; 184: 165-170.
[18] Zhang L, Wang N, Zhou S, Ye W, Jing G and Zhang M. Propofol induces proliferation and invasion of gallbladder cancer cells through activation of Nrf2. J Exp Clin Cancer Res 2012; 31: 66.
[19] Garib V, Lang K, Niggemann B, Zanker KS, Brandt L and Dittmar T. Propofol-induced calcium signalling and actin reorganization within breast carcinoma cells. Eur J Anaesthesiol 2005; 22: 609-615.
[20] Koebel CM, Vermi W, Swann JB, Zerafa N, Rodig SJ, Old LJ, Smyth MJ and Schreiber RD. Adaptive immunity maintains occult cancer in an equilibrium state. Nature 2007; 450: 903-907.
[21] Haabeth OA, Tveita AA, Fauskanger M, Schjesvold F, Lorvik KB, Hofgaard PO, Omholt H, Munthe LA, Dembic Z, Corthay A and Bogen B. How do CD4(+) T cells detect and eliminate tumor cells that either lack or express MHC class II Molecules? Front Immunol 2014; 5: 174.
[22] Ji FH, Wang YL and Yang JP. Effects of propofol anesthesia and sevoflurane anesthesia on the differentiation of human T-helper cells during surgery. Chin Med J (Engl) 2011; 124: 525-529.
[23] Ren XF, Li WZ, Meng FY and Lin CF. Differential effects of propofol and isoflurane on the activation of T-helper cells in lung cancer patients. Anaesthesia 2010; 65: 478-482.
[24] Kushida A, Inada T and Shingu K. Enhancement of antitumor immunity after propofol treatment in mice. Immunopharmacol Immunotoxicol 2007; 29: 477-486.
[25] Salo M, Pirttikangas CO and Pulkki K. Effects of propofol emulsion and thiopentone on T helper cell type-1/type-2 balance in vitro. Anaesthesia 1997; 52: 341-344.
[26] Gao FG, Khammanivong V, Liu WJ, Leggatt GR, Frazer IH and Fernando GJ. Antigen-specific CD4+ T-cell help is required to activate a memory CD8+ T cell to a fully functional tumor killer cell. Cancer Res 2002; 62: 6438-6441.
[27] Nishimura T, Iwakabe K, Sekimoto M, Ohmi Y, Yahata T, Nakui M, Sato T, Habu S, Tashiro H, Sato M and Ohta A. Distinct role of antigen-specific T helper type 1 (Th1) and Th2 cells in tumor eradication in vivo. J Exp Med 1999; 190: 617-627.
[28] Orr MT and Lanier LL. Natural killer cell education and tolerance. Cell 2010; 142: 847-856.
[29] Vivier E, Ugolini S, Blaise D, Chabannon C and Brossay L. Targeting natural killer cells and natural killer T cells in cancer. Nat Rev Immunol 2012; 12: 239-252.
[30] Buckley A, McQuaid S, Johnson P and Buggy DJ. Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: a pilot study. Br J Anaesth 2014; 113 Suppl 1: i56-62.
[31] Kelly PM, Davison RS, Bliss E and McGee JO. Macrophages in human breast disease: a quantitative immunohistochemical study. Br J Cancer 1988; 57: 174-177.
[32] O'Sullivan C and Lewis CE. Tumour-associated leucocytes: friends or foes in breast carcinoma. J Pathol 1994; 172: 229-235.
[33] Gwak JM, Jang MH, Kim DI, Seo AN and Park SY. Prognostic value of tumor-associated macrophages according to histologic locations and hormone receptor status in breast cancer. PLoS One 2015; 10: e0125728.
[34] Leek RD, Lewis CE, Whitehouse R, Greenall M, Clarke J and Harris AL. Association of macrophage infiltration with angiogenesis and prognosis in invasive breast carcinoma. Cancer Res 1996; 56: 4625-4629.
[35] Lewis CE, Leek R, Harris A and McGee JO. Cytokine regulation of angiogenesis in breast cancer: the role of tumor-associated macrophages. J Leukoc Biol 1995; 57: 747-751.
[36] O'Sullivan C, Lewis CE, Harris AL and McGee JO. Secretion of epidermal growth factor by macrophages associated with breast carcinoma. Lancet 1993; 342: 148-149.
[37] Pusztai L, Clover LM, Cooper K, Starkey PM, Lewis CE and McGee JO. Expression of tumour necrosis factor alpha and its receptors in carcinoma of the breast. Br J Cancer 1994; 70: 289-292.
[38] Hsing CH, Chen YH, Chen CL, Huang WC, Lin MC, Tseng PC, Wang CY, Tsai CC, Choi PC and Lin CF. Anesthetic propofol causes glycogen synthase kinase-3beta-regulated lysosomal/mitochondrial apoptosis in macrophages. Anesthesiology 2012; 116: 868-881.
[39] Hsing CH, Chen CL, Lin WC and Lin CF. Propofol treatment inhibits constitutive apoptosis in human primary neutrophils and granulocyte-differentiated human HL60 cells. PLoS One 2015; 10: e0129693.

[40] Tsuchiya M, Asada A, Arita K, Utsumi T, Yoshida T, Sato EF, Utsumi K and Inoue M. Induction and mechanism of apoptotic cell death by propofol in HL-60 cells. Acta Anaesthesiol Scand 2002; 46: 1068-1074.
[41] Pap M and Cooper GM. Role of glycogen synthase kinase-3 in the phosphatidylinositol 3-Kinase/Akt cell survival pathway. J Biol Chem 1998; 273: 19929-19932.
[42] Noh KT, Son KH, Jung ID, Kang TH, Choi CH and Park YM. Glycogen synthase kinase-3beta (GSK-3beta) inhibition enhances dendritic cell-based cancer vaccine potency via suppression of interferon-gamma-induced indoleamine 2,3-dioxygenase expression. J Biol Chem 2015; 290: 12394-12402.
[43] Zhang J, Shan WF, Jin TT, Wu GQ, Xiong XX, Jin HY and Zhu SM. Propofol exerts anti-hepatocellular carcinoma by microvesicle-mediated transfer of miR-142-3p from macrophage to cancer cells. J Transl Med 2014; 12: 279.
[44] Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell 2009; 136: 215-233.
[45] Sonda N, Simonato F, Peranzoni E, Cali B, Bortoluzzi S, Bisognin A, Wang E, Marincola FM, Naldini L, Gentner B, Trautwein C, Sackett SD, Zanovello P, Molon B and Bronte V. miR-142-3p prevents macrophage differentiation during cancer-induced myelopoiesis. Immunity 2013; 38: 1236-1249.
[46] Jinushi M and Komohara Y. Tumor-associated macrophages as an emerging target against tumors: creating a new path from bench to bedside. Biochim Biophys Acta 2015; 1855: 123-130.
[47] Adam C, King S, Allgeier T, Braumuller H, Luking C, Mysliwietz J, Kriegeskorte A, Busch DH, Rocken M and Mocikat R. DC-NK cell cross talk as a novel CD4+ T-cell-independent pathway for antitumor CTL induction. Blood 2005; 106: 338-344.
[48] Mocikat R, Braumuller H, Gumy A, Egeter O, Ziegler H, Reusch U, Bubeck A, Louis J, Mailhammer R, Riethmuller G, Koszinowski U and Rocken M. Natural killer cells activated by MHC class I(low) targets prime dendritic cells to induce protective CD8 T cell responses. Immunity 2003; 19: 561-569.
[49] Kelly JM, Darcy PK, Markby JL, Godfrey DI, Takeda K, Yagita H and Smyth MJ. Induction of tumor-specific T cell memory by NK cell-mediated tumor rejection. Nat Immunol 2002; 3: 83-90.
[50] Inada T, Kubo K and Shingu K. Vaccines using dendritic cells, differentiated with propofol, enhance antitumor immunity in mice. Immunopharmacol Immunotoxicol 2009; 31: 150-157.
[51] Prendergast GC, Khosravi-Far R, Solski PA, Kurzawa H, Lebowitz PF and Der CJ. Critical role of Rho in cell transformation by oncogenic Ras. Oncogene 1995; 10: 2289-2296.
[52] del Peso L, Hernandez-Alcoceba R, Embade N, Carnero A, Esteve P, Paje C and Lacal JC. Rho proteins induce metastatic properties in vivo. Oncogene 1997; 15: 3047-3057.
[53] Yoshioka K, Matsumura F, Akedo H and Itoh K. Small GTP-binding protein Rho stimulates the actomyosin system, leading to invasion of tumor cells. J Biol Chem 1998; 273: 5146-5154.
[54] Liao D and Johnson RS. Hypoxia: a key regulator of angiogenesis in cancer. Cancer Metastasis Rev 2007; 26: 281-290.
[55] Takabuchi S, Hirota K, Nishi K, Oda S, Oda T, Shingu K, Takabayashi A, Adachi T, Semenza GL and Fukuda K. The intravenous anesthetic propofol inhibits hypoxia-inducible factor 1 activity in an oxygen tension-dependent manner. FEBS Lett 2004; 577: 434-438.
[56] Benzonana LL, Perry NJ, Watts HR, Yang B, Perry IA, Coombes C, Takata M and Ma D. Isoflurane, a commonly used volatile anesthetic, enhances renal cancer growth and malignant potential via the hypoxia-inducible factor cellular signaling pathway in vitro. Anesthesiology 2013; 119: 593-605.
[57] Huang H, Benzonana LL, Zhao H, Watts HR, Perry NJ, Bevan C, Brown R and Ma D. Prostate cancer cell malignancy via modulation of HIF-1alpha pathway with isoflurane and propofol alone and in combination. Br J Cancer 2014; 111: 1338-1349.
[58] Xu YB, Du QH, Zhang MY, Yun P and He CY. Propofol suppresses proliferation, invasion and angiogenesis by down-regulating ERK-VEGF/MMP-9 signaling in Eca-109 esophageal squamous cell carcinoma cells. Eur Rev Med Pharmacol Sci 2013; 17: 2486-2494.
[59] Miao Y, Zhang Y, Wan H, Chen L and Wang F. GABA-receptor agonist, propofol inhibits invasion of colon carcinoma cells. Biomed Pharmacother 2010; 64: 583-588.
[60] Xu YB, Jiang W, Zhao FR, Li G, Du QH, Zhang MY and Guo XG. Propofol suppresses invasion and induces apoptosis of osteosarcoma cell in vitro via downregulation of TGF-beta1 expression. Eur Rev Med Pharmacol Sci 2016; 20: 1430-1435.
[61] Roberts PJ and Der CJ. Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. Oncogene 2007; 26: 3291-3310.
[62] Song J, Shen Y, Zhang J and Lian Q. Mini profile of potential anticancer properties of propofol. PLoS One 2014; 9: e114440.
[63] Du QH, Xu YB, Zhang MY, Yun P and He CY. Propofol induces apoptosis and increases gemcitabine sensitivity in pancreatic cancer cells in vitro by inhibition of nuclear factor-kappaB activity. World J Gastroenterol 2013; 19: 5485-5492.

[64] Zhang J, Wu GQ, Zhang Y, Feng ZY and Zhu SM. Propofol induces apoptosis of hepatocellular carcinoma cells by upregulation of microRNA-199a expression. Cell Biol Int 2013; 37: 227-232.
[65] Jia XQ, Cheng HQ, Qian X, Bian CX, Shi ZM, Zhang JP, Jiang BH and Feng ZQ. Lentivirus-mediated overexpression of microRNA-199a inhibits cell proliferation of human hepatocellular carcinoma. Cell Biochem Biophys 2012; 62: 237-244.
[66] Guo W, Qiu Z, Wang Z, Wang Q, Tan N, Chen T, Chen Z, Huang S, Gu J, Li J, Yao M, Zhao Y and He X. MiR-199a-5p is negatively associated with malignancies and regulates glycolysis and lactate production by targeting hexokinase 2 in liver cancer. Hepatology 2015; 62: 1132-1144.
[67] Surh YJ, Kundu JK, Li MH, Na HK and Cha YN. Role of Nrf2-mediated heme oxygenase-1 upregulation in adaptive survival response to nitrosative stress. Arch Pharm Res 2009; 32: 1163-1176.
[68] Gu J, Chi M, Sun X, Wang G, Li M, Liu L and Li X. Propofol-induced protection of SH-SY5Y cells against hydrogen peroxide is associated with the HO-1 via the ERK pathway. Int J Med Sci 2013; 10: 599-606.
[69] Meacham CE and Morrison SJ. Tumour heterogeneity and cancer cell plasticity. Nature 2013; 501: 328-337.
[70] Artis D and Spits H. The biology of innate lymphoid cells. Nature 2015; 517: 293-301.
[71] Grivennikov SI, Greten FR and Karin M. Immunity, inflammation, and cancer. Cell 2010; 140: 883-899.
[72] Ke JJ, Zhan J, Feng XB, Wu Y, Rao Y and Wang YL. A comparison of the effect of total intravenous anaesthesia with propofol and remifentanil and inhalational anaesthesia with isoflurane on the release of pro- and anti-inflammatory cytokines in patients undergoing open cholecystectomy. Anaesth Intensive Care 2008; 36: 74-78.
[73] Liu TC. Influence of propofol, isoflurane and enflurance on levels of serum interleukin-8 and interleukin-10 in cancer patients. Asian Pac J Cancer Prev 2014; 15: 6703-6707.
[74] Gonzalez-Correa JA, Cruz-Andreotti E, Arrebola MM, Lopez-Villodres JA, Jodar M and De La Cruz JP. Effects of propofol on the leukocyte nitric oxide pathway: in vitro and ex vivo studies in surgical patients. Naunyn Schmiedebergs Arch Pharmacol 2008; 376: 331-339.
[75] Zhu M, Ding J, Jiang H, Kong L, Sun Z, Chen J and Miao C. Propofol ameliorates endothelial inflammation induced by hypoxia/reoxygenation in human umbilical vein endothelial cells: Role of phosphatase A2. Vascul Pharmacol 2015; 73: 149-157.
[76] Luo T and Xia Z. A small dose of hydrogen peroxide enhances tumor necrosis factor-alpha toxicity in inducing human vascular endothelial cell apoptosis: reversal with propofol. Anesth Analg 2006; 103: 110-116.
[77] Young SZ and Bordey A. GABA's control of stem and cancer cell proliferation in adult neural and peripheral niches. Physiology (Bethesda) 2009; 24: 171-185.
[78] Watanabe M, Maemura K, Oki K, Shiraishi N, Shibayama Y and Katsu K. Gamma-aminobutyric acid (GABA) and cell proliferation: focus on cancer cells. Histol Histopathol 2006; 21: 1135-1141.
[79] Sizemore GM, Sizemore ST, Seachrist DD and Keri RA. GABA(A) receptor pi (GABRP) stimulates basal-like breast cancer cell migration through activation of extracellular-regulated kinase 1/2 (ERK1/2). J Biol Chem 2014; 289: 24102-24113.