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EDITORIAL

Adrenoceptor modulators and cancer progression

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Introduction

Several recent articles published in the *Journal of Anesthesia* suggest that anesthetic agents, sedatives, and opioids may affect cancer relapse, metastasis, and recurrence [1–3]. In addition, we use adrenoceptor agonists or antagonists in the perioperative setting for hemodynamic maintenance in patients undergoing radical cancer surgery. Moreover, the highly selective α2-agonist dexmedetomidine is often used as a sedative in the intensive care unit and sometimes as an adjuvant in paravertebral block to reduce postoperative opioid consumption and the incidence of nausea and vomiting [4]. However, do we know whether these agents affect prognosis in cancer patients? In this editorial, effects of adrenoceptor modulators on cancer are discussed.

β-Adrenoceptor modulators

It has been reported that β-adrenergic signaling regulates the hallmarks of cancer progression including inflammation, angiogenesis, apoptosis, and invasion. Activation of β-adrenoceptors promotes cAMP production, resulting in activation of several protein kinases and transcription factors. These factors increase the expression of tumor-associated proinflammatory cytokines, angiogenesis, invasion, and tumor cell mobilization and motility, promote resistance to anoikis apoptosis, and induce resistance to chemotherapy-induced apoptosis [5]. Both β1- and β2-adrenoceptors are expressed in most tumor tissues but only β2-receptors in ovarian and prostatic cancer tissues [6]. Therefore, β-adrenergic stimulation may worsen the prognosis of cancer patients.

In contrast, inhibition of β-adrenoceptors might improve prognosis. Stiles and colleagues [7] reported that β-blockers could induce apoptosis in angiosarcoma cells in vitro and also inhibit proliferation of angiosarcoma. However, the data of clinical studies are controversial. Although De Giorgi and colleagues [8] reported that β-blockers may protect against melanoma recurrence and death, McCourt and colleagues [9] found that β-blockers did not reduce the risk of death from melanoma. Heitz and colleagues [10] also reported that survival did not differ between platinum-sensitive recurrent ovarian cancer patients with or without β-blocker medication. In addition, β-blockers may not reduce the risk of cancer recurrence and death in patients with colorectal cancer, breast cancer, malignant melanoma, lung cancer, and prostate cancer [11–16]. Thus, β-blocker efficacy in cancer for recurrence and death remains controversial.

In a retrospective analysis of long-term propranolol use on hepatocellular carcinoma (HCC) incidence in patients with HCV-associated cirrhosis, Nkontchou and colleagues [17] found a decreased HCC risk. Using epidemiological methods and meta-analysis, Monami and colleagues [18] studied the relationship between β-blocker medication and cancer incidence. Both analyses suggest that β-blockers may reduce the risk of cancer development. Therefore, β-blockers might exert preventive effects against cancer incidence.

α-Adrenoceptor modulators

It has been reported that α1-adrenoceptors are expressed in prostate cancer [19–21], malignant mesothelioma

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[22], and thyroid medullary carcinoma [23] and that α2 adrenoceptors are found in breast cancer [24, 25]. Therefore, α-adrenoceptor modulators may affect cancer progression.

As α1-adrenoceptor blocking agents could inhibit prostate growth by including apoptosis in stromal and epithelial cells, these agents have been studied as potential therapeutic agents for the prevention and treatment of prostate cancer. Hori and colleagues [20] reported that an α1-antagonist, naftopidil, suppresses human prostate cancer growth. Yamada and colleagues [21] also reported that patients receiving naftopidil for more than 3 months had a significantly lower risk of prostate cancer than patients receiving tamsulosin, another α1-antagonist. In addition, they found that naftopidil inhibited cancer cell viability and induced apoptosis in cancer cells such as HeLa and LNCaP cell lines. It has been suggested that α1-adrenoceptor-mediating apoptosis may include the death receptors, vascular endothelial growth factor and transforming growth factor (TGF)-β pathways [21]. Although tamsulosin has a high affinity for the α1A-adrenoceptor subtype, naftopidil has high affinity for the α1D-adrenoceptor subtype [26]. Therefore, the α1-adrenoceptor subtype may be important in the apoptotic effects of α1-adrenoceptor antagonists. Indeed, Huang and colleagues [27] found that compound 12, a selective α1D-antagonist, exerts a potent antiproliferative action in the prostate cancer cell line, PC-3 cells, by induction of α1-adrenoceptor-mediated apoptosis and G_0/G_1 cell-cycle arrest.

α2-Adrenoceptors are expressed in breast cancer epithelial and stromal cells [24]. Several reports [24, 28] showed that stimulation of α2-adrenoceptors by the highly selective α2-adrenoceptor agonists dexmedetomidine and clonidine enhance breast cancer cell proliferation, tumor growth, and metastasis, and this could be reversed by the α2-adrenoceptor antagonists yohimbine and rauwolscine. In addition, Shkurnikov and colleagues [29] found a significant correlation between the risk of breast cancer relapse and expression of α2A-adrenoceptors. The mechanism of α2-adrenoceptor-modulating cancer progression has not yet been clearly elucidated. As α2-adrenoceptor antagonists inhibit presynaptic α2-adrenoceptor-mediating autoinhibition of sympathetic transmission, increases in catecholamine release facilitate β-adrenergic signaling, which may promote cancer progression. Indeed, antagonizing the α2-adrenoceptor by phentolamine (nonselective α2-antagonist) and efaroxan (selective α2-antagonist) increased primary breast cancer size and distant metastasis under non-stress conditions, and this breast cancer progression was suppressed by propranolol (a nonselective β-adrenoceptor antagonist) [30]. Thus, because α2-adrenoceptor agonists inhibit the sympathetic nervous system to reduce β-adrenergic signaling, suppression of cancer progression is theoretically expected. However, as already described, α2-adrenoceptor agonists may enhance cancer progression. Szpunar and colleagues [31] found that α2-adrenoceptor agonists could promote breast cancer progression in association with alteration of tumor extracellular matrix, specifically the collagen microstructure, without any direct sympathetic input to the tumor cells. These findings suggest that perioperative α2-adrenoceptor agonists might be used cautiously. Clinical studies are required to clarify this risk.

Cyclic adenosine monophosphate (cAMP)-phosphodiesterase (PDE) modulators

Intracellular cAMP can be destroyed by PDE subtype 1, 2, 3, 4, 7, 8, 10, and 11. Activation of β-adrenoceptors increases cAMP production that activates several protein kinases and transcription factors to induce cancer progression. Thus, PDE inhibitors might induce cancer progression. Indeed, cAMP can promote the growth of certain malignant tumors. However, selective inhibitors of PDE1 through PDE5, and PDE7, have been reported to suppress cancer growth with induction of apoptosis in many different human cancers [32].

Some in vitro studies have shown that PDE1 inhibitors may control cell malignancy, although the relationship between PDE1 and oncogenesis has not been clearly demonstrated [32]. Selective inhibition of PDE1B could induce apoptosis in human leukemic cells, and PDE1C inhibitors may inhibit growth of human malignant melanoma-associated cells. As erythro-9-(2-hydroxy-3-nonyl)adenine, a PDE2 inhibitor, increased intracellular cAMP levels in human umbilical vein endothelial cells and inhibited angiogenesis, PDE2 inhibitors may suppress cancer progression [32]. Cilostazol, an inhibitor of PDE3 and adenosine uptake, has been reported to inhibit breast cancer metastasis in vivo and human colon cancer cell migration in vitro because of its inhibitory effects on platelet aggregation; platelets prevent immune elimination of tumor cells and promote their adhesion to the endothelium to establish their metastasis [32].

Inhibition of PDE4 activity suppresses cell growth and induces apoptosis in malignant but not in nonmalignant cells [32]. Indeed, it has been reported that rolipram, a PDE4 inhibitor, improved the survival of mice with intracranial xenografts of U87 glioblastoma cells and enhanced the antitumor effects of chemotherapy and radiotherapy. Exisulind, a dual inhibitor for PDE4 and PDE5, has been reported to reduce multiplicity and incidence of the oncogenic events in colon cancer cells and rat bladder tumors [32]. Regarding PDE7, elevated PDE7B expression is associated with poor prognosis in chronic lymphocytic

leukemia, and selective PDE7 inhibitors induce apoptosis in chronic lymphocytic leukemia cells [32].

Conclusion

A substantial body of evidence from basic and clinical studies has implicated the modulation of adrenergic signaling in cancer progression. Clinicians should use adrenoceptor modulators with caution in cancer patients during the perioperative period.

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