IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

2019; 10(7): 1622-1632. doi: 10.7150/jca.27780

Review

The Prospective Value of Dopamine Receptors on Bio-Behavior of Tumor

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Received: 2018.06.10; Accepted: 2019.02.07; Published: 2019.03.03

Abstract

Dopamine receptors are belong to the family of G protein-coupled receptor. There are five types of dopamine receptor (DR), including DRD1, DRD2, DRD3, DRD4, and DRD5, which are divided into two major groups: the D1-like receptors (DRD1 and DRD5), and the D2-like receptors (DRD2, DRD3, and DRD4). Dopamine receptors are involved in all of the physiological functions of dopamine, including the autonomic movement, emotion, hormonal regulation, dopamine-induced immune effects, and tumor behavior, and so on. Increasing evidence shows that dopamine receptors are associated with the regulation of tumor behavior, such as tumor cell death, proliferation, invasion, and migration. Recently, some studies showed that dopamine receptors could regulate several ways of death of the tumor cell, including apoptosis, autophagy-induced death, and ferroptosis, which cannot only directly affect tumor behavior, but also limit tumor progress via activating tumor immunity. In this review, we focus mainly on the function of the dopamine receptor on Bio-behavior of tumor as a potential therapeutic target.

Key words: dopamine receptor, autophagy, tumor immunity, ferroptosis

Introduction

Dopamine is a major catecholamine neurotransmitter, could be synthesized in the central nervous system and mesenteric, such as the digestive tract, spleen and pancreas [1-3]. In the mammalian brain, there are four dopaminergic pathways have been found, including nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular. These neurons have an important role in central nervous system, such as locomotor activity, appetite, emotion, reward, sleep, attention, cognition, working memory, and learning. In the periphery dopamine could be a regulator of heart rate, endocrine, cardiovascular function, kidney function, gastrointestinal motility, immune system, and so on [4, 5]. DRs extensively expressed on brain, retina, gastrointestinal tract, kidney, adrenal glands, heart, sympathetic ganglia, and blood vessels [2]. DRs are a family of metabotropic G protein-coupled receptor, which is 7-transmembrane [6]. At present, there are five types of DRs, including DRD1, DRD2, DRD3, DRD4, and DRD5. According to their different regulation of adenylyl cyclase (AC) activity, DRs could be divided into two families: D1-like DRs and D2-like DRs. The production of cAMP can be stimulated by acting D1-like DRs, opposite to D2-like DRs (DRD2, DRD3, and DRD4). Compared with D1-like DRs, D2-like DRs have a larger third cytoplasmic loop and a shorter carboxyl-terminal tail [7]. The genetic structure of two type dopamine receptor could be also different. In coding regions, D1-like DRs do not possess introns, while D2-like DRs

contains several introns. The gene of DRD2, DRD3, and DRD4 respectively contain six, five, and three introns [8]. For this, D2-like DRs can generate splice variants. D2S and D2L are two isoforms of DRD2, generated by alternative splicing of an 87-base-pair exon between introns 4 and 5 [1]. DRD3 can generate splice variants too, but encoding nonfunctional proteins [9]. The gene of DRD4 can generate polymorphic variations, a 48-base-pair sequence in the third cytoplasmic was described as a repeat sequence [10, 11]. In the brain, both DRD1 and DRD2 play a major role in learning and working memory. While the role of DRD3, DRD4, and DRD5 in the brain still unknown. In periphery, DRD1, DRD2, and DRD4 could be a regulator of renal function, blood pressure, and gut motility [1].

Dysfunction of the dopaminergic system is related to schizophrenia and Parkinson's disease (PD), and targeting the dopamine receptor is a major way of treatment [12]. Some epidemiological studies declared that schizophrenia has a lower cancer incidence, while the evidence of schizophrenia has a higher risk of cancer also be reported [13-16]. Even in the same kind of cancer, the result would be very different [17]. An interesting epidemiologic study demonstrated that schizophrenic patients who have elevated DRD2 signaling, the risk of cancers would be increased, and DRD2 antagonists make this risk return to normal [18-20]. There are similar epidemiologic studies demonstrated that the risk of cancer, especially in smoking-related cancer, is declined in patients with PD. While patients with PD would have an increased risk of malignant melanoma, non melanoma skin cancer and breast cancer also be reported [21-23]. These findings imply that the dopaminergic system may be connected to the development of cancer.

Polymorphisms of DRs have been shown to be related to risking of colorectal, non-small cell lung cancer and gastric cancer [24-26]. High levels of DRD2 expression in gastric cancer, neuroendocrine tumors , glioblastoma, breast cancer , and others (**Table 1**) have been founded [26-29]. The elevated expression of DRD2 in patients with neuroendocrine tumors would have longer time to progression [27]. Interestingly, the high level of DRD2 in patients with gastric cancer would have higher survival duration [26]. So DRD2 might play a different role in different type of cancer. DRD4 involved the malignant phenotype of pediatric medulloblastomas [30]. The expression of DRD4 is connected to survival of patients with GBM. High level of DRD4 expression has worse survival than low of DRD4 expression [31]. Accumulated evidence shows that DRs can play a vital role in cancer. In this review, we summarized the potential roles of DRs in cancer.

Table 1. The polymorphisms and level of dopamine receptors in cancers.

Type of cancers	Relationship between dopamine receptors and cancer	References
breast cancer	DRD1 ↑ , DRD2 ↑ , DRD3 ↑ , DRD4 ↑	[29]
cervical cancer	DRD2 ↑	[39]
cholangiocarcinoma	Mz-chA-1: DRD1 ↑ , DRD2 ↑ , DRD3 ↑ , DRD4 ↓ ,DRD5 ↑	[64]
	HuCCT-1: DRD1 ↓ , DRD2 ↑ , DRD4 ↓ ,DRD5 ↓	[64]
	SG231: DRD2 ↓ , DRD3 ↓ , DRD4 ↓ ,DRD5 ↓	[64]
	CCLP-1: DRD1 ↓ , DRD2 ↑ , DRD3 ↓ , DRD4 ↓ ,DRD5 ↓	[64]
colorectal cancer	DRD2 ↓ ;DRD2 polymorphisms -141Cdel, 957T>C, 1412A>G are associate with colorectal cancer.	[123]
	HCT116: DRD1 ↑ , DRD2 ↑ ,DRD5 ↑	[84]
	HT29: DRD1 ↑ , DRD2 ↑ ,DRD5 ↑	[84]
	The DRD2 rs1799732 CT, rs1800497 TT are associated increase cancer risk.	[24]
corticotroph adenomas	DRD2 ↑	[124]
gastric cancer	DRD2 ↑	[26]
glioblastoma	DRD2 ↑	[28]
	U251: DRD1 ↑ , DRD2 ↑ ,DRD5 ↑	[84]
hepatic carcinoma	DRD1 ↓ , DRD5 ↑	[94]
	Hep3B: DRD1 ↑ , DRD5 ↑	[84]
lung cancer	DRD2 ↑	[125]
neuroblastoma	SKNAH: DRD1 ↑ , DRD2 ↑ , DRD4 ↑ ,DRD5 ↑	[84]
neuroendocrine	DRD2 ↑	[126]
	DRD2 ↑	[27]
	DRD2 ↑	[127]
non-small cell lung cancer	DRD2 polymorphisms -141Cdel, 3208G>T; DRD4 -521C>T are associated with increase NSCLC risk.	[25]
ovarian	DRD2 ↑	[53]
pancreatic cancer	DRD2 ↑	[40]
pheochromocytoma	DRD2 ↑	[128]
	DRD2 ↑	[129]
pituitary adenoma	DRD2 ↑	[130]
small cell lung cancer	DRD2 ↑ , DRD4 ↑ ,DRD5 ↑	[70]

Dopamine Receptor and Cell Death

Dopamine receptor and apoptosis

It has been documented that dopamine can decrease cell viability and induce apoptosis in K562 leukaemia cells, human oral tumour cells, rat pituitary tumour cells and human SK-N-MC neuroblastoma cells *in vitro* [32-35]. Meanwhile, dopamine can reduce the frequency of cancer stem cell and induce apoptosis of cancer stem cell *in vitro* have been demonstrated in breast cancer. The combination of dopamine and sunitinib can enhance the response of sunitinib in drug-resistant breast cancer. And DRD1 might play a significant role on this as SCH23390, the antagonist of DRD1, completely reversed the effect [36]. The effect of dopamine in human SK-N-MC neuroblastoma cells can also be partly reversed by SCH23390. So DRD1 involve in the dopamine's cytotoxic on SK-N-MC [35]. Furthermore, induction of apoptosis via targeting DRs has been reported in various cancers. The role of different types of DRs in apoptosis can be different. SKF38393 is an agonist of DRD1, Jun Gao and Feng Gao demonstrated that treated with SKF38393 reduced the viability of osteosarcoma cells (OS732) and cell apoptosis would be raised *in vitro*. The over expression of DRD1 in OS732 cells, the cell apoptosis can also be increased [37]. Thioridazine is known as a blocker of DRD2. Previous studies have implied that thioridazine have an effective role in anti-cancer [38]. Treating with thioridazine for 24h in SiHa cells *in vitro*, the viability of cells was considerably decreased when the concentration was over 20 μM, coupled with a down regulation of DRD2 expression. AnnexinVassay showed that more apoptosis was increased, and comet assay have a higher percentage of comet formed when SiHa cells exposed to thioridazine. That means cell apoptosis can be induced by thioridazine via targeting DRD2 [39]. Dopamine-induced cell death was seen in rat pituitary tumor cell lines *in vitro*. DNA laddering and caspase-3 was triggered by dopamine can be prevented by haloperidol, which means DRD2 involve the process of Dopamine-induced cell death [34]. Pimozide, a DRD2 inhibitor, can induce cell-cycle arrest in the G1 phase in pancreatic cancer cells *in vitro*. The activity of caspase 3/7 can be activated by pimozide, and the number of apoptotic cells was increased [40]. Neurofibromatosis type 1 is just an autosomal-domainant neurogenetic disorder. The gene of neurofibromatosis type 1 can encode a tumor suppressor protein called neurofibromin. The neurofibromin might increase the apoptosis in malignant peripheral nerve sheath tumor cells (MPNST cells) in the condition of serum deprivation [41]. DRD3 involved the function of neurofibromin has been declared [42]. 7-OH-PIPAT, a selective DRD3 agonist, would protect MPNST cells from apoptosis in the condition of serum deprivation *in vitro*. The expression of neurofibromin can be changed by 7-OH-PIPAT. So DRD3 might have an anti-apoptosis role in cancer cells, but the detail mechanisms still unknown [43]. DRD4 can down regulate the expression of cell-cycle genes *in vitro*. Treating with DRD4 antagonists in G411 and G362 cells, a G_0/G_1 phase arrest and the activity of caspase 3/7 can be induced. This result suggests that the inhibition of DRD4 can increase cell apoptosis *in vitro* [31]. In GH3 cells, treatment with the DRD5 agonist SKF83959 can induce apoptosis in a dose-dependent manner [44].

Dopamine receptor and autophagy

Autophagy is a highly conserved progress, function as a scavenger in cells. Autophagy can format a double membrane vesicle named autophagosomes. Some substrates can be engulfing by autophagosomes such as endoplasmic reticulum, ribosomes, mitochondria, nuclear fragments, protein aggregates, bacteria, and viruses [45, 46]. These substrates can be delivered to the lysosome, and degraded by lysosomal enzymes. The basal level of autophagy protects cells from stressful conditions. While redundant autophagy have a function of promoting non-apoptotic cell death [47]. Autophagy is connected to tumorigenesis and acquired chemotherapeutic resistance has been widely demonstrated [48-50]. Targeting autophagy is a promising way of treating tumors.

It has been demonstrated that dopamine can induce autophagic cell death in SH-SY5Y cells [51]. The production of ROS might be responsible for the autophagic cell death cause by dopamine. Sertindole, an antagonist of DRD2s, can induce autophagy in SH-SY5Y cells *in vitro*. And ATG5s play a vital role in the autophagy caused by Sertindol [47]. Inducing autophagy in PC12, MES23.5, and differentiated SH-SY5Y cells by treating pramipexole and quinpirole, the DRD2 and DRD3 agonists, have been demonstrated *in vitro*. This process might be related to an MTOR-independent but BECN1 dependent pathway. Pramipexole and quinpirole can increase the transcription and expression of BECN1 and promote its combined with PtdIns3K [52]. Autophagy induced by thioridazine might be responsible for thioridazine-induced cytotoxicity in ovarian cancer cells [53]. Ammonia, a product of metabolite of proteins and nucleic acids, can induce autophagy *in vitro* [54]. The increase level of LC3B caused by ammonia would be reduced when DRD3 knockdown in HeLa cells. Ammonia changes the location of MTOR, and DRD3 was involved in this process [55]. DRD4 antagonists can increase the level of LC3-II in

glioblastomas neural stem cells *in vitro*, caused by impaired autophagy flux. Accumulation of p62 and ubiquitinated protein conjugates accompanied by the increase of LC3-II has been observed, which show that DRD4 antagonism exert the function of cytotoxicity by blocking autophagy [31]. In pituitary tumor cells, active DRD5 can suppress the function of MTOR by increasing the level of ROS. SKF83959, a DRD5 agonist, can increase the level of LC3-II and block the degradation of SQSTM1. That means active DRD5 can block the autophagic flux [44]. So DRs are a set of prospective regulator of autophagy.

Dopamine receptor and ferroptosis

Ferroptosis, a newly found form of cell death, is characterized by iron and lipid ROS accumulation [56]. Ferroptosis is distinguishable from apoptosis, necroptosis and autophagy in morphological, biochemical, and genetic features [57]. Erastin has been widely used to induce ferroptosis, can enhance sensitivity of the cancer cell to chemotherapeutic [58]. While dopamine can inhibit ferroptosis induced by erastin in PANC1 cells have been documented. The cell viability of cancer cell would be increased when treated with dopamine (12.5-50 μM). Detail study found that the degradation of DRD4 protein is promoted by erastin, while the gene expression of DRD5 is induced. Ferrostatin-1, a ferroptosis inhibitor, can block the change of DRD4 and DRD5 caused by erastin. Dopamine can inhibit the degradation of DRD4 protein induced by erastin, but have no influence on DRD5 expression [59]. Therefore, dopamine receptor of DRD4 and DRD5 might regulate chemosensitivity of cancer via inhibiting ferroptosis.

Dopamine Receptor and Cancer Cell Proliferation

Several *in vivo* studies declared that dopamine can suppress cancer growth. For example, rat adenocarcinoma cells were implanted in two kinds of rat, APO-SUS with high dopaminergic reactivity and APO-UNSUS with low dopaminergic reactivity. In APO-SUS animals, the size of tumors was smaller compared with APO-UNSUS animals [60]. In the model of stress induced ovarian, the level of dopamine is decreased after 3 to 14 of stress. In stressed mice, treatment with 75 mg/kg of dopamine has a significantly function of inhibiting cancer growth *in vivo* [61]. In the tissues of gastric cancer in both humans and MNNG-induced rats, the level of dopamine was lower than normal stomach tissues. A low nontoxic dose of dopamine could be seen as an inhibitor of the growth of gastric cancer and angiogenesis in MNNG-induced model [62]. Dopamine can enhance the efficacy of anticancer drugs in mice models of breast and colon cancer has also been reported [63]. While an *in vitro* study demonstrated that the increased dopamine secretion could stimulate the proliferation of cholangiocarcinoma cells, and pretreatment of L-741,626 25 (DRD2 inhibitor) and L-745,870 trihydrochloride 27 (DRD4 inhibitor) could reverse this effect of dopamine [64].

Previous studies proved that dopamine inhibits tumor growth by suppressing angiogenesis, and DRD2 plays a vital role in this process [65]. Other pathways also involve the process of dopamine inhibit tumor growth, such as induce oxidative stress , inhibit the activity of the enzyme ribonucleotide reductase, increase the activity of intracellular lysosomal enzyme activity, and activation of immune system, however which DRs responsible for these pathways still need further to study [34]. In DRD2 knockout mice, more angiogenesis and tumor growth were noted [66]. DRD2 agonists could abolish lung tumor progression in murine models by inhibition of tumor angiogenesis and reduction of tumor infiltrating myeloid derived suppressor cells *in vivo* [67]. Endocytosis of VEGFR-2 can be induced by dopamine via DRD2, which is important for promoting angiogenesis, thereby preventing vascular permeability factor/vascular endothelial growth factor-A binding, receptor phosphorylation, and subsequent signaling steps [68].

Dopamine can inhibit gastric cancer cell proliferation by activating DRD2 via down-regulation of IGF-IR and AKT phosphorylation. Pretreatment with quinpirole (50 μM), a DRD2 agonist, can inhibit IGF1-induced gastric cancer cell proliferation *in vitro* [69]. Treatment with quinpirole (10 μM) can inhibit the proliferation of primary small cell lung cancer in a dose and time dependent *in vitro* [70]. Furthermore, the proliferation of CD133+ve cancer stem cells in non-small cell lung cancer can also be inhibited by treating quinpirole (1μM or 10 μM) *in vitro* and *vivo* [71]. Fisetin, function as DRD2 agonist, showed significantly inhibitory role in HCC-LM3 proliferation *in vitro* when the concentration over 10 μM [72]. Bromocriptine, a DRD2 agonist, could suppress MCF-7 cells growth at a concentration of 6.25 to 100 μM *in vitro* [73]. In aldosterone-producing adenoma, bromocriptine can inhibit angiotensinII-induced cell proliferation by attenuating angiotensinII-induced phosphorylation of PK-stimulated cyclic D1 protein expression and cell proliferation *in vitro* [74]. The proliferation of Hepa1-6, SMMC-7721 and HCC-LM3 cells can be inhibited by bromocriptine in a concentration-dependent manner [75]. Though bromocriptine has been utilized clinically for reducing tumor mass of prolactinomas, the resistance still existence in 5-18% of patients [76]. Knockdown of

DRD2 expression in the pancreatic cancer cell lines can inhibit the proliferation of cells. Treatment with different concentration of pimozide, an FDA-approved DRD2 inhibitor for the therapy of schizophrenia, can get a dose-dependent inhibitory effect on pancreatic cancer cell lines growth *in vitro*. The higher level of DRD2 in cell lines, the stronger pimozide effect it will be [40]. Treating with thioridazine (32 mg/kg) in a murine breast cancer model, the tumor volume was significantly reduced. And immunohistochemistry showed that the marker of the cell cycle Ki67 was decreased. That means cell proliferation was inhibited by thioridazine *in vivo* [77]. Treating with thioridazine (10 μM) and compared to other known DR antagonists, clozapine (100 μM) and chlorpromazine (10 μM) in AML cell lines. These three of DR antagonists reduced the number of AML cells upon treatment [78]. DRD2 was overexpressed in ovarian cancer cells, and treatment with thioridazine (15 μM) inhibited the proliferation of ovarian cancer cells *in vivo* and *in vitro* [53]. The inhibition of FAK/mTOR signaling was associated to the inhibition of ovarian cancer cells growth *in vitro* by thioridazine [79], the reducing phosphorylation of VEGFR2 and the inhibition of PI3K/mTOR signaling were responsible for the inhibition of ovarian carcinoma growth *in vivo* by thioridazine [80]. Trifluoperazine, a clinically-used antidepressant drug by targeting DRD2, can inhibit the growth and proliferation of glioblastoma in a dose-dependent manner *in vitro* [81]. Furthermore, *in vivo* and *in vitro* study declared that trifluoperazine can inhibit the growth of cancer stem cell and overcome the drug resistance of lung cancer [82, 83]. ONC201's anti-cancer effect has been reported to relate to DRD2, though DRD2 is not responsible for all of this effect. And DRD2-antagonist, L-741,626 and PG01037 could significantly decrease the cell viability in colorectal cancer cells. By the way, the combination with SCH39166, a selective D1/D5 antagonist, increases ONC201's anti-cancer activity in colorectal cancer cell lines *in vitro* [84]. In breast cancer cell, *in vivo* and *in vitro* research shown that sulpiride, can increase the anti-cancer effect of dexamethasone, and DRD2 might responsible for this effect as treating DRD2 agonist 7-OH-DPAI can reverse the enhanced anti-cancer effects *in vivo* and decrease the cancer stem cell population in tumor tissues [85].

Other DRs also involved the process of cancer cell proliferation. Previous *in vivo* study showed that angiogenic induced by mouse ovarian tumor cannot be prevented by DRD1 agonist SKF38393 (10 mg/kg) or DRD1 antagonist SCH23390 (10 mg/kg) [68]. Conflict research demonstrated that DRD1 contributes to dopamine induced tumor angiogenesis. Lewis lung carcinomas were implanted into DRD1 knockout mice and wild-type mice. The growth of the tumor was slower in DRD1 knockout compare with wild-type mice. And tumor vessels from DRD1 knockout mice were decreased [86]. DRD1 are expressed in osteosarcoma cells, treating DRD1 agonist SKF38393 (10 μM) can inhibit the proliferation of osteosarcoma *in vitro*. The effect of SKF38393 on the proliferation of osteosarcoma is related to down-regulation of the ERK1/2 and PI3K-Akt pathways by activating DRD1 [87]. A screening of ~1,000 biological active compounds implied that a selective agonist of DRD1, A77636 (2 μM), could inhibit the proliferation of breast cancer cells *in vitro*. In the animal model of bearing breast cancer cells, the growth of the tumor can be obviously inhibited by injecting of A77636 (2 mg/kg) for 2 weeks [88]. The DR1 agonist SKF82958 can increase the concentration of intratumoral cisplatin in nude mice bearing SKOV3ip1 tumors, and the growth of the tumor was significantly inhibited compared with the group treated with cisplatin alone *in vivo* [89]. Knockdown of DRD4 in GNS cell lines can significantly reduce cell proliferation. L-741,742 function as DRD4 antagonists can selectively inhibit GNS growth and promote differentiation of normal neural stem cells *in vitro* [31]. LQFM018, a novel synthetized piperazin-containing compound, can inhibit the growth and induce death of K562 leukemic cells *in vitro* by binding DRD4 [90]. The viability of GH3 cells can be decreased by SKF83959, a DRD5 agonist. Knock-down the expression of DRD5 can abolish this function. Primary pituitary cells that expressed DRD5 protein was all sensitive to SKF83959, while cells expressed DRD5 extremely low have no effect on SKF83959. And the size of the tumor in nude mice bearing human gastric cancer cells was smaller than control by treating SKF83959 (1 mg/kg) *in vivo* [44].

In summary, targeting DRD1 or DRD2 can suppress cancer cell proliferation have been widely reported, while few studies found other DRs can also have the same effect. But the detail mechanism still needs further research.

Dopamine Receptor and Cancer Cell Invasion and Migration

EGF is a critical factor that is related to tumor invasion and migration. Pretreatment of gastric cell lines with dopamine inhibited EFG (100 ng/ml) -induced invasion and migration, and the maximum inhibitory effect was appeared at 800 nM *in vivo*. MMPs play a pivotal role in the invasion and metastasis of cancer. Dopamine can down-regulate the level of MMP-13 via DRD2. Knockdown of DRD2 abolished the function of dopamine on EGF-induced invasion and migration [91]. A study showed

DRD2-specific agonist BIM53097 can inhibit the proliferation of non-function pituitary *in vitro* [92]. And another study documented that BIM53097 (1 μM) inhibits human tumorous pituitary cells migration and invasion via activating cofilin pathway *in vitro*. Treatment with a selective inhibitor of ROCK can abrogate cofilin pathway induced by DRD2 activation [93]. The Matrigel invasion assay indicated that quinpirole (1μM or 10 μM) can decrease the invasion of CD133+ve tumor cells derived from A549 NSCLC cell line *in vitro* [71]. A77636 have an inhibitory effects on breast cancer cell motility in a dose-dependent manner at the concentrate of 2.5, and 10 μM *in vitro*. In the animal model of bone metastasis, A77636 reduced osteolytic lesions and prevented mechanical weakening of the femur and tibia [88]. Compared with control cells, the motility of Hepatocellular carcinoma (HCC) cells would be reduced when pretreated with thioridazine (10 μM) for 72 hours. The motility-related genes' expression can be decreased by exposing thioridazine [94]. As an antipsychotic drug, the effect of trifluoperazine comes from its ability to abolish DRD2 activity. Downregulate the expression of DRD2 in prostate cancer and fibrosarcoma cell lines by trifluoperazine causes a decrease cell migration compared with control. Haloperidol, another antipsychotic known as DRD2 inhibitor, can reduce migration of prostate cancer cell lines, similar to those treated with trifluoperazine *in vitro* [95]. Breast cancer cell lines treated with fenoldopam (1 nM), a peripheral DRD1 agonist that does not penetrate the brain, significantly suppress FBS-induced invasion [96].

Dopamine Receptor and Tumor Immunity

Recently, immunotherapy has been seen as a promising strategy against tumors. An emerging number of studies indicated that dopamine can be a regulator of the immune system. It has been documented that DRD1 involve the inhibit proliferation and cytotoxicity of CD4+ and CD8+ T cells *in a vitro* experiment [97]. DRs have been found in several immune cells, such as effector T cells, regulatory T cells, B cells, NK cells, Monocytes, Macrophages, Dendritic cells (DCs), Neutrophils, and eosinophils, which implies DRs might involve the regulation of immune cell's activities [98].

Regulatory T cells (Tregs) and effector T cells (Teffs) have the capacity to produce dopamine, and once dopamine is released from Tregs, the function of Tregs would be inhibited via D1-like receptors (probably the DRD5). Suppression of Tregs induced by dopamine can make Teffs be activated and proliferated. Therefore, dopamine can be viewed as a suppressor of the suppressors [99]. While cytokine secretion can be induced by dopamine or selective agonists of DRD2 or DRD3 in normal human T cells via activating the DRD2 and DRD3 (primarily). And the concentration of dopamine is the main factor that influences the function of dopamine on T cells. Dopamine at the physiological concentration is good for Teffs exert its function, while at extremely high concentration (0.1-1 mM) would have a toxic effect on both resting and activated Teffs [100].

DCs, a specialized antigen-presenting cells, can capture and processing of tumor-derived antigens, which play a crucial role in anti-immune response [101]. Tumor-derived antigens are cross-presented to CD8+T cells by dendritic cells, inducing differentiation of CD8+T cells into cytotoxic T lymphocytes (CTLs). Tumor cells are identified as foreign antigens by effector CD8+T cells, and effector CD4+T cells function as an activator of CD8+T cells. Tumor cells would be murdered by effector CD8+T cells via secreting cytotoxic granules [102]. Previous studies have shown that the migration and homing of naive CD8+T cells can be induced by dopamine through DRD3 [103]. CD4+T lymphocyte has three subsets: naive, central memory (T_{CM}), and effector memory (T_{EM}). All the five DR have been found on the CD4+T cells, while the expression patterns of DRs are different in three subsets. The expression level of D1-like DRs is higher than D2-like DRs in naive T cells, which opposite to other two subsets [104]. Notably, down-regulate the function of DRD3 in DCs can promote cytotoxic T response in tumor-bearing mice by enhancing antigen cross presentation and CD8+T cell activation, while it has no effect on CD4+T cell response [105]. But dopamine released by the DCs can influence CD4+T helper differentiation, polarization, cytokine secretion and effector function have been demonstrated [106].

Increasing researches demonstrate that myeloid-derived suppressor cells (MDSCs), a heterogeneous group of immune cells including immature macrophages, DCs, and granulocytes with immunosuppressive function. Suppressing the function of MDSCs is expected to increase host immune responses and improve cancer immunotherapy [107]. DA-treated tumor-bearing mice (50mg/kg/day) showed a smaller tumor size and a decrease accumulation of MDSCs in the spleen compared with control [108]. Stimulation of NO production is responsible for MDSCs inhibit immune responses. Further research declares that dopamine can inhibit NO production through down-regulation of ERK and JNK signaling via D1-like receptor. There are inconsistent studies about the function of D2-like receptor on MDSCs [109]. In the animal model of lung cancer, a study

founded that D2-like receptor agonist quinpirole (10μM) has no effect on inhibitory of MDSCs, which are isolated from splenocytes and bone marrow cells of mice, while another study shown that DRD2 agonist cabergoline (5 mg/kg) can inhibit MDSCs [67].

Table 2. Dopamine receptors agonist or antagonist function as an inhibitor of cancer.

Substance	Targets	Activation or inhibition of dopamine receptor	Type of cancers	References
A77636	DRD1	active	breast cancer	[88]
Fenoldopam	DRD1	active	breast cancer	[96]
SKF82958	DRD1	active	ovarian	[89]
SKF38393	DRD1	active	osteosarcoma	[37, 87]
SCH39166	DRD1, DRD5	inhibit	colorectal cancer	[84]
BIM53097	DRD2	active	pituitary	[92, 93]
Bromocriptine	DRD2	active	breast cancer	[73]
			aldosterone-producing adenoma	[74]
			hepatic carcinoma	[75]
			prolactinomas	[76]
Fisetin	DRD2	active	hepatic carcinoma	[72]
Haloperidol	DRD2	inhibit	pituitary	[34]
			prostate cancer	[95]
L-741,626	DRD2	inhibit	colorectal cancer	[84]
Olanzapine	DRD2	inhibit	glioblastoma	[117, 118]
			lung cancer	[119]
			pancreatic cancer	[119]
PG01037	DRD2	inhibit	colorectal cancer	[84]
Pimozide	DRD2	inhibit	pancreatic cancer	[40]
			prostate cancer	[120]
			glioblastoma	[121]
Quinpirole	DRD2	active	gastric cancer	[69]
			small lung cancer	[70]
			non small lung cancer	[71]
Sertindole	DRD2	inhibit	neuroblastoma	[47]
Sulpiride	DRD2	inhibit	breast cancer	[85]
Thioridazine	DRD2	inhibit	AML	[78]
			breast cancer	[77]
			cervical cancer	[38, 39]
			hepatic carcinoma	[94]
			ovarian cancer	[53, 79, 80]
Trifluoperazine	DRD2	inhibit	prostate cancer	[95]
			glioblastoma	[81]
			lung cancer	[82]
Pramipexole	DRD2, DRD3	active	adrenal pheochromocytoma	[52]
			neuroblastoma	[52]
Quinpirole	DRD2, DRD3	active	adrenal pheochromocytoma	[52]
			neuroblastoma	[52]
7-oh-PIPAT	DRD3	active	MPNST	[43]
L-741,742	DRD4	inhibit	GNS	[31]
SKF83959	DRD5	active	pituitary tumor	[44]
			gastric cancer	[44]
Clozapine	DRs	inhibit	AML	[78]
Chlorpromazine	DRs	inhibit	AML	[78]

NK cells are able to obliterate tumor cells and they play an important role in limiting tumor metastasis [110]. NK cells expression DRD2, DRD3, DRD4, DRD5, and lack of DRD1. IFN-γ, a cytokine that plays an important role in immune responses against tumors, can be produced by NK cells. And NK cells can control the tumor-promoting function of neutrophils depends on IFN-γ [111]. A low dose of dopamine can suppress the production of IFN-γ via DRD5 signaling on activated NK cells [99].

Tumor associated macrophages (TAMs) are usually educated by tumor cells to become their partners, avoiding tumor recognized by immune system [112]. TAMs are presented as either tumor killing macrophages (M1) or tumor promoting macrophages (M2). So, the best way to target tumor-infiltrating macrophage is not depleting them but rather converting M2 into M1 phenotype [113, 114]. A low nontoxic dose of dopamine can modulate TAM polarization from M2 to M1 in rat C6 glioma via DRD2 signaling have been documented [115].

Challenges and Perspectives

Though several DRs agonists or antagonists have been applied to anti-tumor in clinical, there is still some problem exist. First, the efficacy of DRs agonists or antagonists depends largely on the expression level of DRs. The expression level of DRs would be a significant difference in different kinds of tumor and even in different stages of tumor development. High level expression of DRs usually gets a satisfactory therapeutic, contrast to low level expression of DRs. Just as Roney MSI and Park SK said, targeting dopamine receptor by blocking or activating, is an essential strategy to overcome cancer. However, the therapeutic effect depends on the type of tumor and the activity of dopamine receptors [116]. Second, though some dopamine receptor agonists or antagonists have been shown to inhibit tumor growth, there is no clear evidence that the anti-tumor effect is through dopamine receptors. For example, the anti-tumor effect of olanzapine, a DRD2 antagonist, has been demonstrated in glioblastoma cell lines, lung and pancreatic cancer stem cell lines *in vitro* [117-119], while there is no evidence that dopamine receptors are involved in olanzapine anticancer process. Third, in some cancer dopamine receptors involved the anti-cancer of DRs agonists or antagonists, while in other cancers the DRs agonists or antagonists may exert its role of antitumor through a non-DR related mechanisms. For example, pimpzide can inhibit the proliferation of pancreatic cancer cells via inhibition of DRD2 [40], while pimozide can inhibit the growth of prostate cancer via suppression of STAT3 activation [120], and inhibit the growth glioblastoma via serotonin receptor 5-HT7 [121], whether dopamine receptor take part in the pimozide's role of anti-cancer in prostate cancer and glioblastoma still unknown.

Last but not least, treatment of tumors with dopamine analogs can also produce resistance, due to the change expression pattern of DRs [122]. Therefore, it is extremely important to know the detail expression patterns of DRs change in cancerous condition. However, there is still no clear report on this aspect. And current researches are focused on the function of DRD1 and DRD2 in tumors, very few studies on other DRs. Future research should focus on exploring the expression patterns of DRs in different stages of tumor development, so as to select appropriate dopamine-receptor agonist or antagonist to inhibit tumor progression. This is a key factor. And for some non-selective dopamine-receptor agonists or antagonists, we cannot rule out that their anti-cancer effects may not be through dopamine receptors, or that dopamine receptors are not a key factor in their anti-cancer effects. So the development of a more selective dopamine-receptor agonist or antagonist is another key factor in the future treatment of dopamine-receptor related cancers through dopamine receptors.

Search Strategy

A comprehensive literature screening was conducted for publication up to August 30th, 2018 from the following databases: (1) Pubmed; (2) Web of Science; (3) Google Scholar. Search terms:"dopamine, DA", " dopamine receptors, DRs", "cancer, tumor, carcinoma, neoplasm", "autophagy", "ferroptosis", "immunity" were used in combination to retrieve the relevant literature.

Acknowledgments

This work was supported by the National Key Research and Development Program of China (2016YFC1306900), National Natural Science Foundation of China (81573508), and Open Foundation of Innovative Platform in Colleges and University of Hunan Province of China ([2015]54).

Competing Interests

The authors have declared that no competing interest exists.

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