Review

Potential Roles of Peripheral Dopamine in Tumor Immunity

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Abstract

Recent years, immunotherapy has turned out to be a promising strategy against tumors. Peripheral dopamine (DA) has important roles in immune system among tumor patients. Accumulated reports demonstrate variable expression and distribution of DA receptors (DRs) in diverse immune cells. Interestingly, peripheral DA also involves in tumor progression and it exerts anticancer effects on immunomodulation, which includes inflammasomes in cancer, function of immune effector cells, such as T lymphocytes, myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs) and natural killer (NK) cells. Given the specific immunologic status, DA medication may be a valuable candidate in pancreatic cancer treatment. The major purpose of this review is to discuss the novel potential interactions between peripheral dopamine and tumor immunity.

Key words: Dopamine; Immunomodulation; Cancer; Immunotherapy.

Introduction

Dopamine (DA) is an important monoamine neurotransmitter in central nervous system (CNS) and classified as a catecholamine. DA also serves as a precursor of other members in catecholamine family, such as norepinephrine and epinephrine. Since Carlsson discovered the presence of DA in the brain in 1959 [1], the neglected sympathomimetic amine turned its poor status into a genuine neurotransmitter. The dopamine precursor, L-DOPA, was derived from the hydroxylation of tyrosine. DA not only embodies its roles in central nervous system regulating cognition [2], behaviors [3], moods [4], addiction [5] and reward systems [6], but involves in multiple functional modulations of peripheral tissues and organs as well. DA in periphery usually derived from the nervous system [7] and mesenteric organs, for example, the digestive tract, spleen and pancreas [8]. Accumulated evidence indicated DA as an important neurotransmitter mediating cross-talk between nervous and immune system [9]. Intriguingly, DA molecule acts through its receptors in a cAMP dependent manner and gives rise to ascending and descending downstream pathways in a regulatory manner of autocrine or paracrine.

DA concentration in cancer tissues has also been investigated. In early time approaches, Basu and Dasgupta [10] detected tissue dopamine from 36 colon cancer patients using 3[H] dopamine binding assay, and their result suggested that DA content was significantly lower (3~10 folds) than normal tissues and benign controls. In another study of gastric cancer, tissue samples in both human and rat gastric cancer presented even absence of dopamine [11]. Interestingly, plasma DA level in lung carcinoma patients underwent profound increase than healthy controls [12]. Another research conducted by Coufal

and colleagues reported increased DA level in human cholangiocarcinoma samples [13].

Possible roles of DA and its receptors on the growth of some malignant tumors have been noticed for almost 20 years [14]. Dopamine antagonist application was associated with slightly increased risk of breast cancer in a dose-cumulative manner [15]. Moreover, in schizophrenic individuals with probable elevated plasma DA levels, a relatively lower adjusted incidence of some types of cancer brought it wide attention [16, 17], which got further confirmed in a period of time [18]. Increasing evidence has demonstrated the veiled roles of peripheral dopamine on tumor-associated immunologic alteration and prognosis of malignant tumor therapy. The presence of dopamine receptors with immunoreactivity in rat lymphoid organs, thymus and spleen [19] suggests potential interactions between neurotransmitter and immune system [20]. Collectively, studies have evaluated and discussed the interactions of DA and immunity in cancerous status.

Peripheral DA

Sources of peripheral DA for immune system

Due to the incapability of penetrating the blood-brain-barrier (BBB), peripheral dopamine has to work out its own salvation to exert its functions distinct from the central neural pathways. Peripheral origins of dopamine include neural fibers, adrenal medulla and amine precursor uptake and decarboxylation (APUD) cells [21]. Alaniz *et al.* [22] showed physiological catecholamines were not required for normal development of the immune system. But notably, it has been supported that dopamine is synthesized, with rare exception, in most types of immune cells [23] and released to the extracellular milieu under certain circumstance [24]. Nerve-derived DA chiefly maintains plasma DA level, whereas plasma DA consists of only approximately 1% in its free form and the remaining part exiting in an inactive sulfate [7, 24]. DA in circulation is mainly stored in platelets. When cancer occurs, activation and adhesion of platelet is triggered and DA will be released targeting regional tissues [25]. To our knowledge, DA molecule disassimilates at a rapid rate. Though the reported DA concentration in peripheral plasma maintained basically 0.1nmol/L, real DA level might be much higher in circulation than tested and varies sharply in response to numerous exocytotic stimuli [26].

Several initial conditions where immune system gets in contact with DA were proposed: first of all, sharing permeating abilities across blood-brain-barrier, immunocytes 'meet' dopamine in CNS to a large extent; second, typical lymphoid tissues and some peripheral organs are suitable enough for signaling transduction against enemies; at last, running circulation has always been a main battlefield [24], notwithstanding conflicting DA level discussed above in cancer individuals signifies more complicated mechanisms than we expected.

DA receptors on immune cells

DA is traditionally accepted as achieving its function by stimulating five dopamine receptors (DRs) on the cell surface. As described over years, DRs, functionally subclassified as the D1-like (D1 and D5) and the D2-like (D2, D3, and D4) receptors, belong to the superfamily of G protein-coupled receptors (GPCR) [7, 27]. Peripheral DA and DRs have been found in the heart, vessels and other human tissues. DRs were not detected neither in normal primitive hematopoietic stem cells (HSCs) nor progenitors of cord blood. Conversely, analysis of samples from acute myeloid leukemia (AML) patients showed varying levels of all dopamine receptors types [28]. DA receptors were first described in mammalian lymphocytes, which indicated the potential role of DA as a modulator of immune effector cells activities [29]. Using flow cytometric techniques, McKenna *et al.* [30] reported expression of dopamine receptors on peripheral blood leukocytes. Their results showed that DRD3 and DRD5 were expressed on most leukocyte subpopulations, whereas DRD2 and DRD4 expression was quite variable. In addition, DRs were expressed, in consistently high level on B cells and NK cells, moderately on neutrophils and eosinophils, and in low level on T cells and monocytes, respectively. Updated results were collected and rearranged with references to previous outstanding summaries [7, 24] and latest findings at present. Detailed expression of DRs in diverse immune cells are listed in the table below (Table 1).

Table 1. Dopamine receptors expression in immune cells.

Immune cells	Dopamine Receptors	References
Effector T cells	DRD1[low], DRD2, DRD3, DRD4, DRD5	[7,24,31,64,96]
Regulatory T cells	DRD1, DRD3, DRD5	[24,64,96]
B cells	DRD1, DRD2, DRD3, DRD4, DRD5	[30,97]
NK cells	DRD2, DRD3, DRD4, DRD5	[30,85,86]
Monocytes	DRD2, DRD3	[24,30]
Macrophages	DRD1, DRD2, DRD3, DRD4, DRD5	[98]
Dendritic cells	DRD1, DRD2, DRD3, DRD4, DRD5	[7,31,99,100]
Neutrophils	DRD2, DRD3, DRD4, DRD5	[30]

[low]low level of expression

Peripheral DA and tumor immunity

Regulation of immune system by other cells or organs is achieved primarily via binding to various receptors expressed on immune cells. Most, if not all, immune cells constitutively possess DRs on their surface membrane, which will be specifically activated or inhibited in exposure of DA [31, 32]. DA promotes the mobilization and repopulation of immature human CD34+ cells [33]. Besides varied effects on normal cells and homeostasis, increasing evidence suggests DA signaling has anticancer effects. It seems that in tumor cell lines, DA mainly exerts effects on antiproliferation, apoptosis [34] and tumor angiogenesis [35]. Type 2 DA receptor is involved in suppression of gastric cancer cell invasion/migration via EGFR/AKT/MMP-13 pathway [36] and in suppression of pituitary tumors via Rho/ROCK/LIMK signaling pathway [37]. Moreover, DA agonists showed effectiveness in shrinking tumor size in both solid [38] and cystic [39] prolactinomas by controlling serum prolactin level [40]. Meanwhile, prolactin has also been demonstrated to be involved in intricate cytokine network of immunity, manifested as regulatory effects on generation of T cells via IL-2/IL-2R interactions and JAK/STAT pathway [41]. Promising discoveries of DA in malignant glioma and its direct correlation with the pathogenesis of glioma were summarized previously [42]. Here, we mainly present the underlying implications of DA in tumors and its emergent roles for immunotherapy.

Peripheral DA in cancer-related inflammation

The hypothesis that chronic inflammation contributes to cancer origination and progression has been proposed for over 150 years [43]. MDSCs and TAMs were both reported to bridge the inflammation and malignancies [44-46], which as well offer new pharmacological targets of DA agonists/antagonists. It is well recognized that long-term inflammation favors carcinogenesis possibly through genetic variants. Inflammation usually refers to biological process involving immune cells, cytokines and other cell components. While here, in the context of tumor immunology, it represents specific immune responses that lead to cancer development. A growing number of carcinogenic events have been found to be associated with host inflamed status [47]. DA has never gotten rid of the identity as an endogenous inflammation regulator in our prior knowledge of literature [48]. Torres-Rosas group prompted that vagal activation derived from electroacupuncture in the sciatic nerve was unexpectedly linked with dopamine synthesis that regulated innate immunity [49-51].

The multiprotein complexes, inflammasomes, are major elements in host innate immune reaction [52, 53]. Nod-like receptor family pyrin domain-containing protein 3 (NLRP3) is one of the most extensively disquisitive inflammasomes in cancer [52, 54]. As recent works reported, DA exerted inhibitory effects on NLRP3 inflammasome activation [55]. Yan *et al.* [56] investigated *in vitro* that DRD1 signaling increased cAMP levels, thus induced NLRP3 ubiquitination and degradation by autophagy. Their further *in vivo* data showed that DRD1 signaling also impaired inflammation induced by LPS and monosodium urate crystal (MSU), respectively, which indicated a potential therapeutic target for controlling both central and periphery inflammation [56].

Immune cell populations and peripheral DA

T cells

Historically, adaptive immune responses attribute to effector T cells (Teffs) in a large scale. Effector CD8+ T cells identify tumor cells presenting foreign antigens while effector CD4+ T cells are devoted to activation of CD8+ T cells. Peripheral DA and DRs regulate T cell physiology in immune-related disorders and cancer [57]. DA exerts direct effects on molecules and cascades of T cells, for example, ERK, Lck, Fyn, NF-κB [58]. However, T cells from multiple tumors are not working well against abnormal components, probably as a result of tumor itself, chemotherapeutic effects and other potential factors [59]. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) selectively destroyed central dopaminergic neurons and notably enhanced tumor growth of Ehrlich carcinoma in mice due to significant immunosuppression as evident from reduced T cell proliferation, cytotoxic T cell activities and serum IgG and IgM secretion by B cells [60]. Recent evidence indicated that immune cells could be modulated by neurotransmitters and their receptors. It has been shown that antitumor action of DA could stimulate cytotoxic T cells [31, 61]. Circulatory leukocytes express several receptors mainly in the nervous system for neurotransmitters, such as glutamate receptors (GluRs), acetylcholine receptors (AChRs) and dopamine receptors, which represent potential immunomodulatory roles of these neurotransmitters. In cancer patients, several folds increase of plasma DA level (40-80pg/ml) was reported to evidently impair physiological proliferation and cytotoxicity of T cells possibly via DRD1, with no apoptosis detected [62]. Extremely high DA level (up to 1mM) induced lymphocytic cell death due to excess oxidative free radicals [63]. In addition, CD4+ CD25+ regulatory T cells (Tregs) also constitutively produce and store

abundant DA and other catecholamines, with DRs expressed on the membrane. Upon stimulation, released endogenous DA rescues mitogen-induced effector T cells proliferation from Tregs suppression, which subserves a paracrine pattern. Simutaneously, these molecules also inhibit Tregs in an autocrine modulatory loop, causing self-target changes. In resting Teffs, only trace amount of DA was detected, whereas DA amount surged in activated Teffs. Teffs and other target cells carrying DRs will be modulated at different levels, from the second messenger cAMP to cell survival and apoptosis. DRs of Tregs and Teffs involved in aforementioned lymphocytic functional regulation are D1-like receptors (D1 and D5) [64]. Data of this study were collected from healthy individuals; further investigations are making attempts to elucidate clearer evidence of DA-related antitumor immunity.

Aberrant T cells

Previous reports show that stimulation of D1 and D2 dopamine receptors inhibited cell proliferation and cytokine production in activated normal T cells [62, 65]. Though D1 and D2 dopamine receptors were predominantly detected and stimulated, DA failed to inhibit the proliferation of Jurkat cells, a leukemic T cell line bearing uncontrolled proliferative ability, like activated normal T cells. Importantly, no increase in intracellular cAMP level has been noticed. Present observation of defective responsiveness to D1 receptor stimulation, at a deeper level, is probably due to higher phosphodiesterase (PDE) activity instead of significant changes of the receptor structure. In addition, D2 specific agonist also failed to inhibit Jurkat cell proliferation as a consequence of missense mutation in D2 receptor gene sequence. This mutation finally resulted in aberrant ZAP-70 phosphorylation and unmanageable TCR-induced proliferation [66]. Another recent advance reported that DA succeeded in restoring peripheral T cells from major immunological defects via ex vivo incubation within thirty min only in advanced head and neck cancer (HNC) patients. These T cells from cancer were shown to have impaired migration and low cell surface CD3zeta (CD3ζ) and CD3epsilon (CD3ε) expression, which correlated with poor prognosis. DA treatment in low concentration (10 nM) recovered the condition and improved spontaneous migration of T cell towards tumor and its chemotactic migration. However, clear underlying mechanisms responsible for dopamine-induced effects on T cells are still myths and were not figured out in the research, thus requiring further detailed investigations [59]. Taken together, the scanty information herein indicates an adoptive T cell-mediated immunotherapy for some cancer patients in the coming years.

TAMs

Monocytes, especially macrophages, are first-line fighters against tumor cells and their secretory components. The effect of DA on macrophages, in most cases, has been considered to be stimulatory [29]. Alpha-methylparatyrosine (α-MPT)-induced depletion of DA content reduced the recruitment of peripheral macrophages in rats [67]. In tumor-bearing hosts, the role of DA in regulation of immune system seems different from normal healthy ones. TAMs have been described as important cancer mediators [45], among which classically activated (M1-polarized) macrophages are involved in antitumor events and alternatively activated (M2-polarized) subsets are proposed to be correlated with tumor progression, metastasis, chemoresistance and poor prognosis [68,69]. It is now accepted that TAMs are the most abundant cell population in the tumor microenvironment [70], and as a general role, they are inclined to exhibit the M2 phenotype, which causes tumor angiogenic events and blood vessel abnormalities [71]. In early stage of some tumors, M1 macrophages are recruited into the local lesion, leading to massive production of cytokines IL-12 from macrophages and IFN-γ from IL-12-stimulated NK cells in the remodelled stroma [72]. Increasing IFN-γ will in turn activate IL-12 production of the macrophages and thus secretory cytokines IL-12 and IFN-γ form a positive feedback. Also, accumulated IFN-γ evokes tumoricidal effect of M1 macrophages, resulting in eventual cell death. This effective start-up mechanism actually augurs that adaptive immune system is ready to fend for the acquired tumor antigens. Targeting polarization/repolarization of TAMs provides a novel strategy to enhance host antitumor immunity [73]. To our knowledge, however, specific substance that could directionally transform the polarization of TAMs from pro-tumor M2 subgroup to antitumor M1 phenotype remains rare [74]. Of interest, Qin *et al.* [75] have performed inspiring experiments of attempting to switch TAMs polarization in the C6 rat glioma. DA skewed the TAMs from M2 to M1 phenotype *in vivo*, as demonstrated by the downregulation of M2-polarized markers (CD206 and arginase I), accompanied with upregulation of M1-polarized markers (iNOS and CXCL9) [75]. This actually suggested an approach converting the tumor from "cold" to "hot" [76] so as to rescue the response of immunotherapy. Moreover, this distinct effect can be subsided by antagonist of DRD2, indicating that DA at a mild and nontoxic dose can be regarded as a

polarization regulator toward M1 phenotype of TAMs. Parallel studies *in vitro* showed further evidence to support the DRD2-mediated antitumor activity of DA [75].

MDSCs

MDSCs are composed of a heterogeneous group of immune cells. These cells, mainly including dendritic cells (DCs) and immature macrophages, are expected to suppress host immune responses and cause cancer-induced immunosuppression [77]. Accumulated studies on antitumor mechanisms suggest that DA plays emerging roles in MDSCs-related immunomodulation [78]. D1-like receptors (DRD1 and DRD5) genes being detected by RT-PCR and underlying previous experiments and hypothesis, Wu performed investigation of DA effects on tumor-induced inhibition of MDSCs. DA attenuates NO production by Gr1+ CD115+ MDSCs directly via D1-like receptors, mediated by decreased iNOS expression and downregulation of ERK and JNK signaling pathways. Similar inspiring results were obtained in cancer patients as a verification check in human [79]. DRD2 agonists inhibited lung tumor progression and angiogenesis *in vivo*, with possible mechanisms that targeting DRD2 decreased tumor infiltrating MDSCs [80]. Inhibition of immunosuppressive Gr1+ CD11b+ MDSCs is speculated to present a less dreadful tumor microenvironment, followed by improved patient survival [79]. It is still confusing in the current report, however, whether reduction of MDSCs infiltration is due to direct administration of DRD2 agonists or merely the concomitant cause of inhibited tumor growth in mice.

DCs

As key regulators of antitumor immune response, DCs are professional antigen-presenting cells with unique potency for antigen cross-presentation. Tumor-derived exogenous antigens are preferentially presented to CD8+ T cells via major histocompatibility complex (MHC) class I molecules on DCs surface [81, 82]. At this point, naive CD8+ T cells become activated and differentiate into IFN-γ producing T helper-1(Th1) cells and cytotoxic T lymphocytes (CTLs), which exert a direct cytotoxic response on antitumor immunity. DRD3 and DRD3-signaling have been identified in DCs [83]. Of note, DRD3-deficiency and pharmacologic inhibition of DRD3 in DCs could intensify their antigen cross-presentation and CD8+ T cell activation, thus promoting a stronger CTLs response in tumor-bearing mice [84]. It is to imply that DRD3 could be viewed as a targeted agent to drive antigen presenting and stimulatory effect of DCs and improve the immunosuppressive status in cancer.

NK cells

Natural killer (NK) cells have been characterized and serve as innate lymphoid cells that reject malignant transformation. Prolonged inflammatory processes could be avoided by innate immune responses in early stage. Both human and murine NK cells express D2, D3, D4 and D5 receptors, but D1 receptor was absent in human specimens [85, 86] (Table 1). The concept that DA has immunomodulatory effects on NK cells in tumor took its shape from as early as in 1992 when transplantable Ehrlich ascites carcinoma was inhibited due to DA (50mg/kg)-induced splenic NK activity in a mice model [61,87]. In respect with antitumor effects, two subtypes of DRs exert opposite roles on NK cell immunocompetence against YAC-1 lymphoma (a Moloney leukemia virus-induced mouse lymphoma): stimulation of D1-like receptors with specific agonist SKF38393 increased DRD1 and DRD5 density, cAMP and phosphorylated cAMP-response element-binding (CREB) level and augmented NK cell cytotoxicity, whereas D2-like receptors activation suppressed NK cell function. The cAMP-PKA-CREB pathway contributes greatly to DR-mediated antitumor modulation of NK cytotoxicity [86]. So far, quite a few miRNAs and signaling proteins have been critically linked with NK cell function [88]. Another study demonstrated that DA inhibited activated NK cells via the engagement of the D5 receptor, which decreased IFN-γ synthesis in a posttranscriptional manner possibly through miR-29a pathway [85]. After treatment of human rIL-2, stimulated NK cells carried upregulated expression of D5 receptor and incubation with DA reduced NK cell division and effector functions [85].

Potential roles of peripheral DA in pancreatic cancer treatment

Much effort has been expended on traditional chemotherapies but with little satisfactory improvements in prolonged pancreatic cancer survival. Pancreatic cancer has been identified as a complexity that comprises cancer cells, stromal cells and extracellular matrix. Development and progression of pancreatic cancer is often multifactorial. Recent insights have been set on tumor-stromal interactions and immune dysfunction in pancreatic cancer as chronic inflammatory process plays a critical role in pancreatic carcinogenesis [89]. Therefore, treatment attempts focused on the innate and adaptive immune system of cancer are now underway preclinically and clinically [90].

M2-polarized TAMs probably correlated with immunoglobulin G4 (IgG4)-positive plasma cell infiltration in pancreatic cancer, which predicted poor prognosis [91]. In the expression profiles of over 38000 human genes and loci, a total of 1676 and 1166 genes were demonstrated markedly up- or downregulated in pancreatic cancer tissue samples, respectively [92]. DRD2 and cAMP signaling pathway were identified in both pancreatic cancer cell lines and tumor samples and hightlighted as possible therapeutic targets [92]. Advances of immune escaping mechanisms in pancreatic cancer lay emphasis primarily on two aspects [90]: (1) dysfunctional immune cells/effector cells, such as Tregs, MDSCs, TAMs, DCs, NK cells, contributing to promoting immunosuppressive microenvironment; (2) ligand-receptor binding-mediated intercellular contact and secretory immunosuppressive cytokines. The abovementioned findings [92] at least connect DA with pancreatic cancer, but due to its particularity in immunologic elements and status, it remains unclear whether DA medication (agonists and antagonists) will work exactly on PDAC. To address obstacles in coping with chemoresistance, aripiprazole, a partial agonist of dopamine D2 receptors, reverses chemosensitivity with surprise [93], and further exploration by clinicians and investigators on DA-immunity cross-talk might help live up to its promise.

Challenges and Perspectives

A better understanding of the interactions between DA and immune system in tumors will open broad vistas in therapeutics of malignancies. More effective strategies against cancer might target the immunosuppressive milieu and its key components, not only neoplastic parenchyma, but also various interstitial cells, especially these immune cells infiltrated in tumor-specific microenvironment [68, 94]. Nontoxic dose of DA increases the efficacy of anticancer drugs in breast and colon cancer-bearing mice via VEGF receptor-2 (VEGFR-2), mitogen-activated protein kinase (MAPK), and focal adhesion kinase (FAK) phosphorylation [95], nevertheless, we could not rule out the possibility that DA modulated antitumor immunity and altered vulnerability of tumor cells within the body [20]. Revolutionary changes have taken place in cancer treatment these years since the advent of immunotherapy. Of note, thorough interaction between DA and tumor immunity is unknown to date, very few studies addressed the roles of DA on regulating immune system within cancer patients. DA-induced *ex vivo* T cell reset [59] or manipulation of immature human CD34+ cells [33] could be new reference for cancer immunotherapy. DA exerts

biological roles to regulate the functions and phenotypes of immune cells by binding to its different receptors, however, there are many unveiled questions: firstly, why DA selectively binds to certain receptors on immune cells, secondly, whether the expression patterns of different immune cells change in cancerous condition, and thirdly, if the expression patterns change in certain immune cells in cancerous condition, which stimuli trigger these changes. Overall, DA-targeting tumor immunotherapy is still at an infant stage, integrated materials are needed to be more attentively categorized from isolated fragments to a full screen in this issue.

Abbreviations

BBB: Blood-brain-barrier; CNS: Central nervous system; CTLs: Cytotoxic T lymphocytes; DA: Dopamine; DCs: Dendritic cells; DR: Dopamine receptor; GPCR: G protein-coupled receptors; IFN: Interferon; IL: Interleukin; MDSCs: Myeloid-derived suppressor cells; MHC: Major histocompatibility complex; NK cells: Natural killer cells; NLRP3: Nod-like receptor family pyrin domain-containing protein 3; NO: Nitric Oxide; TAMs: Tumor-associated macrophages; Teffs: Effector T cells; Tregs: Regulatory T cells.

Acknowledgments

Competing Interests

The authors have declared that no competing interest exists.

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