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Astrocytes, Microglia, and Parkinson's Disease

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Astrocytes and microglia support well-being and well-function of the brain through diverse functions in both intact and injured brain. For example, astrocytes maintain homeostasis of microenvironment of the brain through up-taking ions and neurotransmitters, and provide growth factors and metabolites for neurons, etc. Microglia keep surveying surroundings, and remove abnormal synapses or respond to injury by isolating injury sites and expressing inflammatory cytokines. Therefore, their loss and/or functional alteration may be directly linked to brain diseases. Since Parkinson's disease (PD)-related genes are expressed in astrocytes and microglia, mutations of these genes may alter the functions of these cells, thereby contributing to disease onset and progression. Here, we review the roles of astrocytes and microglia in intact and injured brain, and discuss how PD genes regulate their functions.

Key words: Parkinson's disease, Glia cell, Astrocyte, Microglia

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease. Its symptoms are related to the death of dopaminergic neurons in the substantia nigra pars compacta. Although most cases of PD are sporadic, researchers have devoted significant effort to studying the function of PD-associated genes in the hope of gaining insight into the pathophysiology of this disease.

Approximately 20 PD genes have been identified to date, and their roles have been studied [1-4]. However, animal models carrying mutations of these genes largely fail to spontaneously develop PD phenotypes with the exception of some alpha-synuclein mu-

tant-carrying animals [5] although brain injury induced by ischemia and/or toxin treatment is potentiated [3, 6-8]. Since neuronal death process itself is rather rapid, it is difficult to see how neuronal defects and/or vulnerability could fully explain the gradual neurodegeneration of PD. It seems more likely that dysfunctions of astrocytes and microglia make the brain microenvironment slowly deteriorate, and that neurons die when the environment becomes too poor for their survival. PD genes are usually expressed in astrocytes and microglia [9-19]. Therefore, astrocytes and microglia that carry PD gene mutations and express these genes may not properly cope with injury. Indeed, it has been reported that astrocytes may not properly exert their beneficial roles in PD and Parkinsonian syndromes [20, 21].

In this review, we summarize the diverse roles of astrocytes and microglia in intact and injured brain (e.g., maintenance of brain homeostasis, survival of neurons, neurotransmission, injury repair, etc.). In addition, we discuss how mutation of PD genes alters the functions of astrocytes and microglia, and how these alterations

may be linked to neurodegeneration in PD.

ROLES OF ASTROCYTES IN INTACT AND INJURED BRAIN

Roles of astrocytes in intact brain

Astrocytes are the most abundant cells in the brain. Astrocytes maintain the homeostasis of the brain microenvironment through uptake of glutamate and potassium ions via the excitatory amino acid transporter, (EAAT)-1/2, and the inward-rectifier potassium channel, Kir4.1, respectively [22-24]. They also regulate the extracellular water content through aquaporin-4 (AQP4) [24], and modulate oxidative stress by producing glutathione (GSH) [25, 26].

Astrocytes are the main cells responsible for regulating glucose metabolism in the brain. They take up glucose from blood and use glycolysis to supply energy to neurons in the form of lactate [26]. Through the pentose phosphate pathway (PPP), astrocytes produce NADPH and nucleic acids/amino acids, which contribute to regulating the redox states of the brain environment and proliferation, respectively [27]. Astrocytes also store glucose as glycogen [28, 29]. In addition, they also provide neurons with glutamine, which is converted from glutamate by the action of glutamine synthetase [30, 31]. The neurons then convert glutamine into glutamate for neurotransmission [31].

The more we study astrocytes, the more new functions are revealed for these cells. Astrocytes actively communicate with neurons, microglia, and other astrocytes [32-35]. Astrocytes release gliotransmitters including γ-aminobutyric acid (GABA) and glutamate [34, 35]. In addition, astrocytes express several types of neurotransmitter receptors and ion channels [33]. Astrocytes inhibit microglial activation in intact brain [32]. In addition, astrocytes regulate the formation of the blood brain barrier, modulate the tone of blood vessels [36-38], and provide neurons with important growth factors [39]. Astrocytes also regulate formation and/or phagocytosis of synapses [40, 41]. Recently, it has been suggested that astrocytes are important for the ability of the glymphatic system to eliminate waste in the brain [42]. Thus, it is easy to see astrocytes as being critical for brain functions, and to understand that a loss of their function may be directly linked to brain diseases.

Roles of astrocytes in injured brain

Astrocytes play critical roles in neuroprotection and regeneration of the injured brain. In response to brain injury, astrocytes become activated; this is termed astrogliosis, or the cells are called 'reactive astrocytes'. Reactive astrocytes become hypertrophic and increase expression of Kir4.1, and GLAST, which assists in the removal of

the elevated extracellular glutamate and K⁺ released from damaged cells [43]. Astrocytes also rapidly respond to reactive oxygen species (ROS) [44], act to protect neurons from oxidative stress [25, 26], and inhibit excessive inflammation by regulating microglial activation [32, 45, 46]. Previously, we and others have reported that activated astrocytes are critical for the protection of neurons and other brain cells in injured brain. For example, in NMDA-injected brain, healthy neurons are observed in the penumbra region near activated astrocytes whereas in kainic acid-injected brain, both astrocytes and neurons gradually die off [43]. Similar to the NMDA example, ATP-injected brain exhibits acute neuronal death, but no further neuronal death in the penumbra region where astrocytes are activated [47]. In contusion-induced spinal cord injury, astrocyte death precedes neuronal death, and neuronal death is spatially and temporally correlated with the death of astrocytes [48]. Accordingly, in glial fibrillary acidic protein (GFAP) - and vimentin-knockout (KO) mice, which do not exhibit astrogliosis, spinal cord injury induces more severe damage than that observed in wild-type (WT) mice [49]. Similarly, selective ablation of reactive astrocytes exacerbates traumatic neuronal damage, and transplantation of astrocytes diminishes brain damage [50, 51]. Astroglial scar has been considered to be occurred in severely damaged brain, irreversible, and inhibits regeneration of damaged neurites [52, 53]. However, a recent study showed that scar formation contributes to neuroprotection and does not inhibit regeneration [54]. Therefore, astrogliosis in injured brain is critical for neuronal survival.

Several studies have suggested that astrocytes produce pro-inflammatory mediators. However, we found that astrocytes express chemokines but barely express other proinflammatory mediators, if any, in injured brain at least in immunohistochemistry levels [46, 55-57]. In addition, in injured brain, neurons do not die in the region where astrocytes are activated, but rather die in absence of reactive astrocytes [43, 48, 58]. In addition, it has been suggested that astrocytes isolated from brains after ischemic injury and intraperitoneal LPS-injection may play beneficial (A2) and harmful roles (A1), respectively [59]. However, it's not clear whether A1 astrocytes play cytotoxic roles for neurons in injured brain since there is no direct evidence to show intraperitoneal LPS-injection induced neuronal death, and yet, neuronal death is due to A1 astrocytes.

Astrocytes participate in repair of injured brain by proliferating and expressing growth factors and extracellular matrix proteins that support axonal growth [57, 60, 61]. In LPS-injured brain, areas lacking astrocytes decrease in size beginning about a week after LPS injection and almost completely disappear at about 3 months post-injection [57]. Myelin, neurites, blood vessels, etc., also reappear and refill the injured area [57]. Studies have also shown that

astrocytes regulate revascularization and remyelination in injured brain [62, 63]. Consistent with this, intrathecal infusion of FGF-2 or EGF, which increase number of astrocytes and ependymal cells, have been shown to improve functional recovery in spinal cord injury [64], whereas astrocyte depletion significantly increase leukocyte infiltration, blood brain barrier disruption, and damage [49, 51]. GFAP-positive neural stem cells in the subventricular zone (SVZ) have also been shown to participate in repairing injury sites [65, 66]. Recent studies suggest that astrocytes play even more active roles in repairing injured brain, as reactive astrocytes in a damaged brain are shown to de-differentiate into stem-like cells and re-differentiate into neurons [67, 68]. In injured brain, therefore, it is critical to preserve astrocytes and/or support their functions to prevent neuronal death and facilitate the regeneration of injured brain.

ROLES OF MICROGLIA IN INTACT AND INJURED BRAIN

Surveillance function of microglia

Microglia (i.e., brain macrophages) continuously extend and retract their processes, and make contacts with synapses for pruning in developing and adult brain, by which microglia may fine tune neural circuits [69, 70]. Thus, disruptions in microglia-mediated synaptic pruning could develop neurodevelopmental, psychiatric, and neurodegenerative disorders [69, 71-73].

In response to brain injury, microglia rapidly extend their processes toward lesion sites and isolate them [74, 75], which is critical to the prevention of further injury due to the disruption of micro-environmental homeostasis [76]. Thus, treatment with an actin-depolymerizing agent is associated with the failure of microglia to properly isolate injury sites, and the subsequent worsening of damage [76].

Inflammatory responses of microglia in injured brain

Microglia are activated and produce inflammatory mediators in injured brain. Microglia in intact brain have many processes, and those in injured brain have thicker processes. Blood cells that infiltrate into damaged brain may be mistakenly identified as microglia because of absence of specific markers for each type of cells. Since CD11b is expressed in microglia and all kinds of white blood cells (e.g., monocytes, neutrophils, and lymphocytes), CD11b-positive and/or Iba-1-positive neutrophils and monocytes, which are round in shape, are often misinterpreted as activated microglia in injured brain [55, 56]. Unlike cultured microglia activated by LPS and/or interferon (IFN)-gamma that express cytotoxic inflammatory mediators such as iNOS [77], microglia in injured brain express limited amounts and/or kinds of non-toxic inflammatory

mediators [55, 56]. Furthermore, neurons and neurites are healthy in injured brain regions that harbor activated microglia [48, 56], suggesting certain roles of inflammatory mediators in injured brain. In fact, cytokines (e.g., IL-1beta, IL-6, and TNF-alpha) have diverse functions including regulation of neurite outgrowth [78-80], metabolism [81], growth factor expression [78, 82], and ion channel activity [83].

In response to injury, cytotoxic inflammatory mediators are produced to prevent infection although they exert toxic effects on surrounding tissues. However, brain injury including ischemic damage and traumatic injury do not open the brain to outside exposure, which means the absence infection. Therefore, in injured brain, diverse mechanisms inhibit cytotoxic inflammation by producing negative regulators of inflammation including suppressor of cytokine signaling (SOCS)-family proteins and antioxidant enzymes [46, 84-88]. In addition, astrocytes and neurons in intact and damaged states attenuate microglial inflammatory responses [32, 45, 89].

Together, the accumulating data indicate that astrocytes and microglia play diverse roles in protecting neurons and other brain cells in injured brain. Therefore, it seems reasonable to expect that insufficient and/or altered functions of astrocytes and microglia will decrease the protection of cells in injured brain.

FUNCTIONS OF ASTROCYTES AND MICROGLIA ARE ALTERED BY MUTATIONS OF PARKINSON'S DISEASE (PD) GENES

Many studies on PD and other neurodegenerative diseases have focused on the death of defective neurons. However, neuronal death can also be induced by a brain environment that does not sufficiently support neuronal survival and/or function. Since PD

	Functions	PD genes that regulate glial functions
Astrocyte	Glucose metabolism	PINK1, DJ-1
	Mitochondrial function	PINK1
	Intracellular ROS	parkin., DJ-1
	Growth factor production	DJ-1
	Astrogenesis	PINK1
	Astrogliosis	DJ-1
	Proliferation	PINK1, parkin
	Endocytosis	DJ-1
	Inflammation	DJ-1
Microglia	Inflammation	DJ-1, PINK1, LRRK2, , α-syn
	Surveillance	LRRK2
	Phagocytosis	DJ-1, α-syn, LRRK2

Fig. 1. Functions of astrocytes and microglia regulated by PD genes.

genes are expressed in astrocytes and microglia, we review how mutations in certain PD genes, affect the functions of astrocytes and microglia (Fig. 1).

PD genes regulate glucose metabolism and mitochondrial function

Mitochondrial dysfunction, a well-known risk factor for PD [90, 91], increases ROS production and alters glucose metabolism [92, 93]. Accordingly, changes in the metabolites and enzymes of the tricarboxylic acid (TCA) cycle are observed in PD brains [94, 95]. Positron emission tomography using ^{18}F-deoxyglucose (^{18}F-FDG PET) analysis also showed that glucose metabolism is reduced in various brain regions of PD patients [96]. In the brain, astrocytes metabolize glucose mainly through glycolysis, whereas neurons use oxidative metabolism for this purpose [26]. It has been reported that lethality or deficient locomotion is seen in Drosophila in which glycolytic enzymes have been knocked down in glia but not in neurons, suggesting that glial glycolysis in the brain is important for survival and normal locomotor behavior [97].

Parkin, PINK1, DJ-1, and LRRK2 regulate mitochondrial function and glucose metabolism [98-100]. Expression of a kinase-dead PINK1 mutant decreased ATP generation, decreased oxygen consumption, and increased ROS production [101]. Parkin may also regulate glycolysis since it directly regulates pyruvate kinase M2, a glycolysis rate-limiting enzyme [102]. In addition, LRRK2 regulates vulnerability to mitochondrial dysfunction in c. elegans [100].

In astrocytes, these genes regulate mitochondrial function and glucose metabolism. PINK1-knockout (KO) astrocytes exhibit decreased mitochondrial mass, decreased membrane potential, decreased glucose uptake, and increased intracellular ROS levels [9]. DJ-1 plays a unique role in glucose metabolism: DJ-1, with its glyoxalase activity metabolizes a toxic product of glycolysis, methylglyoxal, into D-lactate [103]. Methylglyoxal, which is a cell-permeant precursor of advanced glycation end products (AGEs), has been associated with diabetes, aging, and neurodegenerative diseases [104]. Astrocytes actively detoxify methylglyoxal via their glyoxalase [105]. DJ-1 deficiency decreases this metabolism, leading to accumulation of methylglyoxal in the brain [103].

Neuroprotective functions of PD genes

Astrocytes protect neurons in several ways, such as by scavenging ROS and expressing growth factors. GSH is a ROS scavenger produced from astrocytes [106]. Parkin regulates GSH levels in astrocytes. Accordingly, GSH levels are lower in Parkin-KO astrocytes than in WT astrocytes [19]. PINK1 and DJ-1 regulate nuclear translocation and/or stabilization of Nrf2 [107-109], a critical

transcription factor for the expression of antioxidant enzymes such as NAD(P)H quinone oxidoreductase 1 and HO-1 [107-109], although their roles have been reported in cancer cells and SHSY5 neuron cells [107-109]. In endothelial cells, DJ-1 directly functions as an antioxidant via the oxidation of its cysteine residue [110, 111]. In astrocytes, DJ-1 deficiency reduces their ability to protect neurons against the mitochondrial toxin, rotenone [112-115]. In addition, DJ-1 increases mitochondrial antioxidant H2S production in astrocytes through expression of cystathionine β-synthase (CBS), the major enzyme that catalyzes H2S production [116].

Growth factors released from astrocytes including glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), etc., are important for the development and survival of neurons [117, 118]. Recently, we have reported that DJ-1 deficiency reduces GDNF and BDNF expression in astrocytes [119]. Several studies have reported that parkin and PINK1 are linked to the expression and/or functions of GDNF. Parkin prevents degeneration of dopaminergic neurons in cooperation with GDNF [120]. GDNF and its signaling receptor, Ret, rescues PINK1 deficiency-induced muscle degeneration, mitochondrial disintegration, and ATP content in Drosophila [121]. However, there is no direct evidence showing their roles for GDNF expression in astrocytes.

PD genes regulate gliogenesis, astogliosis, and proliferation of astrocytes

PINK1 expression has been shown to increase during brain development and the differentiation of neural stem cells [11]. Interestingly, PINK1 deficiency causes defects in GFAP expression during early brain development and decreases differentiation of neural stem cells (NSCs) into GFAP-positive astrocytes (astrogenesis) [11]. Although astrogenesis is regulated by a number of signaling molecules (e.g., SMAD1/5/8, STAT3, and HES1), these signaling pathways appear normal in PINK1-deficient NSCs [11]. Various microRNAs (miRNAs; e.g., mir-326, -330, and -3099) increase during brain development and NSC differentiation, and thus appear to contribute to regulating GFAP expression [12]. Notably, PINK1 deficiency decreases the expression of these miRNAs during the above mentioned processes [12].

PINK1 deficiency also causes a defect in the proliferative response of astrocytes to epidermal growth factor (EGF) and fetal bovine serum (FBS) [9]. This defect, which is associated with delayed wound healing in cultured astrocytes, appears to be caused by mitochondrial dysfunction through increased p38 MAPK (mitogen-activated protein kinase) activation, decreased AKT activation, and decreased EGF receptor (EGFR) expression [9]. Parkin also regulates proliferation: glia cultured from parkin-KO mice show reduced proliferation, and increase proapoptotic protein

expression [19]. Astrocytes proliferate and participate in repairing the damage in injured brain [57, 122]. Our recent study shows that DJ-1 positively regulates astrogliosis in injured brain [119]. DJ-1 regulates astrogliosis through stabilization of Sox9 [119], a transcription factor that regulates gliogenesis during development of the brain [123, 124], and astgliosis in injured brain [125, 126]. Accordingly, DJ-1 deficiency causes defects in astrogliosis and delays repair of injured brain [119]. Therefore, defects in proliferation, astrogenesis, and/or astrogliosis due to mutation of PD-related genes may delay repair and contribute to the pathogenesis of PD.

PD genes regulate phagocytosis and the functions of lipid rafts

PINK1, α-synuclein, LRRK2, DJ-1, and parkin are all known to associate with lipid rafts, suggesting that dysfunction of these proteins may cause defects in cellular functions related to lipid rafts [16, 17, 127]. DJ-1 regulates lipid raft-dependent endocytosis in astrocytes and MEFs [16, 17], and DJ-1 deficiency impairs uptake of glutamate into astrocytes by altering EAAT2 expression [17]. DJ-1 also positively regulates microglial phagocytosis of alpha-synuclein [128].

Parkin, α-synuclein, and LRRK2 also regulate endocytosis and/or phagocytosis. Parkin deficiency promotes lipid raft-dependent endocytosis through the accumulation of caveolin-1 in MEFs [127]. In addition, aggregated α-synuclein inhibits microglial phagocytosis by binding to FcγRIIB and activating the phosphatase, SHP-1 [129, 130]. In addition, LRRK2 regulates microglial phagocytic activity in a kinase dependent manner [131, 132].

PD genes regulate inflammation and microglial surveillance functions

Accumulating evidence shows that PD genes regulate brain inflammation. For example, DJ-1 attenuates inflammation by regulating diverse signals, including p38 MAPK, STAT1, and ROS [16, 133]. DJ-1 regulates intracellular ROS both by direct scavenging and by increasing the expression of antioxidant enzymes [108, 110, 111]. DJ-1 inhibits STAT1 activation by facilitating the interaction between STAT1 and its phosphatase, Src-homology2-domain containing protein tyrosine phosphatase-1 (SHP1) [15]. DJ-1 also regulates STAT1 activation by upregulating the expression of mir-155 [134], which specifically induces expression of suppressor of cytokine signaling 1 (SOCS1), a negative feedback regulator of STAT1 [134].

PINK1 also regulates inflammation. Brain slices of PINK1-KO mice exhibit increased mRNA expression of inflammatory cytokines, compared to WT brain slices [14]. PINK1 deficiency reduces activation of STAT3 and AKT, which negatively regulate

inflammatory responses [14]. However, others have reported that PINK1 enhances IL-1-beta-induced NF-kB activation in HEK293 cells and mouse embryonic fibroblasts [135].

LRRK2 deficiency has been shown to inhibit inflammation by inhibiting p38 MAPK and decreasing the transcriptional activity of NF-kB [13, 136]. However, overexpression of LRRK2 WT and G2019S yields similar increases in NF-kB activity, suggesting that LRRK2 regulates NF-kB in a kinase-independent manner [13]. Alpha-synuclein also positively regulates microglia inflammatory responses and astrocyte ICAM-1 and IL-6 expression [137-139]. In addition, astrocytes that express A53T alpha-synuclein enhance microglial activation [7]. These information indicate that brain inflammation is enhanced by both loss-of-function mutations of DJ-1 and PINK1 and gain-of-function mutations of LRRK2 and alpha-synuclein.

Parkinson's disease genes may regulate microglial surveillance function. LRRK2 interacts with several actin-regulating proteins and regulates actin dynamics [140-142]. Microglia continuous movement of their processes to survey microenvironments of the brain [74, 75], which is regulated by actin dynamics [76]. LRRK2-knockdown BV2 microglia cells are morphologically different from WT microglia and are highly motile even in the absence of any stimulator [10, 143]. LRRK2 regulates microglial motility in a kinase-dependent manner through the inhibition of FAK, a critical player in cell movement [10, 144]. Furthermore, the LRRK2 G2019S mutation retards the microglial response to injury [10]. Since defects in the ability of microglia to isolate injured brain sites has been shown to increase the damage [76], microglial defects caused by the G2019S mutation may contribute to the development of PD.

CONCLUSION

It has been reported that glial functions are decreased and altered with aging [145], which is the most important risk factor for PD and other neurodegenerative diseases. In this review, we summarize the defects of glial functions associated with the mutation and/or deficiency of PD genes. The existing evidence shows that impaired glial function is closely related to onset and progression of PD. Therefore, defects in the functions of astrocytes and microglia increase the risk of PD. This suggests that studies on glia may facilitate the development of new therapeutic targets for treating PD and other neurodegenerative diseases.

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