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Review

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Age-related energetic reprogramming in glial cells: possible correlations with Parkinson's disease

Boling Chu[1,#], Hongling Xiang[1,#], Han Wang[1], Yuting Lin[1], Rui Li[1], Jing Hu[1,2,*], Hao Qian[1,2,*]

[1]Sichuan Provincial Key Laboratory for Human Disease Gene Study and the Center for Medical Genetics, Department of Laboratory Medicine, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu 610054, Sichuan, China.
[2]School of Medicine, University of Electronic Science and Technology of China, Chengdu 610054, Sichuan, China.
[#]Authors contributed equally.

[*]**Correspondence to:** Prof. Hao Qian, Prof. Jing Hu, School of Medicine, University of Electronic Science and Technology of China, No.4, Section 2, North Jianshe Road, Chengdu 610054, Sichuan, China. E-mail: qianhao@uestc.edu.cn; jinghu_somed@uestc.edu.cn

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Abstract

Glial cells populate the central nervous system and undertake indispensable roles in safeguarding and maintaining optimal neuronal performance. Throughout life, the brain undergoes inevitable changes that impact both neurons and glial cells. Concurrent with age-related neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), metabolic dysfunctions in glial cells are consistently observed. Though widely debated, the idea of treating neurodegenerative disorders by manipulating brain bioenergetics warrants further exploration. This review discusses the distinctive metabolic characteristics of central nervous system (CNS) glia, the metabolic deviations that occur in glial cells in the aging brain, and the ramifications of metabolic rewiring within glia on neurodegenerative disorders, specifically PD. We focus on astrocytes and microglia due to their substantial transformations under aging and diseased states, known as reactivation. Special attention is given to clarifying the complex relationships between dysregulated glial energy metabolism and brain disorders. By discussing both classic theories and current advances in this field, we aim to shed light on promising therapeutic horizons anchored in the strategic calibration of glial metabolic configurations.

Keywords: Glia, energy metabolism, aging, neurodegeneration, Parkinson's disease

INTRODUCTION

The human brain represents one of the most intricately structured tissues in complex organisms, playing a fundamental role in cognition and behavior[1]. With advancing age, both the brain's architecture and its microenvironment undergo transformations, culminating in a gradual decline in cognitive capacities and behavioral functions, including learning, memory, and motor coordination[2]. Neuronal degenerative diseases, characterized by neuronal loss and disruptions in network connections, are frequently associated with aging and exhibit shared underlying mechanisms[3].

Despite comprising just 2% of overall body mass, the human brain demands an estimated 20%-25% of the body's entire energy expenditure, making it one of the most energetically costly organs within the human body[4]. In general, glucose serves as the principal energy substrate supporting brain function. Once across the blood-brain barrier, glucose undergoes transformation into adenosine triphosphate (ATP), a vital energy currency, via dual pathways - namely glycolysis and oxidative phosphorylation (OXPHOS)[2]. Notably, diverse cell types within the central nervous system exhibit markedly dissimilar energy metabolism profiles. Specifically, neurons primarily rely upon OXPHOS for generating ATP[5], whereas astrocytes predominantly employ glycolysis[6]. Moreover, neural cells possess the capacity to harness various substrates such as glutamate, glutamine, pyruvate, and lactate, thereby facilitating intricate intercellular exchange mechanisms among glial and neuronal populations[7,8]. Such complex interactions play pivotal roles in preserving physiological equilibrium and contributing to disease etiology. Another crucial aspect meriting careful attention pertains to the dialogue between neuronal dynamics and regulatory mechanisms governing brain energy balance. Mounting evidence reveals that fluctuations in metabolic rates correspond to disparate cognitive and behavioral modes - quiescent *vs.* activated states[9]. During synchronized neuronal operations, augmented demand for, as well as consumption of, oxygen and glucose ensues, collectively termed neurovascular and neurometabolic coupling. Integral players mediating this symphony of metabolic equilibrium maintenance are none other than glial cells, especially astrocytes, which occupy key positions in this complex regulatory network[10].

There is a growing body of research bolstering the hypothesis that disruptions in energy metabolism play a central role in the onset and advancement of neurological disorders. The present understanding concerning disrupted regional energy expenditure tied to neurodegenerative disorders is consolidated in Table 1[11-16]. Regional biochemical adaptations imply the significant impact of locally transformed microenvironments accompanying neurodegeneration[2]. Acting as a focal participant birthed from manifold metabolic avenues, reactive oxygen species (ROS) meaningfully add to this detrimental local environment. ROS have been identified as increasingly prevalent in the mammalian central nervous system during aging[17]. Mitochondria are among the primary sources of ROS, generating it through oxidative phosphorylation. Normally, ROS participates in physiological functions like inflammation and synaptic plasticity[18]. Nevertheless, an excess production of ROS within cells can trigger oxidative stress, disrupting redox homeostasis and resulting in mitochondrial dysfunction. This chain reaction could potentially exacerbate age-related neurological disorders, including Alzheimer's disease (AD) and Parkinson's disease (PD), as supported by animal research findings[17,19]. Studies have reported significant reductions in ATP synthesis capacity, pyruvate dehydrogenase activity, and calcium buffering abilities in aged animals compared to their younger counterparts[20]. Recent investigations also emphasize the impact of mitochondrial damage induced by ROS on several neurodegenerative illnesses, underscoring the critical significance of energetic malfunctions[21]. Accompanying diminished ATP generation, the amassed ROS foster a markedly proinflammatory setting. Within the aged brain, neurons endure prolonged exposure to this persistent inflammatory atmosphere, conceivably heightening neuronal loss and synaptic abnormalities, thus facilitating the evolution of the senescent brain toward pathological manifestations.

Table 1. The brain regions associated with abnormal glucose metabolism in neurodegenerative diseases

Disorders	Metabolic change	Related brain area	Ref.
AD	Glucose hypometabolism	Posterior cingulate cortex; precuneus; anterior hippocampus; parahippocampal gyrus	[11,12]
PD	Glucose hypometabolism	Premotor; parieto-occipital cortex	[13]
	Glucose hypermetabolism	Cerebellum; pons; paracentral gyrus; lentiform nucleus	
HD	Glucose hypometabolism	Frontal lobe; temporal lobe; striatum	[14]
ALS	Glucose hypometabolism	Prefrontal; cingulate cortex; caudate nuclei; rolandic operculum; thalamus	[15,16]
	Glucose hypermetabolism	Amygdalae; midbrain; pons; cerebellum	

AD: Alzheimer's disease; PD: Parkinson's disease; HD: Huntington's disease; ALS: amyotrophic lateral sclerosis.

Considering the substantial involvement of glial cells in shaping and managing the central nervous system's microenvironment, it is logical to posit that the energy metabolic condition of these cells plays an essential role in the shift from health to disease. Indeed, reactivated astrocytes have emerged as a prominent source of ROS; despite primarily utilizing glycolysis for ATP production, they generate considerable quantities of mitochondrial ROS[22]. These accumulating astrocyte-derived ROS have downstream consequences on neuronal activity and animal behavior[23]. Additionally, it has been extensively established that astrocytes govern cerebral blood flow by fine-tuning the diameter of microvasculature, consequently modulating the delivery of both oxygen and glucose. In terms of other glial subtypes, microglia - given its intimate connection to the central nervous system's inflammatory responses - have shown close ties between metabolic reprogramming and polarization[24]. Glial cells not only construct the microenvironment but are themselves influenced by variations in the metabolic landscape; their functional capabilities and survivability remain subject to these modifications[6]. For instance, the aged brain faces challenges related to the insufficient provision of energy substrates due to compromised local microcirculation, which can fundamentally transform glial cell metabolism, eventually inflicting detriment upon the integrated neuronal circuitry. Nevertheless, the ramifications of modified glial energy metabolism on brain aging and attendant diseases remain an active area of rigorous investigation.

In this review, we will provide a concise overview of established concepts while delving into recent advancements on three key topics: (1) The distinctive characteristics of glial energy metabolism in the central nervous system; (2) The metabolic alterations occurring in glial cells within the aging brain; (3) The impact of metabolic reprogramming in glial cells on neurodegeneration, particularly in PD. Our aim is to offer deeper insights into the association between dysfunction in glial energy metabolism and brain disorders, thereby illuminating the potential for novel therapeutic strategies centered around modulating glial metabolic states.

GLIA ENERGETICS AND THE NORMAL FUNCTION OF THE CENTER NERVE SYSTEM

In recent decades, there has been increasing focus on the study of glial energy metabolism, considering the distinct morphologies and functions of the three major subtypes of glial cells: astrocytes, microglia, and oligodendrocytes. While some similarities exist in their bioenergetic characteristics, each subtype serves different neuronal functions. For instance, both astrocytes and oligodendrocytes favor glycolysis and provide bioenergetic support to neurons[6,25]. However, oligodendrocytes primarily facilitate the propagation of action potentials and maintain a close relationship with axonal mitochondria[26], whereas the energy demands of synaptic transmission are more closely associated with astrocytes[27]. Undeniably, the harmonious bioenergetic collaboration between various glial cells and neurons forms an integral pillar upholding regular brain functions in humans [Figure 1].

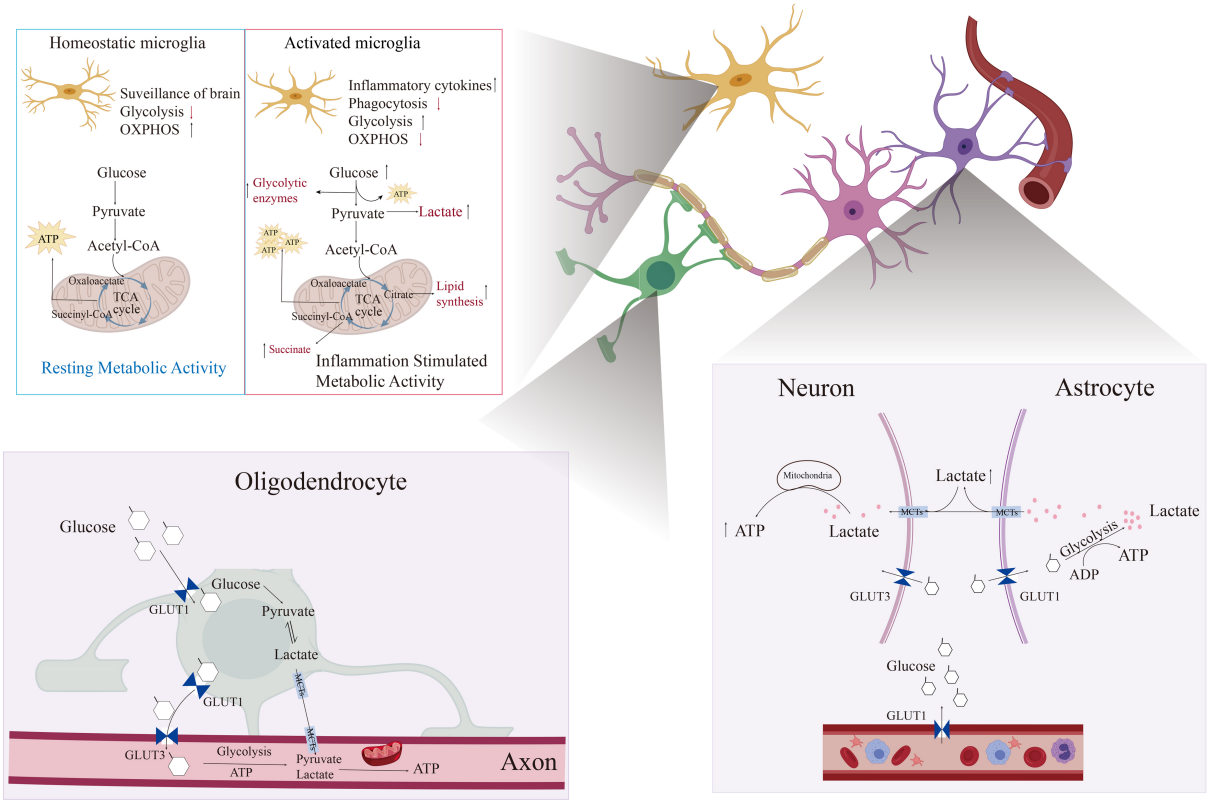

Figure 1. The metabolic types of normal nerve cells.

While it has been reported that oligodendrocyte dysfunction and demyelination may contribute to neuronal death in neurodegenerative diseases[28], particularly AD[29], our current understanding of oligodendrocyte metabolic dysfunctions and their impact on the degeneration of the nigrostriatal pathway remains limited. Therefore, our discussion will primarily focus on astrocytes and microglia, examining their metabolic dysregulations in aging and degenerative brain conditions. We anticipate that future studies will provide deeper insights into oligodendrocyte metabolism and its role in neurodegeneration.

In physiological conditions, distinct metabolic profiles characterize different subtypes of brain cells to facilitate their respective functions. Neurons predominantly utilize mitochondrial oxidative phosphorylation, whereas astrocytes predominantly engage in aerobic glycolysis. Additionally, astrocytes metabolize glucose into lactate, which serves as a crucial metabolic substrate for neurons. Oligodendrocytes primarily rely on glycolysis, and the energy metabolism of microglial cells undergoes reprogramming in response to their specific states.

Normal bioenergetic characteristics of astrocytes

Comprising the majority of glial cells constituting the brain, astrocytes fulfill indispensable metabolic obligations benefitting neighboring neurons. Astrocytes possess distinctive cellular structures and occupy strategic positions that enable them to perceive environmental cues and adapt to associated fluctuations[6]. Positioned within the neurovascular unit, astrocytes consistently mediate the interface between neurons and capillaries. Their end feet establish connections with both blood vessels and synapses, fostering intricate interactions among these integral components[30]. Recently, Nippert *et al.* proposed that astrocytes can facilitate the increase in cerebral blood flow triggered by hypoglycemia via a calcium-dependent mechanism

involving the release of vasodilators[31]. Their study employed insulin-treated mice to simulate hypoglycemia conditions. Under hypoglycemic conditions, arterioles undergo dilation, concomitant with heightened astrocytic Ca^{2+} signaling. Application of specific inhibitors targeting the production of astrocyte-derived vasodilators, such as prostaglandin and epoxyeicosatrienoic acids, resulted in substantial reductions of arterial dilation by 89% and 76%, respectively[31]. This observation suggests a potential mechanism by which astrocytes modulate cerebral blood flow to facilitate glucose transport from blood vessels to astrocytes, thereby generating metabolic substrates crucial for supporting neuronal activity.

Current research indicates that under normal circumstances, astrocytes primarily utilize glucose for energy production. Glucose is taken up into the cell via glucose transporter (GLUTs) proteins, particularly GLUT1, and is phosphorylated by hexokinase (HK) to form glucose-6-phosphate[32]. This glucose can then enter various metabolic pathways, including glycolysis, the pentose phosphate pathway (PPP), OXPHOS, and glycogen synthesis[33]. However, astrocytes predominantly metabolize glucose through aerobic glycolysis, which not only meets their lower energy demands but also produces lactate, a metabolic substrate crucial for neuronal support. As early as 1994, Pellerin *et al.* proposed the astrocyte-neuron lactate shuttle hypothesis[34]. The process through which lactate shuttles between neurons and astrocytes is as follows: following neuronal stimulation, adjacent astrocytes can uptake excess glutamate at the synapse. Subsequently, the entry of sodium into astrocytes activates Na^+/K^+ ATPase, the activation of which consumes ATP produced by glycolysis. Lactate produced by glycolysis is transported extracellularly by monocarboxylate transporters (MCT1 and MCT4), and then transported into neurons via MCT2 on the neuronal membrane, providing oxidative phosphorylation substrates for neurons[35,36]. Roumes *et al.* developed a rat model where they specifically downregulated cortical neuronal MCT2 or astrocytic MCT4. They then measured metabolic and hemodynamic responses to sensory stimulation using functional magnetic resonance spectroscopy and blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI)[37]. Their results convey that the shuttle of lactate between astrocytes and neurons is indispensable for neuro-metabolic and neurovascular coupling. Furthermore, recent research by Muraleedharan *et al.* found that adenosine monophosphate-activated protein kinase (AMPK) is a key enzyme regulating the production of lactate by astrocytes and its transfer to neurons[38]. They generated AMPK-KO astrocytes *in vitro* and cultured them in a medium containing [U-^{13}C] glucose. The results showed that AMPK-KO astrocytes exhibited a 50% reduction in lactate production, along with significantly decreased glucose uptake and membrane translocation of the glucose transporter GLUT1. However, the addition of lactate or wild-type astrocytes to the culture medium restored these functions. In animal experiments, the researchers found that the lactate content in the brains of AMPK knockout mice on postnatal day 28 decreased by 40% as measured by ^{1}H magnetic resonance spectroscopy. Additionally, cortical thinning and neuronal loss were observed in these mice[38]. These findings underscore the importance of AMPK-regulated glycolytic metabolism in astrocytes for maintaining neuronal homeostasis.

Metabolic processes of lipids are intricately linked to energy production in astrocytes[39]. While neurons have limited lipid metabolism capabilities, astrocytes exhibit robust lipid metabolism enzyme activity, necessitating a high energy supply[40]. Astrocytes synthesize cholesterol in the brain and transport it via ApoE-containing lipoproteins[41]. Neurons absorb lipids derived from astrocytes to support synaptic formation and function[42]. When neurons become hyperactive, they produce peroxidized lipids, raising questions about how neurons manage lipid accumulation. Recent research has shed light on this process: hyperactive neurons generate toxic fatty acids (FAs), which are transferred to astrocytes via ApoE-positive lipid droplets. Astrocytes then metabolize FAs through mitochondrial β-oxidation and initiate detoxification gene expression programs[43]. This result highlights the dynamic interplay between neurons and astrocytes in maintaining brain lipid homeostasis. Hence, it becomes entirely justifiable to propose that

impairment in astrocytic energy metabolism would likely compromise neuronal function and viability, given its adverse implications on lipid processing.

Microglia has distinct metabolic patterns in normal brain

Microglia serve as the central nervous system's resident macrophages, maintaining homeostasis throughout brain development and adulthood[44]. They exhibit high plasticity, enabling them to adapt to diverse environmental cues through extensive phenotypic remodeling while surveilling the brain milieu[45]. This adaptability is closely linked to their ability to utilize various energy substrates, such as glucose, lipids, ketone bodies, lactate, and pyruvate[46,47]. Unlike astrocytes, microglia primarily rely on oxidative phosphorylation for ATP production using glucose[48]. FAs undergo ATP production by coupling with peroxisomes to generate acetyl-CoA, which then enters the tricarboxylic acid (TCA) cycle[49]. In their activated state, however, macrophages display diverse metabolic phenotypes. When stimulated by lipopolysaccharide (LPS), proinflammatory macrophages demonstrate heightened glycolytic metabolism alongside compromised mitochondrial oxidative phosphorylation[50,51]. Conversely, anti-inflammatory macrophages induced by interleukin 4 (IL-4) exhibit elevated mitochondrial oxidative phosphorylation[52]. The metabolic alterations of both astrocytes and microglia are depicted in Figure 2.

Astrocytes and microglia exist in two distinct states: resting and activated. In the resting state, astrocytes predominantly rely on glycolysis for energy production. However, upon activation, they primarily depend on OXPHOS. Microglia, on the other hand, exhibit a different metabolic profile. In their resting state, microglia primarily utilize OXPHOS to generate ATP from glucose. However, upon activation, their metabolic patterns vary depending on their physiological functions. Anti-inflammatory microglia show an increase in mitochondrial oxidative phosphorylation. Conversely, in proinflammatory microglia, there is an upregulation of glycolytic metabolism, while mitochondrial oxidative phosphorylation is impaired. Proinflammatory microglia are characterized by a rounded morphology, indicative of their hyperactive state, whereas anti-inflammatory microglia exhibit an elongated morphology.

Microglia possess crucial properties such as phagocytosis and inflammation. They play a significant role in synaptic pruning through phagocytosis, which fosters synapse formation and development, while also maintaining a normal neuronal count in the developing brain[53]. In pathological conditions like pathogen infections or acute ischemic strokes, microglia release cytokines and chemokines, such as interleukin-1 beta (IL-1β) and chemokine (C-X-C motif) ligand 1 (CXCL1), to safeguard the central nervous system by recruiting neutrophils[54,55]. A growing body of evidence suggests that altering the metabolism of microglia directly influences their phagocytic and inflammatory responses. In terms of inflammation, microglia can detect changes in brain metabolism and adjust their own metabolic processes to regulate neuronal activity. For instance, fluctuations in blood glucose levels have been linked to the inflammatory activation of microglia and an increased secretion of proinflammatory factors[56]. It is noteworthy that recent investigations utilizing single-cell RNA sequencing and spatial transcriptomic analysis have provided new insights into microglial subtypes. The traditional classification of microglia into proinflammatory (M1) and anti-inflammatory (M2) subtypes is now considered oversimplified[57]. More complex subtypes of microglia have been identified under specific conditions associated with distinct neurodegenerative disorders[57]. The extent to which metabolic plasticity contributes to the divergence of reactive microglia remains to be further studied.

Microglia not only possess metabolic plasticity but also engage in metabolic interactions with neurons. Triggering receptor expressed on myeloid cells 2 (Trem2), a myeloid cell-specific gene expressed in brain microglia, has been shown to regulate neuronal development by influencing the metabolic fitness of

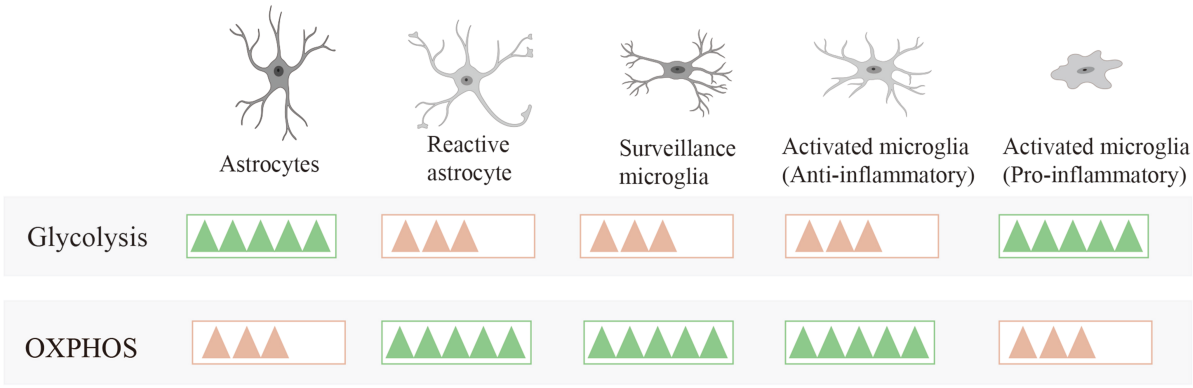

Figure 2. The energy metabolism patterns of astrocytes and microglia in different states.

neurons in a region-specific manner[58]. Additionally, microglia may monitor and protect neurons by sensing changes in mitochondrial energy at the microglia-neuron somatic junction[59]. Impairment in mitochondrial dynamics is associated with pathological processes in neurodegenerative diseases like AD and PD[60]. Microglial metabolic plasticity also responds to metabolic changes in the brain and body. Glial-neuronal interactions form a circuit that senses internal signals and adjusts behavior and metabolism according to metabolic states[61]. For instance, obesity, an energy metabolism disorder, induces brain inflammation and activates microglia, contributing to cognitive impairment by aberrantly phagocytosing synaptic spines. However, the precise mechanisms underlying microglial activation during obesity remain incompletely understood[62].

ALTERED CELLULAR ENERGY METABOLISM IN THE AGING BRAIN

As humans age, notable structural remodeling occurs within the brain, a phenomenon readily detectable through computed tomography and magnetic resonance imaging modalities[63,64]. Prominent examples include the observable decreasing trends observed in both gray matter volume and white matter volume over time. A previous investigation revealed a significant reduction in the overall gray matter volume of the brain, with particularly pronounced atrophy noted in the frontal and temporal lobes[65]. This decrease in gray matter volume is closely linked to the deterioration of cognitive functions. For instance, the atrophy of gray matter in the prefrontal lobe correlates with a decline in executive function[66]. In contrast to gray matter, the alterations in white matter during the aging process exhibit distinct patterns. The integrity of white matter structure undergoes dynamic changes with age, showing a gradual increase before age 40, peaking around 50 years, and subsequently declining after 60 years[67]. Furthermore, the age-related deterioration in cognitive functions is closely linked to alterations in white matter structural integrity, which are implicated in neurodegenerative conditions. Subclinical mild cognitive impairment may elevate the susceptibility to developing such diseases because of these changes[68]. The alterations in brain structures can be attributed primarily to neuronal cell loss and impaired glial function. Given the critical functions of energy metabolism in maintaining central nervous system homeostasis, it is unsurprising that close connections exist between macroscale structural alterations in the brain and microscale functional modifications to cellular metabolic reprogramming[69-71].

Metabolic reprogramming of aging neuron

Progressing age engenders disruptions in neuronal energy metabolism, crystallized along two primary dimensions: (1) anomalous glucose usage patterns; and (2) compromised mitochondrial oxidative phosphorylation[72,73]. Age-induced insulin resistance, accompanied by deficient glucose transportation,

materializes within neuronal communities, yielding substantially curtailed glucose uptake. According to a longitudinal population-based investigation, the incidence of insulin resistance correlates adversely with escalating cognitive deterioration throughout the aging journey[72]. Yarchoan *et al.* uncovered analogous outcomes after analyzing postmortem brain samples sourced from geriatric subjects, wherein elevated levels of serine 312 phosphorylated insulin receptor substrate 1 (IRS-1) were noted, suggesting enhanced insulin resistance[74]. This was paralleled by reduced neuronal glucose assimilation capacities. Over and above external determinants (e.g., hormonal imbalance), internally driven elements, specifically dysregulated glucose ingress attributable to lost GLUT3 transporters, encumber optimal neuronal metabolic efficiency as years accrue[75]. Thus, during aging, declines in both extrinsic (endocrine irregularities) and intrinsic components (neuronal nutrient absorption) potentiate diminished neuronal glucose metabolic efficiencies.

On the other hand, neuronal energy provision primarily relies on mitochondrial oxidative phosphorylation, underscoring the pivotal role of mitochondria in maintaining neuronal energy balance. Mitochondria are distributed throughout both axons and dendrites, serving to generate ATP for sustaining electrochemical neurotransmission, cellular upkeep, and repair processes, crucially supporting the heightened energy demands of axonal activity[76,77]. Nonetheless, aging renders axons particularly vulnerable to its effects, affecting energy metabolism through various mechanisms[78]. Firstly, with aging, there are discernible changes in both the quantity and morphology of mitochondria within axons. Vagnoni *et al.* observed a significant decrease in mitochondrial transport within the axons of fruit fly wing neurons during aging[73]. In advanced mice, the volume and length of individual mitochondria within the axons of the optic nerve notably increase[79]. Secondly, aging contributes to heightened hyperexcitability in cortical networks, consequently escalating the energy requirements for axonal propagation of action potentials and synaptic neurotransmitter release[80,81]. Furthermore, it is imperative to recognize that the elongation of axons reduces energy availability at their distal ends, a factor of significance in long-distance projections like the nigrostriatal pathway, implicated in PD.

Bioenergetic shifts of glial cells in aging brain

As previously discussed, the maintenance of normal neuronal activity relies on the efficient metabolic coordination between neurons and glial cells, with particular emphasis on the metabolic support provided by astrocytes. However, recent research indicates that aging is associated with a decline in glycolysis and an augmentation of mitochondrial oxidative metabolism in astrocytes[82,83]. Utilizing magnetic resonance spectroscopy to investigate mitochondrial metabolism in both neurons and astrocytes, a recent study revealed that, compared to younger individuals, the elderly population demonstrates diminished neuronal mitochondrial metabolism but heightened astrocytic mitochondrial metabolism within the brain[84]. The age-related metabolic transition observed in astrocytes could potentially jeopardize lactate production, consequently restricting the fuel supply available for neuronal OXPHOS. It is noteworthy that alterations in the intrinsic state of astrocytes, characterized by their transition into reactive astrocytes, induce changes in their energy metabolism profile[85]. In studies conducted on rodent models, researchers isolated primary cortical astrocytes from rats aged 7, 13, and 18 months. They observed age-associated shifts in the metabolic pathways of these cells, transitioning from glycolysis to mitochondrial oxidative phosphorylation, accompanied by elevated levels of reactive astrocytes [Figure 2][86]. These results suggest that the increased mitochondrial oxidative phosphorylation may promote a functional shift in astrocytes from a neuro-supportive state to a neurotoxic state. However, recent research has presented contrasting findings. McNair *et al.*, employing stable isotope tracing *in vitro*, observed a significant reduction in astrocytic TCA cycle activity and oxidative phosphorylation metabolism in hippocampal slices of aged mice. Conversely, glycolytic activity and glutamate uptake exhibited a notable increase[87]. These findings suggest a hypothesis that aging could potentially impact the metabolic energy pathways of distinct subpopulations of astrocytes differently across various brain regions[88].

Among all brain cells, astrocytes serve as the primary sites for FA oxidation, and with brain aging, there is an observed increase in the utilization rate of free FAs[40]. Research by Boisvert *et al.* revealed a significant reduction in the expression of cholesterol synthesis genes in astrocytes of aged mouse brains compared to adult mice, indicating a shift in lipid metabolism in these cells[39]. Subsequent studies have demonstrated that during aging, astrocytes not only experience a decline in glycolytic capacity, impeding the effective provision of necessary energy substrates for neurons, but also exhibit an increase in FA oxidation, resulting in the production of acetyl-CoA, thereby further modulating mitochondrial metabolic functions[83]. This mechanism may contribute to the transition of astrocyte function from a resting to a reactive state.

Age-dependent metabolic reprogramming also affects microglial cells. Research by Mela *et al.* revealed that in the brains of elderly animals, microglial cells exhibit significantly elevated glycolysis levels and adopt a proinflammatory phenotype[89]. This underscores that the glucose metabolism activity of microglial cells is not only influenced by intrinsic changes but also undergoes metabolic reprogramming with advancing age. Evidently, the regulatory mechanism involving proinflammatory prostaglandin E2 (PGE2) signaling stands out as a potential candidate controlling the age-associated shift in microglial energy metabolism. Mechanistically, engagement between PGE2 and its cognate EP2 receptor prompts glucose routing into glycogen reserves, leading to activation of the protein kinase B (AKT)-glycogen synthase kinase 3 beta (GSK3β)-glycogen synthase 1 (GYS1) cascade; this eventuality suppresses incoming glucose fluxes destined for mitochondrial OXPHOS, thereby indirectly reducing ATP yields. Quite remarkably, amplified PGE2 signaling triggers direct reconfiguration of aged microglia, shifting them away from customary anti-inflammatory tendencies toward embracing a decidedly proinflammatory phenotype instead[90].

Furthermore, in addition to glucose metabolism, aging also impacts the lipid metabolism of microglial cells. Recent investigations have identified a notable increase in apolipoprotein E (APOE) mRNA expression within isolated microglial cells from aged mice[91,92]. Dysregulation of APOE has been linked to the formation of lipid droplets. Victor *et al.* demonstrated that microglial cells derived from induced pluripotent stem cells of individuals carrying APOE risk variants display abundant lipid droplets (LD)[93]. Transcriptomic analysis of lipid droplet-associated microglia unveiled severely compromised phagocytic activity in microglial cells, accompanied by heightened production of ROS and inflammatory cytokines, exhibiting characteristics partially mirroring those of lipopolysaccharide-treated mouse microglia[94]. Recent studies have also demonstrated that lipid-laden microglia in the aged brain exhibit exacerbated innate immune responses to stroke[95]. However, further investigation is required to elucidate the crosstalk between altered lipid metabolism and shifts in energy production patterns in aged microglia.

DYSREGULATED GLIAL ENERGY METABOLISM IN PD

PD represents the second most common neurodegenerative disorder worldwide, characterized by the selective loss of dopaminergic (DA) neurons in the midbrain. Despite extensive associations drawn between PD-linked DA neuronal death and α-synuclein, along with several influential factors, the precise molecular machinery of such lethal neurodegeneration remains elusive. Unquestionably, given the exceedingly high energy demands imposed upon the nigrostriatal system, it seems plausible that aging-associated energy failures might critically contribute to PD-associated neurotoxicity. Indubitably, numerous lines of evidence point convincingly toward pervasive bioenergetic defects embedded within the PD pathophysiology.

Dysfunctions of energy metabolism in dopaminergic neurons

Advanced age serves as a recognized risk factor for developing PD. Even in the absence of PD, the aging brain experiences gradual depletion of DA neurons located in the substantia nigra zona compacta (SNc), reaching approximately 30%-40%[96]. However, once afflicted with PD, the extent of DA neuronal loss in the

SNc often surpasses 80%[97]. Morphologically speaking, residual healthy DA neurons display signs of hypertrophy during typical aging, whereas those affected by PD demonstrate marked atrophy[98]. Further exploration conducted by researchers such as Elstner *et al.* aimed to distinguish any discrepancies in gene expression changes exhibited by dopaminergic neurons between aging and PD cases. Utilizing laser capture microdissection, they extracted DA neurons from the SNc of PD patients and non-PD controls, followed by comparative expression profiling and subsequent pathway analyses. Findings indicated that PD-impacted DA neurons expressed genes strongly associated with mitochondrial dysfunction and profound energy metabolic distress[99]. Additional parallel observations made by Keeney *et al.* highlighted comparable perturbations in the SNc of PD brains, whereby impairment of electron transport chain (ETC) Complex I activity resulted in overwhelmingly increased production of ROS[100] and severe hindrances to proper ATP synthesis[101,102]. Collectively, these discoveries highlight the striking correlation existing between DA neuronal mortality in the SNc and underlying metabolic disturbances.

The higher energy demands of DA neurons can be attributed to their unique physiological characteristics[103]. Recent perspectives suggest that the activation of SNc DA neurons relies on a specific type of L-type voltage-gated calcium ion channel, facilitating calcium ion efflux that is ATP-dependent[104]. Moreover, SNc DA neuron axons are relatively large, primarily relying on oxidative phosphorylation for energy supply, resulting in higher levels of ROS at their axon terminals[103]. Additionally, SNc DA neurons exhibit another two distinct properties, which make them more vulnerable to bioenergetic dysregulation than other neurons: (1) Dopamine can produce the derivative tetrahydroisoquinoline (TIQ), which, in combination with methylglyoxal - a significant byproduct of glucose metabolism - forms 1-acetyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (ADTIQ), contributing to the degeneration of DA neurons[105]; (2) They contain elevated levels of iron, which can exacerbate oxidative stress, triggering the conversion of α-synuclein from an α-helix to a β-sheet conformation. This transformation promotes α-synuclein aggregation, thereby increasing the pathological risk of PD[106]. Growing evidence suggests that metabolic abnormalities in PD may contribute to disease progression by promoting α-synuclein aggregation. Hyperglycemia has been shown to influence the aggregation of α-synuclein, potentially impairing neuronal glycolytic capacity[107]. Metabolic dysfunctions in PD patients involve not only impaired glucose metabolism but also abnormalities in lipid metabolism. Altered lipid metabolism is closely associated with α-synuclein as well. For instance, oleic acid can induce the formation of α-synuclein aggregates in human neuronal cells[108]. A recent study identified a class of lipid molecules, specifically lysophosphatidylcholine (LPC), that selectively recognize and stabilize the monomeric form of α-synuclein. This research highlights LPC's critical role in maintaining the natural conformation of α-synuclein and preventing its pathological aggregation, thus linking lipid metabolism disturbances to α-synuclein pathology in PD[109].

Although research evidence from patient studies suggests a close association between disrupted energy metabolism and PD, it remains uncertain whether bioenergetic dysfunction precedes or results from neuronal degeneration. Data from PD animal models may shed light on this inquiry. We summarized metabolic disruptions observed in several chemically induced and genetically engineered models in Table 2[110-120]. Intriguingly, whether a Parkinson-like phenotype is induced by neurotoxic compounds or genetic factors, mitochondrial dysfunction emerges as a crucial pathogenic mechanism[110,111]. The escalation in ROS closely correlates with metabolic shifts from mitochondrial OXPHOS to glycolysis. Perhaps, under the compounded stress of disease and aging, prolonged oxidative stress in the brain leads to irreversible mitochondrial damage, hindering compensatory glycolysis increases. Whether preserving or restoring mitochondrial function in neurons emerges as a prospective PD treatment strategy, awaiting further validation.

Table 2. The energy metabolism alternations in different PD models

PD model	Gene/compound	Metabolic change	Ref.
Chemical models	MPP^+	Mitochondrial respiration↓ Glycolysis↑	[110]
	Rotenone	Pentose phosphate pathway↑ Glycolysis↓ Mitochondrial respiration↓	[112]
	6-OHDA	Glycolysis↑	[113,114]
	Paraquat	Pentose phosphate pathway↑ Glycolysis↓ Mitochondrial respiration↓	[114]
Genetic models	α-Synuclein	Lipid metabolism alteration Mitochondrial respiration↓	[111,115,116]
	Parkin; DJ-1; LRRK2; PINK1	Glycolysis↑ Mitochondrial respiration↓	[117-120]

PD: Parkinson's disease; MPP^+: 1-methyl-4-phenylpyridinium; 6-OHDA: 6-hydroxydopamine.

Bioenergetic disruptions of glial cells in PD brain

Investigations centered on both patient populations and relevant genomic animal models reveal that many PD-linked mutated genes indeed find expression within astrocytes, influencing their energy metabolic landscapes accordingly[32]. Table 3 provides a condensed overview detailing the range of astrocytic energy metabolic traits germane to familiar PD pathogenic gene variants[121-127]. Remarkably, divergent pathogenic genes exhibit varying degrees of disruption to astrocytic energy homeostasis, with mutant α-synuclein playing a significant role in bioenergetic deregulation. Once internalized by astrocytes, mutant α-synuclein impairs lipid catabolism by reducing the metabolic turnover rates of arachidonic acid and palmitic acid, thereby skewing cellular energy balance[128,129]. Furthermore, α-synuclein intervention can impede the proper localization of aquaporin-4, undermining efficient glutamate uptake and leading to abnormal glutamate metabolism[124].

Recent research conducted by Sonninen *et al.* has revealed that in PD, alterations in astrocytic metabolism primarily stem from changes in mitochondrial function[127]. Utilizing induced pluripotent stem cells (iPSCs) derived from PD patients and subsequent differentiation into astrocytes, they observed notable shifts. Specifically, both maximal and spare respiratory capacities of astrocytes were significantly diminished, accompanied by a marked attenuation in glycolysis. Additionally, analysis of mitochondrial DNA (mtDNA) indicated lower levels in astrocytes from PD patients. These findings were corroborated by Russ *et al.*, who exposed human astrocytes to α-synuclein fibers, demonstrating a significant reduction in mitochondrial respiration within astrocytes[130]. Under conditions of aging, there is a decrease in glycolysis and an increase in oxidative phosphorylation within astrocytes. Conversely, in PD, both glycolysis and oxidative phosphorylation significantly decrease due to mitochondrial damage and reduced glucose uptake. Consequently, we propose a hypothesis: under normal circumstances, astrocytes predominantly rely on glycolysis for energy production, but as the organism ages and encounters heightened inflammation and oxidative stress, they transition toward mitochondrial oxidative phosphorylation to meet energy demands. This metabolic shift serves multiple purposes, including sustaining astrocytic energy requirements, facilitating the conversion of toxic substances like excitatory glutamate, and bolstering antioxidant capacity such as glutathione synthesis. However, in PD, dysfunctional mitochondrial metabolism in astrocytes compromises energy support, antioxidant function, and detoxification processes. Therefore, disruptions in mitochondrial metabolism may act as a pivotal "switch" in the metabolic reprogramming of astrocytes in PD. It is noteworthy that there are two subtypes of astrocytes in the substantia nigra pars compacta, namely protoplasmic astrocytes and fibrous astrocytes. However, studies suggest that only protoplasmic astrocytes contribute to the accumulation of mutated α-synuclein[131].

Table 3. The energy metabolism characteristics of astrocytes associated with various PD mutations

Mutated genes	Characteristics of metabolic perturbations	Ref.
PARK7	Glutamate uptake↓ Lipid raft assembly↓ Mitochondrial function↓	[121,122]
SNCA	Glutamate uptake↓ TAG↑ Lipid raft assembly↓	[123,124]
PINK1	ATP production↓ Oxygen consumption↓ ROS↑ Lipid raft assembly↓	[125]
PARK2	Glycolysis↓ Lipid raft assembly↓	[126]
LRRK2	Glycolysis↓ OXPHOS↓ Lipid raft assembly↓	[127]

PD: Parkinson's disease; TAG: triacylglycerol; ATP: adenosine triphosphate; ROS: reactive oxygen species; OXPHOS: glycolysis and oxidative phosphorylation.

The energy metabolic reprogramming in the PD brain not only contributes to the demise of DA neurons but may also play a role in the emergence of non-motor symptoms. Our recent research indicates that there is a repression in mitochondrial transcription and function in cortical astrocytes of PD brain, coinciding with the activation of the hypoxia-inducible factor (HIF) pathway. This disruption in energy production within cortical astrocytes could worsen the dysfunction of the neuronal network responsible for mood regulation, potentially triggering the onset of depression associated with PD[132]. Previous studies have often focused on the switch from glycolysis to OXPHOS in disease-related astrocytes. However, our results underscore the importance of mitochondrial energy production and its role in regulating key gene expressions. Interestingly, our study also reveals distinct response patterns of cortical astrocytes to PD-associated neurodegeneration compared to midbrain astrocytes, potentially due to differences in energy metabolic signaling. Although the underlying mechanisms require further investigation, our findings emphasize the importance of studying the region-specific bioenergetics of astrocytes in PD and other neurodegenerative diseases[132].

The molecular regulators of metabolic reprogramming, which are crucial for developing novel therapeutic strategies, however, remain largely unknown. One of the key regulatory pathways is the WNT/β-catenin signaling pathway, implicated in many neurodegenerative diseases[133]. Vallée *et al.* investigated the thermodynamic implications of metabolic reprogramming in PD, discovering a downregulation of WNT/β-catenin signaling and its involvement in the brain hypometabolism observed in PD patients. They propose that in PD, the thermodynamic behavior of metabolic enzymes is altered due to dysregulation of the WNT/β-catenin pathway. For example, downregulation of this pathway leads to the inactivation of glycolytic enzymes such as Glut, pyruvate kinase M2 isoform (PKM2), pyruvate dehydrogenase kinase 1 (PDK1), and monocarboxylate transporter 1 (MCT-1), resulting in decreased metabolism, oxidative stress, and cell death[134]. Furthermore, it has been reported that the crosstalk between midbrain DA neurons and astrocytes is regulated by the Frizzled-1/β-catenin signaling pathway, modulated by WNT1[135]. However, the precise role of the WNT/β-catenin signaling pathway in glial metabolic reprogramming remains under investigation. Additionally, the involvement of other signaling pathways in the metabolic dysregulation observed in neurodegenerative diseases is still being explored.

The excessive activation of microglial cells plays a pivotal role in the progression of PD. Activated microglial cells are previously categorized into M1 and M2 phenotypes. These phenotypes exhibit distinct metabolic patterns in response to various environmental stimuli, enabling them to fulfill their respective functions[136]. In the PD brain, microglia are activated by several factors, including damage-associated molecular patterns (DAMPs) released by dying neurons, proinflammatory factors from astrocytes, and extracellular α-synuclein oligomers[137]. These stimuli promote the activation of M1 microglial cells, triggering neuroinflammation and leading to the loss of dopaminergic neurons[138]. In a recent study, Lavisse *et al.* directly observed activated microglial cells and elevated levels of proinflammatory factors in the brains of PD patients using [^{18}F]-DPA714 TSPO positron emission tomography (PET) imaging[139]. The primary inquiry revolves around delineating the alterations in energy metabolism within microglial cells in PD. The bulk of evidence addressing this question stems from studies conducted on animal or cell-culture models of PD. Researchers have identified metabolic reprogramming in microglial cells of 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice, characterized by a transition from oxidative phosphorylation to aerobic glycolysis, accompanied by an upsurge in proinflammatory responses[140]. Additionally, both *in vivo* and *in vitro* PD models have demonstrated heightened activity of glucose-6-phosphate dehydrogenase within the pentose phosphate pathway, leading to the accumulation of ROS and subsequent neuronal damage[141].

The metabolic reprogramming of microglial cells entails intricate modulation involving multiple signaling pathways and cytokines. Firstly, *in vitro* experiments have revealed a significant elevation in the mRNA levels of PKM2, glyceraldehyde 3-phosphate dehydrogenase (GAPDH), and GLUT1, alongside increased lactate production, following α-synuclein treatment of microglial cells[142]. This highlights that there are changes in the glucose metabolism of activated microglial cells. Secondly, upon activation of microglial cells, hypoxia-inducible factor 1 alpha (HIF-1α) stimulates the targets of rapamycin (mTOR), leading to the upregulation of glycolytic enzymes[143,144]. Previous studies have also found that in a mouse model of PD, microglia induce metabolic reshaping (transition from oxidative phosphorylation to aerobic glycolysis) through the mTOR/HIF-1α pathway, thereby exacerbating the pathophysiological phenotype of PD[145]. Consequently, the mTOR/HIF-1α pathway emerges as a promising targeted regulatory axis for modulating these metabolic alterations. Notably, the mTOR signaling pathway exerts a multifaceted regulatory role encompassing glucose, lipid, and other metabolic pathways, thereby influencing mitochondrial function and dynamics[146]. This suggests that metabolic reprogramming of microglial cells in the context of PD may involve multiple metabolic processes.

In addition to glucose metabolism, there is a growing focus on changes in the lipid metabolism of microglia in PD. Researchers have observed lipid accumulation in microglial cells in both animal models and PD patients, which, along with microglial cell damage, contributes to neuroinflammation and disruptions in neural circuits[147]. This suggests a potential pathogenic mechanism of microglial cells in PD progression. However, understanding of the mechanisms underlying microglial cell lipid metabolism and PD progression remains limited. Hence, further research is necessary to elucidate the metabolic characteristics of microglial cells in PD, facilitating more effective treatment and prevention strategies.

Metabolic analysis of human tissues and biological fluids reveals the complex interactions among individual genetics, proteins, and environmental factors[3]. We are optimistic about using metabolite analysis to monitor PD progression. Specifically, lipid metabolism-related products may serve as biomarkers for diagnosing PD. Current research indicates that α-synuclein is linked to FA uptake, cholesterol metabolism, and phospholipid activity. Recent population cohort studies have investigated lipid metabolism patterns in PD patients. For example, Choe *et al.* performed lipid profiling in 294 PD patients and 588 healthy

individuals, finding that PD patients had lower levels of high-density lipoprotein cholesterol but higher levels of lipoprotein A compared to controls[148]. Additionally, Dahabiyeh *et al.* discovered that PD patients had higher serum levels of saturated lysophosphatidylcholine, unsaturated triglycerides, and hydroxyeicosatetraenoic acid, while levels of neuroamide, sphingomyelin, and phosphatidylserine were lower[149]. These findings suggest that lipid imbalances and dysfunctions in lipid pathways are significant biomarkers for PD diagnosis.

CONCLUSION

In conclusion, the accumulating evidence highlights the importance of dysregulated energy metabolism in glial cells in relation to aging and neurodegeneration. Nonetheless, substantial strides are necessary to devise novel therapeutic approaches for neurodegenerative ailments, including PD, through the manipulation of glial bioenergetics. Numerous pivotal inquiries remain unresolved and await comprehensive elucidation. Firstly, initial investigations on elderly individuals and patients primarily focus on observing correlations rather than establishing causation. Unraveling the metabolic alterations that either result from or lead to neuronal death poses a significant challenge. The substantial disparities between rodent models and human physiology limit the ability of animal studies to comprehensively address this issue. Innovative imaging techniques that integrate PET, computed tomography (CT), and magnetic resonance imaging (MRI) show promise in potentially unlocking insights into this complex problem. Secondly, the intricate molecular mechanisms governing the transition between different metabolic patterns in glial cells remain largely elusive. While the HIF-1α is a recognized key regulator, it fails to account for all observations, particularly the shift from glycolysis to mitochondrial oxidative phosphorylation in reactive astrocytes. Unraveling the regulatory network that underlies energy metabolic reprogramming is crucial for identifying novel druggable targets. Last but not least, the investigation into the interplay among diverse metabolic pathways in disease-associated glial cells is imperative, given that many patients with neurodegenerative disorders also present with metabolic dysregulations like hyperlipidemia and hyperglycemia. Ideally, a comprehensive patient management approach for neurodegenerative diseases should be devised to address metabolic disorders while safeguarding vulnerable neurons.

DECLARATIONS

Authors' contributions

Literature search, writing, and original draft preparation: Chu B, Xiang H, Wang H, Lin Y, Li R
Conceptualization, review, revision, and editing: Qian H, Hu J

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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