[1]Yi Xue An

Circular RNA Regulation of CNS Neuroinflammatory Mechanisms

Journal of Electrical Systems

Abstract: - Circular RNA (circRNA) involve in the regulation of gene expression and functions as non-coding RNA molecules produced from back-splicing process which form circular structures. the main types of circRNAs include ciRNA, EciRNA, ecircRNA, tricRNA, of which the ecircRNA is more prevalent and mainly distributed in the cytoplasm. CircRNAs have several biogenesis methods including lariat circularization, RBP dependent circularization, and intron pairing circularization. In the context of CNS, circRNA expression profiles are reported tissue type-dependent and developmental stage-specific. These patterns are highly associated with the development of neurons, changes in synapses as well as the aging of neurons. In the neurodegenerative diseases which include Alzheimer's disease (AD), Parkinson's disease (PD), and acute ischemic stroke (AIS), circRNAs act important functions. These they mostly act through binding and storing of miRNAs, and modulation of immune activities and protein actions during neuroinflammation. These diseases therefore hold circRNA deregulation as a promising biomarker in NDDs and novel therapeutic targets. RNA interference, CRISPR-Cas9, exosome or nanoparticle delivery are some of the approaches developed in current research to regulate circRNA with the purpose of alleviating symptoms of central nervous system diseases.

Keywords: CircRNA, Neuroinflammation, Central Nervous System

INTRODUCTION

Circular RNAs (circRNAs) are newly identified non-coding RNA molecules attracting more attention in biological and medical fields. Because of their circular structure, they have a specific ability that allows them to stay stable and resistant to nucleases compared to linear RNA inside cells; hence, they have a longer half-life. Due to this characteristic, circRNAs can be considered as biomarkers for diseases and new targets for the treatment of diseases. CircRNAs modulate the expression of the encoded genes by ceRNA, interact with microRNAs, and have functional activities in aiding transcription, encoding proteins, and signal transduction. For instance, the number of cell types in the CNS can distinguish particularly and specifically expressed circRNAs by the tissue and development phases. These patterns suggest that they play critical part in the control of neurogenesis, neuronal plasticity, and neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease. As technology progresses further, the numerous regulatory circuits of circRNAs year by year are gradually revealed, which helps researchers obtain a new vision on the upper level of gene regulation and show promise for the early diagnosis or targeted treatment of diseases.

BIOGENESIS AND FUNCTIONS OF CIRCRNA

CircRNAs are a specific category of noncoding RNA produced by back-splicing, which is a method of RNA

[1]College of Life Sciences of Shanghai University Shanghai 200000, Shnaghai, China.Email:13565182606@shu.edu.cn

splicing. This is obtained when the 5' splice donor site of a downstream exon is ligated with the 3' splice acceptor site of an upstream exon to form a circular structure made out of exons belonging to different mRNA molecules. Structurally, circRNAs can be classified into three main types: , there are exonic circRNAs (ecircRNAs), circular intronic RNAs (ciRNAs), and exon-intron circRNAs (EIciRNAs). More than 88% of circRNAs are ecircRNAs which are mainly present in the cytoplasm of the cell while the rest includes the EIciRNAs and ciRNAs that are localized in the nucleus. Moreover, not only the naturally existing circRNAs which are found in all eukaryotic cells, but exogenous circRNAs that are artificially produced can also be stably and efficiently expressed and translated in eukaryotic cells [1].

The process of circularization of circRNAs is mainly categorized into intron circularization and exon circularization. Generally, three biological mechanisms lead to back-splicing: The first one is circular lariat-driven circularization or exon skipping, the second one is RNA-binding protein – mediated circularization and the third one is intronic pairing-mediated circularization. In circular lariat-driven circularization, exon skipping forms circular RNA structures with a 'lariat' created by the skipped exons and internal lariat cleavage to form circRNAs. Several RBPs have been identified to interact with intronic sequences surrounding the exons, namely - quaking (QKI), muscleblind (MBL /MBNL1), and fused-in-sarcoma(FUS) and these help in circRNA synthesis [2]. There are different classifications of RBPs concerning their structure and concerning the molecules they bind. For instance, there are some conserved proteins comprising one or multiple dsRBPs that can bind dsRNA, which play an important role in the recognition and binding of complementary RNA sequences within introns to facilitate intron pairing, hence circRNA. Certain RNA-binding proteins which lack the dsRBDs can bind to certain RNA sequences that are recognised to be situated in the flanking introns. These interactions are referred to as playing roles in regulation of circRNA formation. Intronic pairing driven circularization can be done by using complementary base pairing of the repetitive sequence in the adjacent introns. This pairing mechanism helps to arrange 5' splice donor site and 3 splice acceptor site of a downstream exon and upstream exon respectively in the same plane. Therefore, exon sequences are retained in the circular molecule through back-splicing, which is essential for the generation of circRNAs [3].

Current studies reveal that the accumulation and existence of circRNAs in some diseases pointed out that they are potential biomarkers for such diseases. Also, circRNAs play a role in the regulation of gene expression at epigenetic levels in both physiological and pathological conditions. They act as sponges, which implies that these genes bind on the miRNAs and prevent them from binding on another gene. This interferences affected the manner in which miRNAs control the amount of their target gene [4]. Furthermore, in the nucleus, circRNAs may influence several physiological processes of parent genes, such as transcription and translation, as they can bind their linear mRNAs. They also affect RNA polymerase binding and even influences the status of transcription factors and the chromatin conformation change which in turn affects gene expression [5]. In addition to the control of gene transcription, circRNAs participate in protein transportation and localization in cells, participate in translocation processes between the cytoplasm and nuclear compartments, and act as the framework for protein-protein interaction [3]. those circRNAs are involved in the regulation of intracellular signaling and regulatory networks as they interact with different proteins and facilitate the formation and stabilization of the identified protein complexes [6].

CIRCRNA IN THE CENTRAL NERVOUS SYSTEM

Studies have shown that circRNAs are abundantly present in the brains of mice, fruit flies, and humans. During the development of the central nervous system (CNS), circRNAs display patterns of expression that are specific to particular tissues and stages of development. Certain regions of the brain, such as the olfactory bulb, frontal lobe, cortex, hippocampus, and cerebellum, exhibit distinct sets of highly expressed circRNAs compared to other tissues. CircRNAs are upregulated during neurogenesis, but they are not uniformly distributed in all neuronal compartments; instead, they are highly enriched in synaptic neuronal bodies [7]. In addition to tissue-specific expression, the developmental stage-specific expression profile of circRNAs indicates their significant regulatory functions in CNS development and differentiation. Due to the high synaptic density in the human cortex, circRNAs are most highly expressed during periods of synaptic plasticity and exhibit differential expression during the maturation and differentiation of primary neurons. Analysis of circRNA sequencing data during mouse brain development from embryos to postnatal stages reveals significant upregulation during mouse brain maturation, particularly during postnatal developmental stages. Furthermore, researchers have found that in the cortex of mice of different ages, 50% of circRNAs significantly increase between 1 to 6 months, with all detected circRNAs showing a significant increase between 6 to 22 months [8]. In a study using a D-galactose-induced astrocyte aging model, 319 circRNAs were upregulated and 643 circRNAs were downregulated, with some circRNAs increasing with aging [9]. These studies indicate that circRNAs are critical potential regulatory factors in the CNS, accumulating in a tissue-specific, developmental stage-specific, and age-dependent manner, thereby influencing neuronal development and aging processes in CNS-related diseases.

CIRCRNA REGULATION OF NEUROINFLAMMATION IN THE CENTRAL NERVOUS SYSTEM

Neurological disorders like Alzheimer's disease, Parkinson’s disease, and ischemic stroke are often characterized by nerve damage and neuroinflammation, posing significant challenges for diagnosis, treatment, and prognosis. In a healthy brain, neuroinflammation serves as a critical immune response that, under normal conditions, contributes to tissue repair and neuroprotection within the central nervous system (CNS). The inflammatory processes primarily involve several mechanisms: (1) an imbalance between pro-inflammatory and anti-inflammatory actions of microglia and astrocytes; (2) activation of the NLRP3 inflammasome; (3) release of inflammatory molecules such as IL-1, TNF-α, and IL-6; and (4) oxidative stress due to mitochondrial dysfunction, leading to the overproduction of reactive oxygen species (ROS). Among these mechanisms, microglia is implicated as main contributor to CNS inflammation and exert neuronal toxicity by releasing ROS, NO, along with cytokines IL-6 and TNF-α [10]. Also, microglia, astrocytes, and oligodendrocytes modulate the activation of infiltrating immune cells, including T cells, monocytes, and macrophages, in innate and adaptive immune response during neuroinflammation in neurodegenerative diseases [11]. In addition to the CNS neurodevelopment roles, the other body processes and cellular functions affected by circRNAs include innate immune response, adaptive immune response, inflammation and anti Inflammatory response in diseases associated with CNS.

A. Alzheimer’s disease (AD)

Alzheimer's disease (AD) is the most common neurodegenerative disease. Over 10% of people aged 65 and older, and 30% of those aged 85 and older, are affected by AD. AD is characterized by progressive deterioration of memory and cognitive functions, with its prevalence increasing continuously with age. It has been reported that aging is associated with increased mild chronic inflammation, which may contribute to the neurodegenerative process of AD. Researchers have found significant changes in inflammatory markers in the blood and cerebrospinal fluid of AD patients, indicating a neuroinflammatory response within the central nervous system during the pathological process [12]. A study identified 164 AD-related differential circRNAs in the cortical circRNA expression profile of AD patients' brains, suggesting that these differential circRNAs may play important roles in regulating AD neuroinflammatory responses [13]. Current research mechanisms regarding circRNAs mainly involve their role as miRNA sponges. For instance, upregulation of circ_0005835 in AD patients and cell models can be attenuated by knocking down circ_0005835, which improves neuroinflammation in BV2 cells through miR-576-3p sponging, thereby delaying AD progression. Researchers have identified several circRNAs implicated in Alzheimer's disease (AD) progression. circ_0000950, by acting as a sponge for miR-103, promotes neuronal apoptosis, inhibits neurite outgrowth, and increases levels of inflammatory cytokines [14]. Another circRNA, circHDAC9, functions as a miR-142-5p sponge to mitigate Aβ42-induced neurotoxicity and neuroinflammation in human neuronal cells. CircLPAR1 contributes to cell apoptosis, inflammation, and oxidative stress induced by Aβ42 through the miR-212-3p/ZNF217 axis. Moreover, knocking down circ-HUWE1 activates the WNT signaling pathway in SK-N-SH cells processing amyloid-β, thus mitigating cell apoptosis and inflammation via the miR-433-3p/FGF7 axis [15]. Knocking down circ_0004381 promotes M2 polarization of microglia by sponging miR-647/PSEN1, suppressing inflammatory cytokine production to improve AD cognitive function. In addition to acting as miRNA sponges, circRNAs can also bind to proteins. For example, circNF1-419 significantly upregulates during astrocyte aging, enhancing autophagy by binding Dynamin-1 and AP2B1 to regulate TNF-α and NF-κB expression levels, thereby slowing AD progression [16]. CircRNAs also regulate the distribution of proteins between the nucleus and cytoplasm, such as ciRS-7 inhibiting NF-κB protein synthesis and promoting NF-κB translocation from the nucleus to the cytoplasm to reduce Aβ levels and delay AD [17]. Recent studies have identified numerous circRNAs significantly associated with AD, such as circAPP, circPSEN1, and circMAPK9, which may be critical targets in regulating neuroinflammation in the central nervous system during AD pathogenesis [18]. The neuroinflammatory processes of Alzheimer's disease are closely related to abnormal circRNA expression. These circRNAs play important roles in disease progression through their roles as miRNA sponges, regulation of protein functions, and interactions with inflammatory pathways. Intervention strategies targeting specific circRNAs show potential in regulating neuroinflammation and slowing cognitive decline, providing new directions and possibilities for Alzheimer's disease treatment.

B. Parkinson's disease (PD)

Parkinson's disease (PD) ranks as the second most prevalent neurodegenerative disorder following Alzheimer's disease (AD). It is characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the presence of diffuse α-synuclein (α-syn) protein aggregates. Increasing evidence

indicates that neuroinflammation plays a significant role in both the onset and progression of PD. Studies have demonstrated that heightened levels of pro-inflammatory cytokines (such as TNF, IL-1β, IL-6, and IFN-γ) observed in PD pathology can exacerbate neurodegeneration and contribute to neuronal injury in experimental models of PD [19]. In investigations using MPTP-induced PD mouse models, researchers identified differentially expressed circRNAs in various brain regions including the cortex, hippocampus, striatum, and cerebellum. Specifically, 24 circRNAs were noted in the cortex, 66 in the hippocampus, 71 in the striatum, and 121 in the cerebellum. Each region exhibited distinct circRNA profiles, with mmu_circRNA_0001320 prominently expressed in the cerebellum (CB), while mmu_circRNA_0004144, mmu_circRNA_0000468, and mmu_circRNA_0013321 displayed lower expression levels in the striatum (ST) [20]. In PD, circRNAs are reduced in the substantia nigra and correlate with age-related accumulation, and differential circRNAs may contribute to neuronal damage by modulating PD neuroinflammation. Inflammatory mediators secreted by astrocytes and microglia, such as pro-inflammatory cytokines, reactive oxygen species, and nitric oxide, regulate the progression of neuronal cell death in PD. CircRNAs play important roles in regulating neuroinflammation mediated by PD microglial cell activation. For example, CircHIPK3 promotes BV2 cell secretion of inflammatory factors IL-6, IL-1β, TNF-α, and inflammasome NLRP3 in PD by modulating the miR-124-3p/STAT3/NLRP3 signaling pathway. In addition to inflammation factor secretion by microglial cell activation, mitochondrial dysfunction-induced oxidative stress also promotes inflammatory responses [21]. For example, circDLGAP4 reduces PD cell mitochondrial damage and enhances autophagy through the miR-134-5p/CREB axis, exerting neuroprotective effects. CircSV2b is implicated in reducing oxidative stress-induced damage in Parkinson’s disease (PD) through modulation of the miR-5107-5p-Foxk1-Akt1 signaling pathway. This mechanism helps preserve dopaminergic neurons and sustain striatal function, presenting a promising target for both the diagnosis and treatment of PD. On the other hand, CircSLC8A1 exacerbates PD-related oxidative stress by binding with Ago2 and acting as a sponge for miR128. This interaction influences neuronal survival and aging processes. Additionally, Circ_0004381 promotes apoptosis, inflammatory responses, and oxidative stress in MPP-treated SK-N-SH cells by targeting the miR-185-5p/RAC1 axis, thereby contributing to neuronal damage. These circRNAs highlight diverse roles in PD pathology, suggesting their potential as therapeutic targets. CircEPS15 acts as an MIR24-3p sponge to upregulate PINK1, accelerating mitochondrial autophagy and protecting dopaminergic neurons. Circ_0070441 regulates inflammation-related factor expression levels through the miR-626/IRS2 axis in SH-SY2Y cells, thereby modulating cell apoptosis and inflammation to alleviate MPP-induced neuronal damage. The complex pathological mechanisms of Parkinson's disease involve neuroinflammation, mitochondrial dysfunction, and dynamic regulation of circRNAs. These circRNAs play dual roles in finely regulating gene expression and cellular signaling pathways, contributing both to neuronal damage and protective effects in disease progression. They provide potential molecular targets and new research directions for Parkinson's disease treatment strategies.

C.Acute ischemic stroke (AIS)

Acute ischemic stroke (AIS) is defined by neuroinflammation as the foremost pathological consequence

subsequent to cerebral ischemia. This initiates secondary damage to brain tissue and impedes functional recovery. Following the initial ischemic insult, neuroglial cells undergo activation and release neuroinflammatory mediators. Concurrently, disruption of the blood-brain barrier leads to peripheral immune infiltration, further amplifying the neuroinflammatory response and ultimately resulting in neuronal damage [22]. CircRNA HECTD1 exhibits elevated expression levels in AIS patients and significantly higher levels of inflammatory cytokines in their serum compared to healthy controls. It suppresses astrocyte activation and autophagy in AIS by regulating the miR-142/TIPARP pathway, which is crucial for improving stroke prognosis. In contrast, CircCELF1 recruits the DDX5 factor to enhance NFAT54 expression, promoting astrocyte apoptosis and autophagy, thereby exacerbating neuronal damage. CircHIPK3 interacts with miR-1b-1p and relies on the CDK5R1/SIRT1 pathway to modulate apoptosis and mitochondrial dysfunction in a mouse model of ischemic stroke. Exosomes from hypoxia-preconditioned ADSCs deliver Circ-Rps5 to mitigate brain damage induced by acute ischemic stroke, promoting M2 microglia/macrophage polarization to reduce hippocampal neuronal damage after stroke and improve cognitive function. Circ_0000831 reduces apoptosis and inflammation in microglial cells induced by oxygen-glucose deprivation (OGD) through the miR-16-5p/AdipoR2 axis, thereby alleviating neuroinflammation and neurofunctional disorders in MCAO mice. Circ_0001360 activates the NF-kappa B pathway by targeting the miR-671-5p/BMF network, promoting inflammatory cytokine expression in oxidative stress-induced SK-N-SH cells. Overexpression of CircDLGAP4 regulates the miR-503-3p/NEGR3 axis to inhibit cell death and inflammatory cytokine levels in OGD-treated HCN-2 cells, thus mitigating neuronal damage. Circ-Memo1 expression increases in ischemic stroke patients, and knocking down Circ-Memo1 regulates the miR-17-5p/SOS1 axis to inhibit ERK/NF-κB signaling pathway activation, reducing oxidative stress and inflammatory responses [23]. CircRIMS reduces apoptosis and inflammatory cytokine secretion by regulating the miR-96-5p/JAK/STAT1 axis, thus promoting neuroinflammation. Different circRNAs impact neuroinflammation and neuronal damage in ischemic stroke through various mechanisms, revealing their complex roles in disease progression and providing new potential targets for neuroprotection and treatment strategies.

D.Other central nervous system diseases

There are many types of central nervous system diseases. circRNAs regulate not only common neurodegenerative diseases but also other disorders such as traumatic brain injury (TBI), depression, and multiple sclerosis (MS). In TBI models, circLrp1b upregulates Dram2 expression by acting as a sponge for miR-27a-3p, inhibiting inflammation and autophagy in vivo in TBI [24]. In spinal cord injury, in astrocytes treated with tumor necrosis factor α, knocking down circPrkcsh increases miR-2 expression, reducing Ccl488 expression and decreasing the secretion of inflammatory cytokines in vitro [25]. In a mouse model of depression, downregulating circHIPK2 expression suppresses astrocyte activation significantly by regulating the MIR124-2HG/SIGMAR1 axis, thereby mitigating inflammatory responses and neuronal tissue damage [26]. In MS, circ_0000518 promotes M1 polarization of macrophages/microglia through the FUS/CaMKK beta/AMPK pathway, enhancing infiltration of inflammatory cells in the central nervous system and exacerbating MS progression [27].

E. Targeting circRNA Therapy for Central Nervous System Diseases

Due to their unique circular structure and highly stable nature, as well as their tissue- or cell-type-specific expression patterns, circRNAs have become a focus in research targeting treatments for central nervous system (CNS) diseases characterized by dysregulation. Particularly noteworthy is the significant differential expression of circRNAs in CNS diseases, indicating their potential involvement in disease pathogenesis through specific biological pathways. Their high expression levels in the brain compared to other tissues underscore their critical role in CNS disease development, making circRNAs potential targets for disease diagnosis and treatment. Thus, precise modulation of endogenous circRNA expression levels theoretically offers a strategy to effectively improve neuroinflammation in CNS diseases, providing new avenues for disease management.

Currently, strategies targeting circRNAs for diseases with high or low expression levels mainly include:

1. RNA interference (RNAi) technology involving the design and synthesis of siRNA or shRNA molecules that specifically target and reduce the expression of the corresponding circRNA.

2. Antisense oligonucleotide (ASO)-mediated specific silencing of circRNAs.

3. CRISPR/Cas9-mediated knockdown or knockout of circRNAs.

4. Blocking the binding between circRNAs and miRNAs or RBPs by saturating conserved binding sites on circRNAs.

5. Reintroducing circRNAs that act as sponges for miRNAs or RBPs.

Exogenous circRNA delivery strategies mainly involve exosome delivery and nanoparticle delivery. Exosomes are small extracellular vesicles, usually measuring between 30 to 100 nm in diameter. They are currently under investigation for their potential as carriers for agents that target circRNAs and as vehicles for transporting circRNA expressions. In Alzheimer's disease, exosomes act as inflammatory mediators inducing neuroinflammation through intercellular communication between neurons and neuroglial cells. Exosomes carrying dysregulated circRNAs and other substances can lead to neuronal dysfunction. These exosomes can cross the blood-brain barrier, spreading neuroinflammatory responses peripherally. Similarly, plasma-derived exosomes can enter the brain, targeting neurons and neuroglial cells, triggering a series of pathophysiological responses. Additionally, exosomes can serve as carriers to deliver engineered circRNAs. Using RVG virus-packaged exosomes, circSCMH1 can be selectively delivered to the brain, reducing glial cell activation and peripheral immune cell infiltration post-stroke in mice, thereby improving neuroinflammatory responses. Apart from exosome delivery, nanomaterials such as nanoparticles can also be utilized for circRNA delivery [32].

CONCLUSION AND FUTURE PERSPECTIVES

Circular RNAs (circRNAs) are RNA molecules with closed continuous circular structures; they are involved in the regulation of a variety of processes related to CNS diseases, including neuroinflammation. Of them, circRNAs participate in gene expression regulation and protein function modulation through their biogenesis mechanisms, and directly affect neuroinflammation. It plays important functions in diseases like Alzheimer’s

disease, Parkinson's disease, acute ischemic stroke and so on, through immune response regulation and microRNA sponge. In addition, genomic studies have indicated that circRNAs are tissue specific, and map and predictive location in the CNS in developmental stages and for diseased stage they are expressed abnormally and hence they can be consider as promising biomarkers and therapeutic targets [33].

Looking at the future research, it is essential to conduct further in-depth research on the roles of circRNAs and their molecular mechanisms in CNS diseases' neuroinflammation. This regards knowledge on how circRNAs regulate the activation status of microglia and astrocytes, and the leukocyte attraction and roles, in addition to the synthesis and pathways of neuroinflammatory factors. Furthermore, the use of high-throughput sequencing, single-cell sequencing, and computational based bioinformatics method to systematically characterize the dynamic behavior of circRNAs in different CNS disease statuses will also aid in identifying more disease associated circRNAs and possible action targets [33]. Clinical validation of circRNA-based diagnostic markers and therapeutic strategies will be pivotal in translating circRNA research findings into clinical applications. This endeavor holds the potential to provide new therapeutic targets and intervention approaches for CNS diseases, especially refractory neuroinflammatory disorders, thereby improving patient prognosis and enhancing quality of life [34]. In conclusion, circRNAs represent a new frontier in CNS disease research, and their exploration and application exploration hold significant promise for future neuroscience and medical research directions.

REFERENCE

[1] EGER N, SCHOPPE L, SCHUSTER S, et al. Circular RNA Splicing [J]. Adv Exp Med Biol, 2018, 1087: 41-52.

[2] ZANG J, LU D, XU A. The interaction of circRNAs and RNA binding proteins: An important part of circRNA maintenance and function [J]. J Neurosci Res, 2020, 98(1): 87-97.

[3] YANG L, WILUSZ J E, CHEN L L. Biogenesis and Regulatory Roles of Circular RNAs [J]. Annu Rev Cell Dev Biol, 2022, 38: 263-89.

[4] ZHANG L, GAO H, LI X, et al. The important regulatory roles of circRNA-encoded proteins or peptides in cancer pathogenesis (Review) [J]. Int J Oncol, 2024, 64(2).

[5] LI J, SUN D, PU W, et al. Circular RNAs in Cancer: Biogenesis, Function, and Clinical Significance [J]. Trends Cancer, 2020, 6(4): 319-36.

[6] MISIR S, WU N, YANG B B. Specific expression and functions of circular RNAs [J]. Cell Death Differ, 2022, 29(3): 481-91.

[7] LI M L, WANG W, JIN Z B. Circular RNAs in the Central Nervous System [J]. Front Mol Biosci, 2021, 8: 629593.

[8] MA N, ZHANG W, WAN J. Research Progress on circRNA in Nervous System Diseases [J]. Curr Alzheimer Res, 2020, 17(8): 687-97.

[9] XIE L, MAO M, XIONG K, et al. Circular RNAs: A Novel Player in Development and Disease of the Central Nervous System [J]. Front Cell Neurosci, 2017, 11: 354.

[10] QUICK J D, SILVA C, WONG J H, et al. Lysosomal acidification dysfunction in microglia: an emerging pathogenic mechanism of neuroinflammation and neurodegeneration [J]. J Neuroinflammation, 2023, 20(1): 185.

[11] PATANI R, HARDINGHAM G E, LIDDELOW S A. Functional roles of reactive astrocytes in neuroinflammation and neurodegeneration [J]. Nat Rev Neurol, 2023, 19(7): 395-409.

[12] CALSOLARO V, EDISON P. Neuroinflammation in Alzheimer's disease: Current evidence and future directions [J]. Alzheimers Dement, 2016, 12(6): 719-32.

[13] WEN X, HUANG C, XIE H, et al. The Applications of CircRNA in the Diagnosis and Treatment of Alzheimer's Disease [J]. Mol Neurobiol, 2024.

[14] TANG L, WANG Y, XIANG J, et al. lncRNA and circRNA expression profiles in the hippocampus of Aβ(25-35)-induced AD mice treated with Tripterygium glycoside [J]. Exp Ther Med, 2023, 26(3): 426.

[15] SINGH D. Astrocytic and microglial cells as the modulators of neuroinflammation in Alzheimer's disease [J]. J Neuroinflammation, 2022, 19(1): 206.

[16] AKHTER R. Circular RNA and Alzheimer's Disease [J]. Adv Exp Med Biol, 2018, 1087: 239-43.

[17] SINGH M, GURU A, MURUGAN R, et al. Circular RNA ciRS-7 signature as a potential biomarker for the early detection of diabetes with Alzheimer's disease: a hypothesis [J]. Mol Biol Rep, 2023, 50(10): 8705-14.

[18] URDáNOZ-CASADO A, SáNCHEZ-RUIZ DE GORDOA J, ROBLES M, et al. circRNA from APP Gene Changes in Alzheimer's Disease Human Brain [J]. Int J Mol Sci, 2023, 24(5).

[19] ARAúJO B, CARIDADE-SILVA R, SOARES-GUEDES C, et al. Neuroinflammation and Parkinson's Disease-From Neurodegeneration to Therapeutic Opportunities [J]. Cells, 2022, 11(18).

[20] BOUGEA A, STEFANIS L. microRNA and circRNA in Parkinson's Disease and atypical parkinsonian syndromes [J]. Adv Clin Chem, 2023, 115: 83-133.

[21] TITZE-DE-ALMEIDA S S, TITZE-DE-ALMEIDA R. Progress in circRNA-Targeted Therapy in Experimental Parkinson's Disease [J]. Pharmaceutics, 2023, 15(8).

[22] MOROTTI A, POLI L, COSTA P. Acute Stroke [J]. Semin Neurol, 2019, 39(1): 61-72.

[23] XU G, LIU G, WANG Z, et al. Circular RNAs: Promising Treatment Targets and Biomarkers of Ischemic Stroke [J]. Int J Mol Sci, 2023, 25(1).

[24] HUANG C, SUN L, XIAO C, et al. Circular RNA METTL9 contributes to neuroinflammation following traumatic brain injury by complexing with astrocytic SND1 [J]. J Neuroinflammation, 2023, 20(1): 39.

[25] LI X, KANG J, LV H, et al. CircPrkcsh, a circular RNA, contributes to the polarization of microglia towards the M1 phenotype induced by spinal cord injury and acts via the JNK/p38 MAPK pathway [J]. Faseb j, 2021, 35(12): e22014.

[26] ZHANG Y, HUANG R, CHENG M, et al. Gut microbiota from NLRP3-deficient mice ameliorates depressive-like behaviors by regulating astrocyte dysfunction via circHIPK2 [J]. Microbiome, 2019, 7(1): 116.

[27] CIPRIANO G L, SCHEPICI G, MAZZON E, et al. Multiple Sclerosis: Roles of miRNA, lcnRNA, and circRNA and Their Implications in Cellular Pathways [J]. Int J Mol Sci, 2024, 25(4).

[28] GUARNERIO J, ZHANG Y, CHELONI G, et al. Intragenic antagonistic roles of protein and circRNA in tumorigenesis [J]. Cell Res, 2019, 29(8): 628-40.

[29] DONG J, ZENG Z, HUANG Y, et al. Challenges and opportunities for circRNA identification and delivery [J]. Crit Rev Biochem Mol Biol, 2023, 58(1): 19-35.

[30] FAN L, YAO L, LI Z, et al. Exosome-Based Mitochondrial Delivery of circRNA mSCAR Alleviates Sepsis by Orchestrating Macrophage Activation [J]. Adv Sci (Weinh), 2023, 10(14): e2205692.

[31] LI B, XI W, BAI Y, et al. FTO-dependent m(6)A modification of Plpp3 in circSCMH1-regulated vascular repair and functional recovery following stroke [J]. Nat Commun, 2023, 14(1): 489.

[32] LIU G W, GUZMAN E B, MENON N, et al. Lipid Nanoparticles for Nucleic Acid Delivery to Endothelial Cells [J].

Pharm Res, 2023, 40(1): 3-25.

[33] PATOP I L, WüST S, KADENER S. Past, present, and future of circRNAs [J]. Embo j, 2019, 38(16): e100836.

[34] LONG F, LIN Z, LI L, et al. Comprehensive landscape and future perspectives of circular RNAs in colorectal cancer [J]. Mol Cancer, 2021, 20(1): 26.

ABOUT THE AUTHOR

YiXue An was born inXinjiang，Xinjiang. China, in 2002. She currently studying at the School of Life Sciences, Shnghai University. Her main research direction is biomedical engineering.

E-mail: 13565182606@shu.edu.cn