# World Journal of *Stem Cells*

World J Stem Cells 2023 June 26; 15(6): 502-653





Published by Baishideng Publishing Group Inc

W J S C World Journal of Stem Cells

### Contents

### Monthly Volume 15 Number 6 June 26, 2023

### **REVIEW**

- 502 Adipokines regulate mesenchymal stem cell osteogenic differentiation Xu ZH, Xiong CW, Miao KS, Yu ZT, Zhang JJ, Yu CL, Huang Y, Zhou XD
- 514 Advances of nanotechnology applied to cancer stem cells Yue M, Guo T, Nie DY, Zhu YX, Lin M
- 530 Neural lineage differentiation of human pluripotent stem cells: Advances in disease modeling Yan YW, Qian ES, Woodard LE, Bejoy J
- 548 Factors affecting osteogenesis and chondrogenic differentiation of mesenchymal stem cells in osteoarthritis Peng Y, Jiang H, Zuo HD

### **MINIREVIEWS**

- 561 Potential regulatory effects of stem cell exosomes on inflammatory response in ischemic stroke treatment Chen N, Wang YL, Sun HF, Wang ZY, Zhang Q, Fan FY, Ma YC, Liu FX, Zhang YK
- 576 Clinical relevance of stem cells in lung cancer Romeo HE, Barreiro Arcos ML

### **ORIGINAL ARTICLE**

### **Basic Study**

589 Single cell RNA sequencing reveals mesenchymal heterogeneity and critical functions of Cd271 in tooth development

Zhang YY, Li F, Zeng XK, Zou YH, Zhu BB, Ye JJ, Zhang YX, Jin Q, Nie X

- 607 Culture and identification of neonatal rat brain-derived neural stem cells Zhou QZ, Feng XL, Jia XF, Mohd Nor NHB, Harun MHB, Feng DX, Wan Sulaiman WA
- Synergism of calycosin and bone marrow-derived mesenchymal stem cells to combat podocyte apoptosis 617 to alleviate adriamycin-induced focal segmental glomerulosclerosis

Hu QD, Tan RZ, Zou YX, Li JC, Fan JM, Kantawong F, Wang L

### SYSTEMATIC REVIEWS

632 Current overview of induced pluripotent stem cell-based blood-brain barrier-on-a-chip

Alves ADH, Nucci MP, Ennes do Valle NM, Missina JM, Mamani JB, Rego GNA, Dias OFM, Garrigós MM, de Oliveira FA, Gamarra LF



# Contents

Monthly Volume 15 Number 6 June 26, 2023

### **ABOUT COVER**

Editorial Board Member of World Journal of Stem Cells, Luminita Labusca, MD, PhD, Senior Researcher, National Institute of Research and Development in Technical Physics Iasi, 47 D Mangeron Boulevard, Iasi 70050, Romania. drlluminita@yahoo.com

### **AIMS AND SCOPE**

The primary aim of World Journal of Stem Cells (WJSC, World J Stem Cells) is to provide scholars and readers from various fields of stem cells with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJSC publishes articles reporting research results obtained in the field of stem cell biology and regenerative medicine, related to the wide range of stem cells including embryonic stem cells, germline stem cells, tissue-specific stem cells, adult stem cells, mesenchymal stromal cells, induced pluripotent stem cells, embryonal carcinoma stem cells, hemangioblasts, lymphoid progenitor cells, etc.

### **INDEXING/ABSTRACTING**

The WJSC is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, PubMed, PubMed Central, Scopus, Biological Abstracts, BIOSIS Previews, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports cites the 2021 impact factor (IF) for WJSC as 5.247; IF without journal self cites: 5.028; 5-year IF: 4.964; Journal Citation Indicator: 0.56; Ranking: 12 among 29 journals in cell and tissue engineering; Quartile category: Q2; Ranking: 86 among 194 journals in cell biology; and Quartile category: Q2. The WJSC's CiteScore for 2021 is 5.1 and Scopus CiteScore rank 2021: Histology is 17/61; Genetics is 145/335; Genetics (clinical) is 42/86; Molecular Biology is 221/386; Cell Biology is 164/274.

### **RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Xiang-Di Zhang; Production Department Director: Xu Guo; Editorial Office Director: Jia-Ru Fan.

NAME OF JOURNAL	INSTRUCTIONS TO AUTHORS	
World Journal of Stem Cells	https://www.wjgnet.com/bpg/gerinfo/204	
ISSN	GUIDELINES FOR ETHICS DOCUMENTS	
ISSN 1948-0210 (online)	https://www.wjgnet.com/bpg/GerInfo/287	
LAUNCH DATE	GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH	
December 31, 2009	https://www.wjgnet.com/bpg/gerinfo/240	
FREQUENCY	PUBLICATION ETHICS	
Monthly	https://www.wjgnet.com/bpg/GerInfo/288	
EDITORS-IN-CHIEF	PUBLICATION MISCONDUCT	
Shengwen Calvin Li, Carlo Ventura	https://www.wjgnet.com/bpg/gerinfo/208	
EDITORIAL BOARD MEMBERS	ARTICLE PROCESSING CHARGE	
https://www.wjgnet.com/1948-0210/editorialboard.htm	https://www.wjgnet.com/bpg/gerinfo/242	
PUBLICATION DATE	<b>STEPS FOR SUBMITTING MANUSCRIPTS</b>	
June 26, 2023	https://www.wjgnet.com/bpg/GerInfo/239	
COPYRIGHT	ONLINE SUBMISSION	
© 2023 Baishideng Publishing Group Inc	https://www.f6publishing.com	

© 2023 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com



W J S C World Journal of Stem Cells

Submit a Manuscript: https://www.f6publishing.com

World J Stem Cells 2023 June 26; 15(6): 561-575

DOI: 10.4252/wisc.v15.i6.561

ISSN 1948-0210 (online)

MINIREVIEWS

# Potential regulatory effects of stem cell exosomes on inflammatory response in ischemic stroke treatment

Na Chen, Yan-Lin Wang, Hui-Fang Sun, Zhuo-Ya Wang, Qi Zhang, Fei-Yan Fan, Yu-Cheng Ma, Fei-Xiang Liu, Yun-Ke Zhang

Specialty type: Cell and tissue engineering

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

### Peer-review report's scientific quality classification

Grade A (Excellent): 0 Grade B (Very good): B Grade C (Good): C, C Grade D (Fair): 0 Grade E (Poor): 0

P-Reviewer: Chen X, United States; Song BW, South Korea; Liu W, China

Received: January 7, 2023 Peer-review started: January 7, 2023 First decision: April 10, 2023 Revised: April 22, 2023 Accepted: May 16, 2023 Article in press: May 16, 2023 Published online: June 26, 2023



Na Chen, Fei-Yan Fan, Yu-Cheng Ma, First School of Clinical Medicine, Henan University of Chinese Medicine, Zhengzhou 450046, Henan Province, China

Yan-Lin Wang, Hui-Fang Sun, Zhuo-Ya Wang, Qi Zhang, Department of Neurology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China

Fei-Xiang Liu, Yun-Ke Zhang, Department of Neurology, The First Affiliated Hospital of Henan University of Chinese Medicine, Zhengzhou 450000, Henan Province, China

Yun-Ke Zhang, School of Rehabilitation Medicine, Henan University of Chinese Medicine, Zhengzhou 450008, Henan Province, China

Corresponding author: Yun-Ke Zhang, PhD, Doctor, School of Rehabilitation Medicine, Henan University of Chinese Medicine, No. 156 Jinshui East Road, Zhengdong New District, Zhengzhou 450008, Henan Province, China. henanzyk@126.com

## Abstract

The high incidence and disability rates of stroke pose a heavy burden on society. Inflammation is a significant pathological reaction that occurs after an ischemic stroke. Currently, therapeutic methods, except for intravenous thrombolysis and vascular thrombectomy, have limited time windows. Mesenchymal stem cells (MSCs) can migrate, differentiate, and inhibit inflammatory immune responses. Exosomes (Exos), which are secretory vesicles, have the characteristics of the cells from which they are derived, making them attractive targets for research in recent years. MSC-derived exosomes can attenuate the inflammatory response caused by cerebral stroke by modulating damage-associated molecular patterns. In this review, research on the inflammatory response mechanisms associated with Exos therapy after an ischemic injury is discussed to provide a new approach to clinical treatment.

Key Words: Mesenchymal stem cell-derived exosome; MicroRNA; Inflammation; Ischemic stroke; Adipose-derived stem cell; Toll-like receptor

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Mesenchymal stem cell-derived exosome (MSC-Exos) transplantation is a novel treatment method for ischemic stroke that exhibits certain achievements in trials. Here, we review the strategies developed for MSC-Exos in the neuroinflammatory response of patients with stroke and provide potential therapeutic targets. These methods provide new insights for the future clinical application of MSC-Exos in the treatment of ischemic stroke.

Citation: Chen N, Wang YL, Sun HF, Wang ZY, Zhang Q, Fan FY, Ma YC, Liu FX, Zhang YK. Potential regulatory effects of stem cell exosomes on inflammatory response in ischemic stroke treatment. World J Stem Cells 2023; 15(6): 561-575

URL: https://www.wjgnet.com/1948-0210/full/v15/i6/561.htm DOI: https://dx.doi.org/10.4252/wjsc.v15.i6.561

### INTRODUCTION

Stroke is a common clinical condition that frequently occurs in middle-aged and elderly people and is a global public health problem with high disability and mortality rates; it ranks third in the list of diseases affecting human lifespan<sup>[1]</sup>. The main goals of stroke treatment are vascular recanalization and reduction of cerebral ischemic injury. At present, the main recanalization methods are intravenous thrombolysis and endovascular mechanical thrombectomy; however, owing to the restricted time window and various comorbidities, few patients can benefit from these procedures [2,3]. Increasing evidence has suggested that inflammatory cytokines promote the migration of immune cells to damaged tissues through the blood-brain barrier (BBB) after stroke, aggravating the inflammatory response and leading to nerve cell injury [4,5]. However, the exact molecular mechanisms underlying the inflammatory response after stroke remain unclear, hindering the development of effective and specific treatments

The effectiveness of stem cell transplantation, which can regulate the immune-inflammatory response and the permeability of the BBB, in the treatment of ischemic stroke (IS) has been verified [6,7]. However, pluripotent stem cells are obstructed by the BBB and cannot effectively enter the central nervous system, leading to risks, such as tumorigenicity, thrombosis, and pulmonary embolism, limiting their clinical application. It has been suggested that the therapeutic mechanism of mesenchymal stem cells (MSCs) may involve secreted exosomes (Exos) rather than the direct replacement of brain cells[8]. MSC-derived extracellular vesicles (MSC-EVs) possess the biological characteristics of cells and can penetrate the BBB, reduce the risk of tumors and pulmonary embolism, considerably improve therapeutic efficiency, and reduce complications, thereby having broad therapeutic prospects. MSC-derived Exos (MSC-Exos) reduce inflammatory responses after stroke[9-12]. However, the specific mechanism by which Exos alleviate the inflammatory response after stroke has not yet been explored.

Therefore, in this review, we present the current progress in research on the unique biological characteristics of MSC-Exos and the specific mechanism of action of MSC-Exos in the neuroinflammatory response after stroke. This review aims to explore the role of Exos in the neuroinflammatory response in stroke and provide potential therapeutic targets, with the expectation of offering a reference for future clinical treatments.

### PATHOLOGICAL CHANGES AFTER CEREBRAL ISCHEMIA

Brain cell death after stroke can lead to a series of pathological processes including cell energy failure, neuronal apoptosis, leukocyte infiltration, inflammatory immune responses, tight junction (TJ) protein breakage and degradation, BBB destruction, and increased permeability[13,14]. The main goals of IS treatment are to restore blood flow and improve functional outcomes as soon as possible[15]. In addition, methods of regulating immune inflammation and oxidative stress responses, anti-apoptosis, and promotion of angiogenesis and neurogenesis are of great significance for the treatment of cerebral apoplexy in ischemic and hypoxic injured brain tissues [16]. The BBB controls the inflow and outflow of biological substances necessary for metabolic activity and neuronal function in the brain; therefore, its structural and functional integrity is essential for maintaining the brain microenvironment. The BBB is mainly comprised of vascular endothelial cells, pericytes, the basement membrane, astrocytes, neurons, and microglia, which exchange substances that connect the central and peripheral nervous systems. The mechanisms of BBB injury after stroke include modification of TJ proteins, regulation of transporter expression, and inflammatory damage[17]. The intravascular inflammatory response marks the beginning of BBB disruption and leukocyte infiltration in ischemic brain tissue[18]. The inflammatory response after stroke is an important factor in BBB disruption and nerve cell edema, leading to damage to mental function and even death (Figure 1).





DOI: 10.4252/wjsc.v15.i6.561 Copyright ©The Author(s) 2023.

Figure 1 Pathological changes after stroke. Blood-brain barrier (BBB) disruption after stroke is permeable to leukocytes and blood proteins. Microglia are stimulated, and these activated microglia (M1), in turn, release tumor necrosis factor-α, interleukin (IL)-6, and IL-1β, which activate the nuclear factor kappa-B inflammatory response of reactive astrocytes (A1) and further amplify this effect. Exosomes can penetrate BBB, promote microglial M1 polarization to M2 and T cell activation, mediate lipocalin-2, sirtuin 1, methionine adenosyl transferase 2B, pyrin domain-containing protein, cysteinyl leukotriene receptor 2, and other signaling pathways to promote the release of anti-inflammatory cytokines IL-10, transforming growth factor- $\beta$ , and IL-4. By BioRender.com. BBB: Blood-brain barrier; CysLT2: Cysteinyl leukotriene receptor 2; IL: Interleukin; LNC2: Lipocalin-2; MAT2B: Methionine adenosyl transferase 2B; NF-kB: Nuclear factor kappa-B; SIRT1: Sirtuin 1; TLRs: Pyrin domain-containing protein; TNF-a: Tumor necrosis factor-a.

> Microglia are the resident immune cells of the brain that polarize into different phenotypes (M1 or M2)[19]. M1 inflamed microglia lead to BBB dysfunction and vascular 'leakage,' whereas M2 microglia have inflammation-inhibiting, immune-regulating, tissue-repair, and damage-eliminating functions; they also protect the BBB[20]. Activated M1 microglia release the pro-inflammatory factors tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-1, and IL-6, which activate the nuclear factor kappa-B (NFκB)-mediated inflammatory response of reactive astrocytes (A1s) and further amplify this effect[21]. Owing to inflammatory response stimulation, the structure of the neurovascular unit (NVU) changes, which inhibits central nervous system restoration. This change in the microenvironment stimulates M2 microglia to initiate phagocytosis and secrete transforming growth factor- $\beta$  (TGF $\beta$ ), IL-4, and IL-10, and the engulfment of immune cells, indirectly protecting against inflammation-induced BBB disruption [22]. M2 polarization promotes the release of anti-inflammatory cytokines and tissue repair, including neurogenesis, axonal remodeling, angiogenesis, and oligodendrogenesis[21,23]. Activated matrix metalloproteinase (MMP)-2 and MMP-9 by microglia after stroke degrade the basement membrane and TJ proteins, resulting in BBB disruption, leukocyte infiltration, and angioedema, thus aggravating brain injury[17,24,25]. Pericytes also release cytokines that play vital roles in maintaining the structural integrity of the BBB. Under pathological conditions, dysfunctional pericytes can cause basement membrane degradation or alter NVU coordination, leading to BBB instability[17]. In addition, BBB injury along with the activation of TGF $\beta$  signaling in astrocytes may be a mechanism to disrupt NVU structure, as TGF $\beta$  overproduction affects the function of pericytes and vascular smooth muscle cells[26, 27]. Microglial polarization is closely related to stroke progression; M1 microglia promote astrocyte differentiation to the A1 phenotype through a variety of signaling pathways, including the immune inflammatory response, angioedema, BBB disruption, neuronal apoptosis, and glutamate excitotoxicity, thereby exacerbating brain injury caused by IS[28,29]. The inflammatory reaction of the nervous system is closely related to the polarization of microglia, pericyte-secreted factors, astrocyte differentiation, and leukocyte species. However, the underlying mechanism of action of Exos in the treatment of neuroinflammation in stroke remains unclear.

### **BIOLOGICAL CHARACTERISTICS OF MESENCHYMAL STEM CELL EXOSOMES**

MSCs are pluripotent stem cells with self-renewal, differentiation, secretion, and homing properties. They were first discovered in the bone marrow, where they are abundant and easily extractable, and are



also found in the dental pulp, umbilical cord, hemocytes, and adipose tissue (such as bone marrow MSCs, dental MSCs, umbilical cord-derived MSCs, adipose-derived MSCs, and hematopoietic stem cells)[30,31]. To overcome the problems with primary MSCs, human pluripotent stem cells (hPSCs), including human embryonic stem cells (hESCs) and pluripotent stem cells (iPSCs), represent a promising solution[32]. MSCs can differentiate into lipogenic, chondrogenic, osteoblastic, endothelial, neural, and epithelial lineages, both in vivo and in vitro[33,34]. MSCs can reduce inflammatory responses, release trophic factors to promote therapeutic effects, induce angiogenesis, promote neurogenesis, reduce infarct volume, and replace damaged cells via immunomodulation[10,35,36]. Extracellular vesicles secreted by MSCs can be divided into three types based on their size and intracellular origin: Apoptotic bodies, microvesicles, and Exos. Apoptotic bodies are  $\geq$  1000 nm and microvesicles are 100-1000 nm in diameter. Exos (30-100 nm in diameter) originate from multivesicular bodies and are released by exocytosis, which is dependent on cytoskeletal reorganization, but independent of intracellular Ca<sup>2+</sup> concentration[37,38]. When multivesicular bodies fuse with the cell membrane, Exos are released from the cells. Previously, these vesicles were considered waste products actively excreted by cells; however, studies have shown that Exos have key functions, such as transmitting information between cells, tissue regeneration, and immune regulation[39] (Figure 2).

Exos are released upon fusion with the cell membrane and trigger the release of different cellular substances. Exos can carry the same bioactive substances as their source cells and are vital for information transmission between cells, such as immune regulation and promotion of cell migration, proliferation, differentiation, and matrix synthesis[40]. Moreover, the exogenous Exos of stem cells express specific surface markers (CD9, CD63, CD81, and CD92), express specific phenotypes of stem cells (CD29, CD44, CD73, and CD90)[41], and carry heat shock proteins (HSP) proteins (HSP8, HSP60, HSP70, and HSP9), signal transduction proteins, and multivesicular production-related proteins. More importantly, they can directly transfer bioactive molecules, including non-coding regulatory microRNAs (miRNAs), messenger RNAs (mRNAs), and proteins from donor cells to recipient cells. MiRNAs are short (approximately 22 nucleotides), single-stranded, non-coding RNAs transcribed in the nucleus by RNA polymerase II from one gene or between two different genes to regulate different cellular processes such as differentiation, proliferation, metabolism, inflammation, stress response, angiogenesis, and signaling transduction<sup>[42]</sup>. miRNAs mainly affect gene expression by degrading the corresponding miRNAs or suppressing translation[43]. Alexander et al[44] showed that exosomal miRNAs participate in regulating inflammatory responses; miR-146a-containing Exos can inhibit inflammation, whereas miR-155-containing Exos promote inflammation following exposure to the same inflammatory stimulus.

Exos contain a variety of active substances that form the basis for disease treatment. These bioactive substances carried by Exos can target specific cells for information transmission and enter the cytoplasm by fusion with receptor cell membranes or endocytosis, thereby changing the target cell function by transmitting proteins, lipids, and nucleic acids[45]. Exos can be effectively isolated from donor cells and protect their contents from the external environment, ensuring the complete transmission of effective information[46]. Exos act as mediators that facilitate intercellular communication and influence the recipient cell activity by delivering content. DiR-labeled MSC-Exos were injected into a rat model of stroke *via* the caudal vein, and the *in vivo* tracer showed that Exos could penetrate the BBB and reach the brain tissue. The fluorescence signal peaked on the third day and then gradually decreased[47]. Matsumoto *et al*[48] also demonstrated that Exos can increase long-term neuroprotective effects after stroke, modulate peripheral immune responses, and increase angiogenesis and axonal dendritic remodeling. Therefore, the use of Exos for the treatment of neurological diseases has great potential[49, 50]. These results suggest that Exos is an important therapeutic target for the treatment of stroke (Figure 3).

### **MSC-EVS REGULATE INFLAMMATORY RESPONSE IN IS TREATMENT**

The potential therapeutic mechanisms of stem cell Exos involve promoting dendritic and axonal growth, repairing nerves, and promoting angiogenesis through direct actions[51,52]. Through indirect action, it can promote the secretion of inflammatory factors by cells by exogenously producing Exos that appear to interact with recipient brain cells, thereby stimulating them to release their own Exos and playing a role in anti-inflammation and neurological repair. Transplantation of MSC-Exos improves inflammatory responses in IS, maintaining BBB function, decreasing brain edema, regulating energy metabolism, and promoting antioxidant, anti-inflammatory, and anti-apoptotic effects[53]. In IS, miRNAs are involved in a variety of cellular functions, such as injured tissue repair and remodeling, and different neuronal activities. Their target genes play a crucial regulatory role in the inflammatory process of post-ischemic reperfusion injury, which explains their potential use as therapeutic targets in IS and is the focus of Exos research[54,55]. According to current research, the main signaling pathways mediated by Exos after cerebral ischemia are as follows (Table 1)[12,41,56-63].

Zaisbidena® WJSC | https://www.wjgnet.com

Table 1 Application of stem cell exogenous exosomal miRNA in treatment of ischemic stroke						
MicroRNA	Source	Model(s)	Functional effects	Pathway(s)	Ref.	
miR-21a-5p	MSCs	OGD microglia	Induces microglial M2 polarization by targeting STAT3	STAT3	Xin <i>et al</i> [12], 2022	
miR-138-5p	BMSCs	MCAO mouse, OGD astrocytes	Promotes astrocyte proliferation and inhibits inflammatory response	LCN2	Deng <i>et al</i> [ <mark>41</mark> ], 2019	
miR-542-3p	MSCs	MCAO mice, OGD human glial cells	Suppresses inflammation and prevents cerebral infarction	TLR4	Cai <i>et al</i> [ <mark>56</mark> ], 2021	
miR-146a-5p	HUMSCs	MCAO mouse, OGD microglia	Anti-inflammation	IRAK1/TRAF6	Zhang et al[ <mark>57</mark> ], 2021	
miR-223-3p	MSCs	MCAO Rats, OGD microglia	Anti-inflammation	CysLT2R	Zhao <i>et al</i> [ <mark>58,59</mark> ], 2020	
miR-21-3p	MSCs	MCAO rats	BBB protection, anti-inflammation, anti-apoptosis	MAT2B	Li et al <mark>[60</mark> ], 2019	
miR-26a-5p	HUMSCs	I/R mice, OGD microglia	Inhibits microglial M1 polarization	TLRs	Li et al <mark>[61</mark> ], 2020	
miR-150-5p	BMSCs	MCAO rats	Decelerates neuronal apoptosis, reduces inflammation	TLR5	Li et al <mark>[62</mark> ], 2022	
miR-30d-5p	ADSCs	Patients, MCAO rats, OGD microglia	Promotes M2 microglial/macrophage polarization	Inflammatory mediators	Jiang <i>et al</i> [ <mark>63</mark> ], 2018	

ADSCs: Adipose-derived stem cells; BMSCs: Bone marrow mesenchymal stem cell; CysLT2R: Cysteinyl leukotriene receptor 2; HUMSCs: Human umbilical cord blood mesenchymal stem cells; I/R: Ischemia/reperfusion; IRAK1: Interleukin-1receptor-associated kinase 1; MCAO: Middle cerebral artery occlusion; MAT2B: Methionine adenosyl transferase 2B; MSCs: Mesenchymal stem cells; OGD: Oxygen-glucose deprivation; STAT3: Signal transducer and activator of transcription 3; TLRs: Toll-like receptors; TRAF6: Tumor necrosis factor receptor-associated factor 6; TLR4: Toll-like receptor 4; TLR5: Toll-like receptor 5.



DOI: 10.4252/wjsc.v15.i6.561 Copyright ©The Author(s) 2023.

Figure 2 Sources and potential function for stroke of mesenchymal stromal cells. These cells are found in bone marrow, dental pulp, umbilical cord, hemocyte, and adipose tissue. Mesenchymal stromal cells reduce the inflammatory response, release trophic factors, induce angiogenesis, and promote neurogenesis in stroke. By BioRender.com. MSC: Mesenchymal stem cell.

### NF-kB signaling pathway

The transcription factor NF-KB regulates many aspects of innate and adaptive immunity and plays an important role in the inflammatory response. It is also involved in the migration of immune effector cells to the inflammatory system, thereby allowing the secretion of pro-inflammatory cytokines[64]. Han et al[65] showed that MSCs-Exos protect MCAO-injured rats, possibly by regulating the AMP-activated protein kinase (AMPK) and JAK2/STAT3/NF-κB signaling pathways. NF-κB is a central inflammatory mediator responding to many immune receptors. NF-KB mediates the induction of pro-inflammatory

Chen N et al. Stem cell exosomes in stroke treatment



DOI: 10.4252/wjsc.v15.i6.561 Copyright ©The Author(s) 2023.

Figure 3 Exosomes. Extracellular vesicles are classified into three types: Apoptotic bodies, microvesicles, and exosomes (Exos). Apoptotic bodies are ≥ 1000 nm, microvesicles are 100–1000 nm, and Exos are 30–100 nm in diameter. The contents carried by the Exos are mainly DNA, mRNA, microRNA, functional proteins, and other active substances. The membrane structure can express a variety of antigens and antibody molecules. The surface markers of the Exos mainly include CD63, CD81, CD9, and heat shock protein 70. By Figdiaw. MSCs: Mesenchymal stem cells.

cytokines, such as TNF- $\alpha$ , IL-1, and IL-6, in monocytes/macrophages[66]. Fann *et al*[67] confirmed the involvement of NF-KB signaling in the activation of pyrin domain-containing inflammasomes following IS. Preconditioning MSCs with lithium modifies EV secretion patterns, enhancing the therapeutic potential of the derived EVs (Li-EVs) and significantly increasing the resistance of cultured astrocytes, microglia, and neurons to hypoxic injury compared with control and native EVs. Li-EVs reduce the abundance of post-hypoxic and post-ischemic TLR4 (leading to activation of the NF-KB signaling pathway) and decrease proteasomal activity, which together contribute to reduced levels of poststroke encephalitis[68]. The miRNAs carried by Exos play a significant physiological role. Cai et al[56] confirmed that MSC-derived exosomal microRNA-542-3p (miR-542-3p) prevented ischemia-induced glial cell inflammatory responses by inhibiting TLR4. Interleukin-1 receptor-associated kinase 1 (IRAK1) and tumor necrosis factor receptor-associated factor 6 (TRAF6) may be parts of an NF-KB-induced negative feedback loop[69]. Zhang et al[57] found that injected Exos produced by human umbilical cord MSCs (HUMSC-Exos) enter the site of ischemic injury and be internalized by cells, both in vivo and in vitro. In vitro, HUMSC-Exos treatment attenuates microglial inflammation induced by oxygen-glucose deprivation (OGD). In vivo, HUMSC-Exos treatment significantly reduced infarct volume, alleviated behavioral deficits, and improved microglial activation 3 d after transient cerebral ischemia. MiR-146a-5p from HUMSC-Exos can attenuate microglial-mediated neuroinflammation through the IRAK1/ TRAF6 pathway and ensuing neurological deficits after IS. NF-κB signaling pathway activation is a 'master regulator' of inflammation and is associated with the generation of free radicals and the activation of proteolytic enzymes and pro-inflammatory cytokines, playing an important role in regulating apoptosis after stroke [70,71]. Taken together, these results show that NF- $\kappa$ B signaling is essential for the regulation of brain tissue inflammasomes under ischemic conditions. In addition, MSC-Exos treatment decreased the activation of the NF-KB signaling pathway, thereby attenuating inflammasome expression and activation under ischemic conditions. These findings suggest that therapeutic interventions targeting neuroinflammasome activation may provide new opportunities for the treatment of IS.

### NOD-like receptor family pyrin domain-containing 3 signaling pathway

NOD-like receptor family pyrin domain-containing 3 (NLRP3) plays an important role in mediating the inflammatory responses during cerebral IS[72]. The NLRP3 inflammasome is a multiprotein complex comprising NLRP3 and pyroptosis-related factors (ASC and caspase 1)[73]. The NF-κB and mitogenactivated protein kinase (MAPK) pathways play a major role in the expression and activation of NLRP1 and NLRP3 inflammasomes in primary cortical neurons[67]. Bone marrow MSC-Exos (BMSC-Exos) can reduce brain infarct area and cerebral edema, thus improving neurological function. MSC-Exos can downregulate the expression of NLRP3 inflammasome and pyroptosis-related proteins on the surface of neurons[74]. Moreover, it improved the transition from M1 to M2 phenotype both *in vivo* and *in vitro*. BMSC-Exos relieve cerebral ischemia/reperfusion (I/R) injury by suppressing NLRP3 inflammasomemediated inflammation and pyroptosis *via* modulation of microglial polarization[74]. Sarmah *et al*[75] came to similar conclusions by treating a rat MCAO model with intra-arterial injections of MSCs; the levels of NLRP-1 and NLRP-3 inflammasomes and their related components IL-1β, caspase-1, and ASC were significantly reduced. NLRP3 apoptotic bodies are involved in astrocyte and microglial



polarization and are closely related to the development of the inflammatory cascade after stroke, and BMSC-Exos reduce the inflammatory response after stroke by inhibiting NLRP3 activation.

### Sirtuin signaling pathway

Sirtuins (SIRTs) are NAD+-dependent deacylases with multiple roles in energy metabolism regulation, cell survival, transcriptional regulation, inflammation, circadian regulation, and DNA repair[76]. SIRT-1 and SIRT-3 are both associated with the inflammatory response in stroke patients. Xin *et al*[12] used an *in vivo* neonatal male mouse model of hypoxic-ischemic (HI) injury and induced *in vitro* hypoxia-glucose deficiency, thus simulating microglial BV-2 cells to deliver miR-21a-5p (miR-21a-5p) as a therapeutic intervention through MSC-Exos. Treatment of BV-2 cells with MSC-EVs increased cell viability and miR-21a-5p levels, which were decreased after glucose-oxygen deprivation. In both *in vitro* and *in vivo* models of HI injury, the effects on microglial polarization and STAT3 phosphorylation decreased when miR-21a-5p levels were reduced in MSC-Exos. These results suggest that MSC-Exos attenuate HI brain injury in neonatal mice by delivering miR-21a-5p, which induces microglial M2 polarization by targeting STAT3. Adipose-derived MSC-derived miR-22-3p reduces infarct volume and apoptosis in a stroke model[77]. Sarmah *et al*[75] demonstrated that intraarterial MSCs increase SIRT-1 to inhibit the NF-κB pathway, reducing inflammasome signaling and apoptosis, thereby exerting a neuroprotective effect. SIRT1 may be an independent risk factor for cerebral infarction, and a high concentration of SIRT1 in cerebral infarction may be associated with disruption of the BBB[78].

### Cysteinyl leukotriene signaling pathway

Cysteinyl leukotrienes (CysLTs), including leukotriene C4 (LTC4), leukotriene D4 (LTD4), and leukotriene E4 (LTE4), are derived from 5-lipoxygenase metabolites of arachidonic acid after cell necrosis and are effective mediators of inflammation[79]. The effects of CysLTs are mainly mediated by the CysLT1 and CysLT2 receptors (CysLT1R and CysLT2R), which are active in various cell types during pathological brain injury. CysLT2 is expressed in the cerebral cortex, hippocampus, substantia nigra, and lateral ventricle[80]. Zhao *et al*[58,59] showed that the overexpression of miR-223-3p (miR-223-3p) in MSC-Exos can reduce MCAO-induced infarction, improve neurological deficits, and promote learning and memorization. MiR-223-3p inhibits the expression of pro-inflammatory factors and promotes the secretion of anti-inflammatory factors in the ischemic cortex and hippocampus. Western blot and quantitative real-time PCR analyses also showed that exosomal miR-223-3p from MSCs alleviated cerebral I/R injury by inhibiting the pro-inflammatory response mediated by M1 polarization of microglia, which may be related to the inhibition of CysLT2R by exosomal miR-223-3p.

### Lipocalin-2

Lipocalin-2 (LCN2), a 25 kDa protein, is a neutrophil gelatinase-associated protein that affects different cellular processes during stroke. The pro-inflammatory mediator LCN2 plays a key role in I/R injury [81]. Genetic or pharmacological inhibition of these pro-inflammatory mediators (iNOS, IL-6, CCL2, and CCL9) provides neuroprotection against stroke and reduces the expression of inflammatory factors by down-regulating LCN2[41]. Deng *et al*[41] used a mouse MCAO model to explore the effects of BMSC-derived exosomal miR-138-5p in IS *in vivo*. Overexpression of miR-138-5p promoted cell proliferation and inhibited apoptosis of OGD-damaged astrocytes, accompanied by decreased expression of inflammatory factors. This was achieved by downregulating LCN2, and the expression of LCN2 protein was subsequently detected by Western blot analysis. More importantly, BMSCs attenuated neuronal injury in IS mice by delivering miR-138-5p to astrocyte Exos. Therefore, the exogenous exosomal miR-138-5p from BMSCs promotes astrocyte proliferation and inhibits the inflammatory response after IS by targeting LCN2, thereby reducing neurological impairment, which may provide a new target for IS treatment.

### Methionine adenosyl transferase 2B

Methionine adenosyl transferase (MAT) is an enzyme involved in cell cycle regulation. Mammals have three major MAT genes: MAT1A, MAT2A, and MAT2B[60]. TNF-induced activation of MAT2B promotes tumor growth through the NF- $\kappa$ B pathway in hepatoma cells[81]. MiR-21-3p antagomir can control the inflammatory response by inhibiting NF- $\kappa$ B signaling; these functions of miR-21-3p are exerted by directly targeting MAT2B[82]. This interaction forms the basis of the function of miR-21-3p/ MAT2B in regulating inflammation. Li *et al*[60] found that miR-21-3p expression was elevated in the MCAO model, and the inhibition of exogenous adipose-derived stem cell Exos miR-21-3p could inhibit the expression of MAT2B in neural cells, thereby improving the BBB status and inhibiting apoptosis and inflammatory responses. MiR-21-3p antagomir could inhibit the expression of pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , and IL6) and promote the expression of anti-inflammatory cytokines (IL-10). Thus, miR-21-3p can protect neural cells by inhibiting the expression of MAT2B and thus inhibiting apoptosis and inflammatory responses.

Zaishidena® WJSC | https://www.wjgnet.com

### Toll-like receptors (TLRS)

Evidence suggests that Toll-like receptors (TLRs) play important roles in the development of ischemic brain injury in adults[83]. TLRs, comprising 13 members (TLR-1 to TLR-13), are type 1 integral membrane proteins responsible for detecting invading pathogens and initiating immune responses[84, 85]. The microglial TLR pathway is activated following cerebral ischemia and inhibition of TLR signaling by exosomal miR-26a-5p decreases cholesterol 25-hydroxylase protein expression, which in turn inhibits microglial M1 polarization and relieves nerve injury after brain injury[61]. The gene expression of many inflammatory mediators, such as TNF-α, IL-1, and IL-6, can reduce the development of nervous system inflammation by inhibiting TLR4 transduction pathway downregulation[86]. Upregulation of miR-326 attenuates IL-10, IL-1 $\beta$ , and TNF- $\alpha$  pro-inflammatory cytokine expression in response to lipopolysaccharide stimulation by targeting TLR4[87]. TLR5 activates NF-kB and MAPK pathways that regulate the transcription of genes encoding immune mediators[88]. Qiao et al[89] elucidated that TLR5 downregulation is accompanied by alleviated neurological deficits, reduced infarct volume, and reduced edema after IS[90]. Li et al[62] validated that BMSC-Exos can improve neurological function and pathological changes, decelerate neuronal apoptosis, and reduce inflammatory factors in MCAO rats. Exosomal miR-150-5p from BMSCs mitigates cerebral I/R injury by inhibiting TLR5 expression. These studies showed that TLRs and their related miRNAs are associated with inflammation after IS.

### Inflammatory mediators

Dabrowska et al[91] transplanted human bone marrow stem cells and their secreted Exos into a rat model of local brain injury. The results showed that monocyte chemoattractant protein-1 (MCP-1) expression increased locally after brain injury, whereas MCP-1 expression decreased in the transplanted HUMSCs and Exos groups. In addition, they observed that the infusion of pro-inflammatory cytokines and chemokines with HUMSCs or EVs in rats with untreated focal brain injury was associated with reduced microglial/macrophage and astrocyte activation. MSC-Exos therapy can reduce the expression of the inflammatory cytokines TNF- $\alpha$  and IL-6, increase the expression of the cytokines IL-4 and IL-10, and reduce brain injury. Exos from stem cells can enhance the activation of CD4+ and CD8+ lymphocytes, decrease the number of dendritic cells, regulate peripheral immunosuppression caused by stroke[9], and pass antigens to the immune system through the BBB[92]. IL-4, CD206, and IL-10 are markers of M2 microglial secretion, whereas TNF-a, IL-6, and iNOS are markers of M1 microglial secretion[93]. Yang et al[94] found that the MCAO model also verified that Exos intervention reduced the infarct volume and promoted the polarization of microglia to M2 phenotype. These results demonstrate that adipose-derived stem cell Exos can prevent stroke by shifting microglia from an M1 to M2 phenotype in the hippocampus<sup>[94]</sup>.

### Microglial polarization

Microglia are macrophages of the central nervous system and are important components of innate and adaptive immune responses [95]. The microglial M1 type can secrete pro-inflammatory factors, whereas the M2 type can secrete anti-inflammatory factors; therefore, the fact that MSCs and Exos can promote the polarization of microglia to M2 is notable for the treatment of IS. The M2 type protects nerve cells mainly by engulfing debris and promoting the repair and regeneration of brain tissue. In contrast, inflammatory factors of the M1 phenotype aggravate post-stroke symptoms. Therefore, the microglial response after stroke is an important prognostic factor[96]. Different miRNAs transported by Exos contribute to the differentiation of microglia into distinct phenotypes. Increased levels of miR-124-3p in microglial Exos promote M2 microglial polarization, reduce brain damage, and improve stroke outcomes[97]. Adipose-derived MSCs (ADMSCs) participate in the repair process of tissues through paracrine effects after relieving nerve injury; ADMSCs have similar biological characteristics to MSCs. Stimulation of AMSC-derived Exos with inflammatory factors was found to convert M1 microglia into M2 microglia, suggesting that AMSC-derived Exos promote microglial polarization by activating proinflammatory microenvironment signals[98]. miRNAs are critical regulators of genes involved in various biological processes; miR-146a-5p-enriched BMSC-Exos directly target IRAK1 and nuclear factor-activated T cell 5 (NFAT5), which contributes to inflammatory responses and polarize M1 microglia/macrophages[99]. Exos containing miR-216a-5p, miR-124, miR-155, miR-182, miR-17-5p, miR-30d-5p, and miR-223-3p were found to promote microglial M2 polarization[63,100-103]. BMSC-Exos promote microglial polarization from M1 to M2, inhibit inflammation-related signaling pathways, and reduce endothelial cell injury and neurological impairment caused by IS[104-106]. Although astrocytes may play a role in brain inflammation, little is known about their role in stroke pathology[107].

### Activated regulatory T cells

Changes in regulatory T cell (Treg) numbers and function after stroke are accompanied by a decrease in immunosuppressive function, which affects stroke prognosis[108]. The immunosuppressive function of Tregs is largely impaired during stroke and Treg-derived anti-inflammatory factors, including transforming growth factor-beta (TGF-b) and IL-10, are reduced [109,110]. MiRNAs delivered by stem cell Exos can induce anti-inflammatory polarization as important regulators of Treg homeostasis and



function[111,112]. MSC-Exos induce anti-inflammatory IL-10 and TGF-β transcription, attenuate proinflammatory factors IL-1 $\beta$ , IL-6, and TNF- $\beta$ , and inhibit the differentiation and activation of Tregs[113, 114]. Furthermore, MSC-Exos are absorbed by endothelial cells, impair T-cell function by inhibiting Tcell proliferation *in vitro*, and increase endothelial cell proliferation, migration, and capillary formation in a dose-dependent manner [115]. Wang et al [116] showed that the intravenous injection of MSC-EVs reduced neurological deficits, cerebral infarct volume, brain edema, and neuronal injury in both young and old mice. The neuroprotective and anti-inflammatory effects of MSC-EVs were demonstrated through a decrease in leukocyte infiltration and, specifically, polymorphonuclear neutrophil, monocyte, and macrophage infiltration, in the cerebral ischemic areas of aged mice. In addition, MSC-EVs significantly decreased the number of monocytes and activated Tregs. The expression and phosphorylation of signal transducer and activator 1 (STAT1) are increased in mice with miR-146a deficient Tregs, and miR-125a is involved in the differentiation of Tregs[117]. Exosomal miR-16 and miR-21, derived from bone marrow stem cells, can increase the production of Tregs and exert anti-inflammatory effects[118]. Although breakthroughs have been made in elucidating the working mechanism of Tregs over the past decade, the mechanism by which this minor population of peripheral immune cells has a significant beneficial effect after stroke injury remains largely unknown[108].

### CONCLUSION

Brain injury after stroke is a complex pathological process. This review summarizes the recent studies on the mechanism of action of MSC-Exos in regulating inflammatory responses during IS treatment. MSC-Exos regulate microglial polarization through various pathways such as NF-KB, NLRP3, and STATs, indicating that microglial M1 to M2 phenotype polarization is closely related to the inflammatory response after IS.

However, some essential questions remain unanswered. Stroke-induced brain injury involves multiple mechanisms that cannot be explained by a single one. Immune inflammation plays a crucial role in this process, especially the NF-KB, NLRP3, and other signaling pathways. After immune inflammation, microglia, leukocytes, and other inflammatory cells are activated and release many pro-inflammatory factors. Additionally, nerve cells are affected by varying degrees of damage caused by ischemia and hypoxia after stroke.

However, these studies have some limitations. MSC-Exos can mediate different signaling pathways to reduce inflammatory responses after stroke in animal models. However, these results have not been translated into clinical practice. Most studies have focused on exosomal miRNAs, indicating that they play an important role in regulating cellular functions. However, research on other bioactive molecules contained in Exos, such as miRNAs, mRNAs, and proteins, is limited. This does not mean that this mechanism of action of miRNAs can explain how Exos attenuate post-stroke inflammation. The dosage, mode of administration, and duration of action of the Exos should be elucidated. Exos are considered ideal biomarkers and drug delivery vehicles, with great potential for overcoming the limitations of stem cell therapy[119]. The use of Exos as drug-loaded systems will facilitate breakthroughs in the research and development of targeted drugs for clinical treatment. Moreover, new directions and methods will be provided for stroke treatment.

### FOOTNOTES

Author contributions: Chen N drafted the manuscript; Wang YL, Sun HF, Wang ZY, and Zhang Q reviewed the literature, and designed and revised the manuscript; Fan FY, Liu FX, and Ma YC generated the graphs; Zhang YK guided the construction of the manuscript; all the authors have read and approved the manuscript.

Supported by the National Natural Science Foundation of China, No. 81974564 and No. 82104730; the Zhongyuan Science and Technology Innovation Leading Talent Project, No. 224200510027; the National Natural Science Foundation of China, No. 82001973; the Youth Project Co-established by Henan Province and a Ministry grant, No. SBGJ2020003017; and the Health Science and Technology Innovation Excellent Youth Training Project in Henan Province, No. YXKC2020057.

Conflict-of-interest statement: The authors declare no conflict of interest. The funding body played no role in the design of the study; collection, analysis, and interpretation of data; or in writing the manuscript.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is noncommercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

### Country/Territory of origin: China

ORCID number: Na Chen 0000-0001-6862-4635; Yan-Lin Wang 0009-0005-6539-8456; Hui-Fang Sun 0000-0002-5450-0962; Zhuo-Ya Wang 0009-0007-5595-4089; Qi Zhang 0009-0003-5471-9301; Fei-Yan Fan 0009-0004-0075-2453; Yu-Cheng Ma 0009-0004-0783-8655; Fei-Xiang Liu 0000-0001-7713-8049; Yun-Ke Zhang 0000-0003-1500-1535.

Corresponding Author's Membership in Professional Societies: Henan Stroke Association.

S-Editor: Li L L-Editor: Wang TQ P-Editor: Li L

### REFERENCES

- Yang L, Qian J, Yang B, He Q, Wang J, Weng Q. Challenges and Improvements of Novel Therapies for Ischemic Stroke. Front Pharmacol 2021; 12: 721156 [PMID: 34658860 DOI: 10.3389/fphar.2021.721156]
- Ungvari Z, Tarantini S, Donato AJ, Galvan V, Csiszar A. Mechanisms of Vascular Aging. Circ Res 2018; 123: 849-867 2 [PMID: 30355080 DOI: 10.1161/CIRCRESAHA.118.311378]
- 3 Yang P, Zhang Y, Zhang L, Treurniet KM, Chen W, Peng Y, Han H, Wang J, Wang S, Yin C, Liu S, Wang P, Fang Q, Shi H, Yang J, Wen C, Li C, Jiang C, Sun J, Yue X, Lou M, Zhang M, Shu H, Sun D, Liang H, Li T, Guo F, Ke K, Yuan H, Wang G, Yang W, Li Z, Xing P, Zhang P, Zhou Y, Wang H, Xu Y, Huang Q, Wu T, Zhao R, Li Q, Fang Y, Wang L, Lu J, Li Y, Fu J, Zhong X, Wang Y, Goyal M, Dippel DWJ, Hong B, Deng B, Roos YBWEM, Majoie CBLM, Liu J; DIRECT-MT Investigators. Endovascular Thrombectomy with or without Intravenous Alteplase in Acute Stroke. N Engl J Med 2020; 382: 1981-1993 [PMID: 32374959 DOI: 10.1056/NEJMoa2001123]
- Tariq MB, Lee J, McCullough LD. Sex differences in the inflammatory response to stroke. Semin Immunopathol 2022 4 [PMID: 36355204 DOI: 10.1007/s00281-022-00969-x]
- Zou L, Han R. Inflammatory Response and Immune Regulation in Brain-Heart Interaction after Stroke. Cardiovasc Ther 5 2022; 2022: 2406122 [PMID: 36474712 DOI: 10.1155/2022/2406122]
- 6 Pittenger MF, Discher DE, Péault BM, Phinney DG, Hare JM, Caplan AI. Mesenchymal stem cell perspective: cell biology to clinical progress. NPJ Regen Med 2019; 4: 22 [PMID: 31815001 DOI: 10.1038/s41536-019-0083-6]
- Stonesifer C, Corey S, Ghanekar S, Diamandis Z, Acosta SA, Borlongan CV. Stem cell therapy for abrogating strokeinduced neuroinflammation and relevant secondary cell death mechanisms. Prog Neurobiol 2017; 158: 94-131 [PMID: 28743464 DOI: 10.1016/j.pneurobio.2017.07.004]
- Li Y, Cheng Q, Hu G, Deng T, Wang Q, Zhou J, Su X. Extracellular vesicles in mesenchymal stromal cells: A novel 8 therapeutic strategy for stroke. Exp Ther Med 2018; 15: 4067-4079 [PMID: 29725359 DOI: 10.3892/etm.2018.5993]
- Doeppner TR, Herz J, Görgens A, Schlechter J, Ludwig AK, Radtke S, de Miroschedji K, Horn PA, Giebel B, Hermann 0 DM. Extracellular Vesicles Improve Post-Stroke Neuroregeneration and Prevent Postischemic Immunosuppression. Stem Cells Transl Med 2015; 4: 1131-1143 [PMID: 26339036 DOI: 10.5966/sctm.2015-0078]
- Dabrowska S, Andrzejewska A, Lukomska B, Janowski M. Neuroinflammation as a target for treatment of stroke using 10 mesenchymal stem cells and extracellular vesicles. J Neuroinflammation 2019; 16: 178 [PMID: 31514749 DOI: 10.1186/s12974-019-1571-8]
- Yu H, Xu Z, Qu G, Wang H, Lin L, Li X, Xie X, Lei Y, He X, Chen Y, Li Y. Hypoxic Preconditioning Enhances the 11 Efficacy of Mesenchymal Stem Cells-Derived Conditioned Medium in Switching Microglia toward Anti-inflammatory Polarization in Ischemia/Reperfusion. Cell Mol Neurobiol 2021; 41: 505-524 [PMID: 32424775 DOI: 10.1007/s10571-020-00868-5]
- Xin DQ, Zhao YJ, Li TT, Ke HF, Gai CC, Guo XF, Chen WQ, Liu DX, Wang Z. The delivery of miR-21a-5p by 12 extracellular vesicles induces microglial polarization via the STAT3 pathway following hypoxia-ischemia in neonatal mice. Neural Regen Res 2022; 17: 2238-2246 [PMID: 35259844 DOI: 10.4103/1673-5374.336871]
- 13 An H, Zhou B, Ji X. Mitochondrial quality control in acute ischemic stroke. J Cereb Blood Flow Metab 2021; 41: 3157-3170 [PMID: 34551609 DOI: 10.1177/0271678X211046992]
- Datta A, Sarmah D, Mounica L, Kaur H, Kesharwani R, Verma G, Veeresh P, Kotian V, Kalia K, Borah A, Wang X, 14 Dave KR, Yavagal DR, Bhattacharya P. Cell Death Pathways in Ischemic Stroke and Targeted Pharmacotherapy. Transl *Stroke Res* 2020; **11**: 1185-1202 [PMID: 32219729 DOI: 10.1007/s12975-020-00806-z]
- Mendelson SJ, Prabhakaran S. Diagnosis and Management of Transient Ischemic Attack and Acute Ischemic Stroke: A 15 Review. JAMA 2021; 325: 1088-1098 [PMID: 33724327 DOI: 10.1001/jama.2020.26867]
- Onose G, Anghelescu A, Blendea D, Ciobanu V, Daia C, Firan FC, Oprea M, Spinu A, Popescu C, Ionescu A, Busnatu Ș, 16 Munteanu C. Cellular and Molecular Targets for Non-Invasive, Non-Pharmacological Therapeutic/Rehabilitative Interventions in Acute Ischemic Stroke. Int J Mol Sci 2022; 23 [PMID: 35055089 DOI: 10.3390/ijms23020907]
- 17 Abdullahi W, Tripathi D, Ronaldson PT. Blood-brain barrier dysfunction in ischemic stroke: targeting tight junctions and transporters for vascular protection. Am J Physiol Cell Physiol 2018; 315: C343-C356 [PMID: 29949404 DOI: 10.1152/ajpcell.00095.2018]
- Jurcau A, Simion A. Neuroinflammation in Cerebral Ischemia and Ischemia/Reperfusion Injuries: From Pathophysiology 18 to Therapeutic Strategies. Int J Mol Sci 2021; 23 [PMID: 35008440 DOI: 10.3390/ijms23010014]
- 19 Xiong XY, Liu L, Yang QW. Functions and mechanisms of microglia/macrophages in neuroinflammation and neurogenesis after stroke. Prog Neurobiol 2016; 142: 23-44 [PMID: 27166859 DOI: 10.1016/j.pneurobio.2016.05.001]
- Durafourt BA, Moore CS, Zammit DA, Johnson TA, Zaguia F, Guiot MC, Bar-Or A, Antel JP. Comparison of 20



polarization properties of human adult microglia and blood-derived macrophages. Glia 2012; 60: 717-727 [PMID: 22290798 DOI: 10.1002/glia.22298]

- Hu X, Leak RK, Shi Y, Suenaga J, Gao Y, Zheng P, Chen J. Microglial and macrophage polarization-new prospects for 21 brain repair. Nat Rev Neurol 2015; 11: 56-64 [PMID: 25385337 DOI: 10.1038/nrneurol.2014.207]
- 22 Qiu YM, Zhang CL, Chen AQ, Wang HL, Zhou YF, Li YN, Hu B. Immune Cells in the BBB Disruption After Acute Ischemic Stroke: Targets for Immune Therapy? Front Immunol 2021; 12: 678744 [PMID: 34248961 DOI: 10.3389/fimmu.2021.678744]
- Wang N, Liang H, Zen K. Molecular mechanisms that influence the macrophage m1-m2 polarization balance. Front 23 Immunol 2014; 5: 614 [PMID: 25506346 DOI: 10.3389/fimmu.2014.00614]
- Shu ZM, Shu XD, Li HQ, Sun Y, Shan H, Sun XY, Du RH, Lu M, Xiao M, Ding JH, Hu G. Ginkgolide B Protects 24 Against Ischemic Stroke Via Modulating Microglia Polarization in Mice. CNS Neurosci Ther 2016; 22: 729-739 [PMID: 27306494 DOI: 10.1111/cns.12577]
- Zhu J, Cao D, Guo C, Liu M, Tao Y, Zhou J, Wang F, Zhao Y, Wei J, Zhang Y, Fang W, Li Y. Berberine Facilitates 25 Angiogenesis Against Ischemic Stroke Through Modulating Microglial Polarization via AMPK Signaling. Cell Mol Neurobiol 2019; 39: 751-768 [PMID: 31020571 DOI: 10.1007/s10571-019-00675-7]
- Sweeney MD, Ayyadurai S, Zlokovic BV. Pericytes of the neurovascular unit: key functions and signaling pathways. Nat 26 Neurosci 2016; 19: 771-783 [PMID: 27227366 DOI: 10.1038/nn.4288]
- 27 Kato T, Sekine Y, Nozaki H, Uemura M, Ando S, Hirokawa S, Onodera O. Excessive Production of Transforming Growth Factor β1 Causes Mural Cell Depletion From Cerebral Small Vessels. Front Aging Neurosci 2020; 12: 151 [PMID: 32581764 DOI: 10.3389/fnagi.2020.00151]
- 28 Wan T, Huang Y, Gao X, Wu W, Guo W. Microglia Polarization: A Novel Target of Exosome for Stroke Treatment. Front Cell Dev Biol 2022; 10: 842320 [PMID: 35356292 DOI: 10.3389/fcell.2022.842320]
- Jolivel V, Bicker F, Binamé F, Ploen R, Keller S, Gollan R, Jurek B, Birkenstock J, Poisa-Beiro L, Bruttger J, Opitz V, 29 Thal SC, Waisman A, Bäuerle T, Schäfer MK, Zipp F, Schmidt MHH. Perivascular microglia promote blood vessel disintegration in the ischemic penumbra. Acta Neuropathol 2015; 129: 279-295 [PMID: 25500713 DOI: 10.1007/s00401-014-1372-11
- Sherman LS, Romagano MP, Williams SF, Rameshwar P. Mesenchymal stem cell therapies in brain disease. Semin Cell 30 *Dev Biol* 2019; **95**: 111-119 [PMID: 30922957 DOI: 10.1016/j.semcdb.2019.03.003]
- Srithanyarat SS, Choosiri M, Sa-Ard-Iam N, Petcharat P, Osathanon T. Characteristics of mesenchymal stem cells from 31 supracrestal gingival connective tissue. J Periodontol 2023; 94: 439-450 [PMID: 36218191 DOI: 10.1002/JPER.22-0306]
- Liu TM. Application of mesenchymal stem cells derived from human pluripotent stem cells in regenerative medicine. 32 World J Stem Cells 2021; 13: 1826-1844 [PMID: 35069985 DOI: 10.4252/wjsc.v13.i12.1826]
- Chen YH, Pruett-Miller SM. Improving single-cell cloning workflow for gene editing in human pluripotent stem cells. 33 Stem Cell Res 2018; 31: 186-192 [PMID: 30099335 DOI: 10.1016/j.scr.2018.08.003]
- Maqsood M, Kang M, Wu X, Chen J, Teng L, Qiu L. Adult mesenchymal stem cells and their exosomes: Sources, 34 characteristics, and application in regenerative medicine. Life Sci 2020; 256: 118002 [PMID: 32585248 DOI: 10.1016/j.lfs.2020.118002
- Zhang Y, Dong N, Hong H, Qi J, Zhang S, Wang J. Mesenchymal Stem Cells: Therapeutic Mechanisms for Stroke. Int J 35 Mol Sci 2022; 23 [PMID: 35269692 DOI: 10.3390/ijms23052550]
- Gu Y, Zhang Y, Bi Y, Liu J, Tan B, Gong M, Li T, Chen J. Mesenchymal stem cells suppress neuronal apoptosis and 36 decrease IL-10 release via the TLR2/NFkB pathway in rats with hypoxic-ischemic brain damage. Mol Brain 2015; 8:65 [PMID: 26475712 DOI: 10.1186/s13041-015-0157-3]
- Willms E, Johansson HJ, Mäger I, Lee Y, Blomberg KE, Sadik M, Alaarg A, Smith CI, Lehtiö J, El Andaloussi S, Wood 37 MJ, Vader P. Cells release subpopulations of exosomes with distinct molecular and biological properties. Sci Rep 2016; 6: 22519 [PMID: 26931825 DOI: 10.1038/srep22519]
- Yang Y, Ye Y, Su X, He J, Bai W, He X. MSCs-Derived Exosomes and Neuroinflammation, Neurogenesis and Therapy 38 of Traumatic Brain Injury. Front Cell Neurosci 2017; 11: 55 [PMID: 28293177 DOI: 10.3389/fncel.2017.00055]
- Jafari D, Shajari S, Jafari R, Mardi N, Gomari H, Ganji F, Forouzandeh Moghadam M, Samadikuchaksaraei A. Designer Exosomes: A New Platform for Biotechnology Therapeutics. BioDrugs 2020; 34: 567-586 [PMID: 32754790 DOI: 10.1007/s40259-020-00434-x
- Kawabori M, Shichinohe H, Kuroda S, Houkin K. Clinical Trials of Stem Cell Therapy for Cerebral Ischemic Stroke. Int 40 J Mol Sci 2020; 21 [PMID: 33036265 DOI: 10.3390/ijms21197380]
- Deng Y, Chen D, Gao F, Lv H, Zhang G, Sun X, Liu L, Mo D, Ma N, Song L, Huo X, Yan T, Zhang J, Miao Z. Exosomes 41 derived from microRNA-138-5p-overexpressing bone marrow-derived mesenchymal stem cells confer neuroprotection to astrocytes following ischemic stroke via inhibition of LCN2. J Biol Eng 2019; 13: 71 [PMID: 31485266 DOI: 10.1186/s13036-019-0193-0
- Rahmani A, Saleki K, Javanmehr N, Khodaparast J, Saadat P, Nouri HR. Mesenchymal stem cell-derived extracellular 42 vesicle-based therapies protect against coupled degeneration of the central nervous and vascular systems in stroke. Ageing Res Rev 2020; 62: 101106 [PMID: 32565329 DOI: 10.1016/j.arr.2020.101106]
- Chen TS, Lai RC, Lee MM, Choo AB, Lee CN, Lim SK. Mesenchymal stem cell secretes microparticles enriched in pre-43 microRNAs. Nucleic Acids Res 2010; 38: 215-224 [PMID: 19850715 DOI: 10.1093/nar/gkp857]
- Alexander M, Hu R, Runtsch MC, Kagele DA, Mosbruger TL, Tolmachova T, Seabra MC, Round JL, Ward DM, 44 O'Connell RM. Exosome-delivered microRNAs modulate the inflammatory response to endotoxin. Nat Commun 2015; 6: 7321 [PMID: 26084661 DOI: 10.1038/ncomms8321]
- Chen J, Chopp M. Exosome Therapy for Stroke. Stroke 2018; 49: 1083-1090 [PMID: 29669873 DOI: 45 10.1161/STROKEAHA.117.018292]
- Choi DS, Kim DK, Kim YK, Gho YS. Proteomics of extracellular vesicles: Exosomes and ectosomes. Mass Spectrom Rev 46 2015; 34: 474-490 [PMID: 24421117 DOI: 10.1002/mas.21420]
- 47 Xu R, Bai Y, Min S, Xu X, Tang T, Ju S. In vivo Monitoring and Assessment of Exogenous Mesenchymal Stem Cell-



Derived Exosomes in Mice with Ischemic Stroke by Molecular Imaging. Int J Nanomedicine 2020; 15: 9011-9023 [PMID: 33235449 DOI: 10.2147/IJN.S271519]

- Matsumoto J, Stewart T, Sheng L, Li N, Bullock K, Song N, Shi M, Banks WA, Zhang J. Transmission of α-synuclein-48 containing erythrocyte-derived extracellular vesicles across the blood-brain barrier via adsorptive mediated transcytosis: another mechanism for initiation and progression of Parkinson's disease? Acta Neuropathol Commun 2017; 5: 71 [PMID: 28903781 DOI: 10.1186/s40478-017-0470-4]
- Xiong Y, Mahmood A, Chopp M. Emerging potential of exosomes for treatment of traumatic brain injury. Neural Regen 49 Res 2017; 12: 19-22 [PMID: 28250732 DOI: 10.4103/1673-5374.198966]
- Liu W, Bai X, Zhang A, Huang J, Xu S, Zhang J. Role of Exosomes in Central Nervous System Diseases. Front Mol 50 Neurosci 2019; 12: 240 [PMID: 31636538 DOI: 10.3389/fnmol.2019.00240]
- Xu Y, Hu Y, Xu S, Liu F, Gao Y. Exosomal microRNAs as Potential Biomarkers and Therapeutic Agents for Acute 51 Ischemic Stroke: New Expectations. Front Neurol 2021; 12: 747380 [PMID: 35173663 DOI: 10.3389/fneur.2021.747380]
- Otero-Ortega L, Laso-García F, Gómez-de Frutos MD, Rodríguez-Frutos B, Pascual-Guerra J, Fuentes B, Díez-Tejedor 52 E, Gutiérrez-Fernández M. White Matter Repair After Extracellular Vesicles Administration in an Experimental Animal Model of Subcortical Stroke. Sci Rep 2017; 7: 44433 [PMID: 28300134 DOI: 10.1038/srep44433]
- Wang J, Chen S, Zhang W, Chen Y, Bihl JC. Exosomes from miRNA-126-modified endothelial progenitor cells alleviate 53 brain injury and promote functional recovery after stroke. CNS Neurosci Ther 2020; 26: 1255-1265 [PMID: 33009888 DOI: 10.1111/cns.13455]
- Vasudeva K, Munshi A. miRNA dysregulation in ischaemic stroke: Focus on diagnosis, prognosis, therapeutic and 54 protective biomarkers. Eur J Neurosci 2020; 52: 3610-3627 [PMID: 32022336 DOI: 10.1111/ejn.14695]
- Ghoreishy A, Khosravi A, Ghaemmaghami A. Exosomal microRNA and stroke: A review. J Cell Biochem 2019; 120: 55 16352-16361 [PMID: 31219202 DOI: 10.1002/jcb.29130]
- Cai G, Cai G, Zhou H, Zhuang Z, Liu K, Pei S, Wang Y, Wang H, Wang X, Xu S, Cui C, Sun M, Guo S, Jia K, Zhang D. 56 Mesenchymal stem cell-derived exosome miR-542-3p suppresses inflammation and prevents cerebral infarction. Stem Cell *Res Ther* 2021; **12**: 2 [PMID: 33407827 DOI: 10.1186/s13287-020-02030-w]
- Zhang Z, Zou X, Zhang R, Xie Y, Feng Z, Li F, Han J, Sun H, Ouyang Q, Hua S, Lv B, Hua T, Liu Z, Cai Y, Zou Y, 57 Tang Y, Jiang X. Human umbilical cord mesenchymal stem cell-derived exosomal miR-146a-5p reduces microglialmediated neuroinflammation via suppression of the IRAK1/TRAF6 signaling pathway after ischemic stroke. Aging (Albany NY) 2021; 13: 3060-3079 [PMID: 33479185 DOI: 10.18632/aging.202466]
- Zhao Y, Gan Y, Xu G, Hua K, Liu D. Exosomes from MSCs overexpressing microRNA-223-3p attenuate cerebral 58 ischemia through inhibiting microglial M1 polarization mediated inflammation. Life Sci 2020; 260: 118403 [PMID: 32926923 DOI: 10.1016/j.lfs.2020.118403]
- Zhao Y, Gan Y, Xu G, Yin G, Liu D. MSCs-Derived Exosomes Attenuate Acute Brain Injury and Inhibit Microglial 59 Inflammation by Reversing CysLT2R-ERK1/2 Mediated Microglia M1 Polarization. Neurochem Res 2020; 45: 1180-1190 [PMID: 32112178 DOI: 10.1007/s11064-020-02998-0]
- 60 Li C, Fei K, Tian F, Gao C, Yang S. Adipose-derived mesenchymal stem cells attenuate ischemic brain injuries in rats by modulating miR-21-3p/MAT2B signaling transduction. Croat Med J 2019; 60: 439-448 [PMID: 31686458 DOI: 10.3325/cmj.2019.60.439]
- 61 Li G, Xiao L, Qin H, Zhuang Q, Zhang W, Liu L, Di C, Zhang Y. Exosomes-carried microRNA-26b-5p regulates microglia M1 polarization after cerebral ischemia/reperfusion. Cell Cycle 2020; 19: 1022-1035 [PMID: 32208888 DOI: 10.1080/15384101.2020.1743912
- Li X, Bi T, Yang S. Exosomal microRNA-150-5p from bone marrow mesenchymal stromal cells mitigates cerebral 62 ischemia/reperfusion injury via targeting toll-like receptor 5. Bioengineered 2022; 13: 3030-3043 [PMID: 34898357 DOI: 10.1080/21655979.2021.2012402
- Jiang M, Wang H, Jin M, Yang X, Ji H, Jiang Y, Zhang H, Wu F, Wu G, Lai X, Cai L, Hu R, Xu L, Li L. Exosomes from 63 MiR-30d-5p-ADSCs Reverse Acute Ischemic Stroke-Induced, Autophagy-Mediated Brain Injury by Promoting M2 Microglial/Macrophage Polarization. Cell Physiol Biochem 2018; 47: 864-878 [PMID: 29807362 DOI: 10.1159/000490078
- Barnabei L, Laplantine E, Mbongo W, Rieux-Laucat F, Weil R. NF-KB: At the Borders of Autoimmunity and 64 Inflammation. Front Immunol 2021; 12: 716469 [PMID: 34434197 DOI: 10.3389/fimmu.2021.716469]
- Han M, Cao Y, Xue H, Chu X, Li T, Xin D, Yuan L, Ke H, Li G, Wang Z. Neuroprotective Effect of Mesenchymal 65 Stromal Cell-Derived Extracellular Vesicles Against Cerebral Ischemia-Reperfusion-Induced Neural Functional Injury: A Pivotal Role for AMPK and JAK2/STAT3/NF-κB Signaling Pathway Modulation. Drug Des Devel Ther 2020; 14: 2865-2876 [PMID: 32764885 DOI: 10.2147/DDDT.S248892]
- 66 Liu T, Zhang L, Joo D, Sun SC. NF-KB signaling in inflammation. Signal Transduct Target Ther 2017; 2: 17023-17023 [PMID: 29158945 DOI: 10.1038/sigtrans.2017.23]
- Fann DY, Lim YA, Cheng YL, Lok KZ, Chunduri P, Baik SH, Drummond GR, Dheen ST, Sobey CG, Jo DG, Chen CL, 67 Arumugam TV. Evidence that NF-KB and MAPK Signaling Promotes NLRP Inflammasome Activation in Neurons Following Ischemic Stroke. Mol Neurobiol 2018; 55: 1082-1096 [PMID: 28092085 DOI: 10.1007/s12035-017-0394-9]
- Haupt M, Zheng X, Kuang Y, Lieschke S, Janssen L, Bosche B, Jin F, Hein K, Kilic E, Venkataramani V, Hermann DM, 68 Bähr M, Doeppner TR. Lithium modulates miR-1906 levels of mesenchymal stem cell-derived extracellular vesicles contributing to poststroke neuroprotection by toll-like receptor 4 regulation. Stem Cells Transl Med 2021; 10: 357-373 [PMID: 33146943 DOI: 10.1002/sctm.20-0086]
- 69 Zilahi E, Tarr T, Papp G, Griger Z, Sipka S, Zeher M. Increased microRNA-146a/b, TRAF6 gene and decreased IRAK1 gene expressions in the peripheral mononuclear cells of patients with Sjögren's syndrome. Immunol Lett 2012; 141: 165-168 [PMID: 22033216 DOI: 10.1016/j.imlet.2011.09.006]
- Harari OA, Liao JK. NF-κB and innate immunity in ischemic stroke. Ann N Y Acad Sci 2010; 1207: 32-40 [PMID: 70 20955423 DOI: 10.1111/j.1749-6632.2010.05735.x]
- Vidale S, Consoli A, Arnaboldi M, Consoli D. Postischemic Inflammation in Acute Stroke. J Clin Neurol 2017; 13: 1-9 71



[PMID: 28079313 DOI: 10.3988/jcn.2017.13.1.1]

- Gong Z, Pan J, Shen Q, Li M, Peng Y. Mitochondrial dysfunction induces NLRP3 inflammasome activation during 72 cerebral ischemia/reperfusion injury. J Neuroinflammation 2018; 15: 242 [PMID: 30153825 DOI: 10.1186/s12974-018-1282-6
- Alfonso-Loeches S, Ureña-Peralta JR, Morillo-Bargues MJ, Oliver-De La Cruz J, Guerri C. Role of mitochondria ROS 73 generation in ethanol-induced NLRP3 inflammasome activation and cell death in astroglial cells. Front Cell Neurosci 2014; 8: 216 [PMID: 25136295 DOI: 10.3389/fncel.2014.00216]
- Liu X, Zhang M, Liu H, Zhu R, He H, Zhou Y, Zhang Y, Li C, Liang D, Zeng Q, Huang G. Bone marrow mesenchymal 74 stem cell-derived exosomes attenuate cerebral ischemia-reperfusion injury-induced neuroinflammation and pyroptosis by modulating microglia M1/M2 phenotypes. Exp Neurol 2021; 341: 113700 [PMID: 33741350 DOI: 10.1016/j.expneurol.2021.113700]
- Sarmah D, Datta A, Kaur H, Kalia K, Borah A, Rodriguez AM, Yavagal DR, Bhattacharya P. Sirtuin-1 Mediated NF-KB 75 Pathway Modulation to Mitigate Inflammasome Signaling and Cellular Apoptosis is One of the Neuroprotective Effects of Intra-arterial Mesenchymal Stem Cell Therapy Following Ischemic Stroke. Stem Cell Rev Rep 2022; 18: 821-838 [PMID: 35112234 DOI: 10.1007/s12015-021-10315-7]
- Kane AE, Sinclair DA. Sirtuins and NAD(+) in the Development and Treatment of Metabolic and Cardiovascular 76 Diseases. Circ Res 2018; 123: 868-885 [PMID: 30355082 DOI: 10.1161/CIRCRESAHA.118.312498]
- Li B, Wang Z, Yu M, Wang X, Chen C, Zhang Z, Zhang M, Sun C, Zhao C, Li Q, Wang W, Wang T, Zhang L, Ning G, 77 Feng S. miR-22-3p enhances the intrinsic regenerative abilities of primary sensory neurons via the CBL/p-EGFR/p-STAT3/GAP43/p-GAP43 axis. J Cell Physiol 2020; 235: 4605-4617 [PMID: 31663116 DOI: 10.1002/jcp.29338]
- Liang X, Liu Y, Jia S, Xu X, Dong M, Wei Y. SIRT1: The Value of Functional Outcome, Stroke-Related Dementia, 78 Anxiety, and Depression in Patients with Acute Ischemic Stroke. J Stroke Cerebrovasc Dis 2019; 28: 205-212 [PMID: 30361109 DOI: 10.1016/j.jstrokecerebrovasdis.2018.09.037]
- Sasaki F, Yokomizo T. The leukotriene receptors as therapeutic targets of inflammatory diseases. Int Immunol 2019; 31: 79 607-615 [PMID: 31135881 DOI: 10.1093/intimm/dxz044]
- 80 Wang Y, Yang Y, Zhang S, Li C, Zhang L. Modulation of neuroinflammation by cysteinyl leukotriene 1 and 2 receptors: implications for cerebral ischemia and neurodegenerative diseases. Neurobiol Aging 2020; 87: 1-10 [PMID: 31986345 DOI: 10.1016/j.neurobiolaging.2019.12.013]
- Iadecola C, Anrather J. The immunology of stroke: from mechanisms to translation. Nat Med 2011; 17: 796-808 [PMID: 81 21738161 DOI: 10.1038/nm.2399]
- Yang H, Ara AI, Magilnick N, Xia M, Ramani K, Chen H, Lee TD, Mato JM, Lu SC. Expression pattern, regulation, and 82 functions of methionine adenosyltransferase 2beta splicing variants in hepatoma cells. Gastroenterology 2008; 134: 281-291 [PMID: 18045590 DOI: 10.1053/j.gastro.2007.10.027]
- Ge X, Li W, Huang S, Yin Z, Yang M, Han Z, Chen F, Wang H, Lei P, Zhang J. Increased miR-21-3p in Injured Brain 83 Microvascular Endothelial Cells after Traumatic Brain Injury Aggravates Blood-Brain Barrier Damage by Promoting Cellular Apoptosis and Inflammation through Targeting MAT2B. J Neurotrauma 2019; 36: 1291-1305 [PMID: 29695199 DOI: 10.1089/neu.2018.5728]
- Paschon V. Takada SH, Ikebara JM, Sousa E, Raeisossadati R, Ulrich H, Kihara AH, Interplay Between Exosomes, 84 microRNAs and Toll-Like Receptors in Brain Disorders. Mol Neurobiol 2016; 53: 2016-2028 [PMID: 25862375 DOI: 10.1007/s12035-015-9142-1
- 85 Vaure C, Liu Y. A comparative review of toll-like receptor 4 expression and functionality in different animal species. Front Immunol 2014; 5: 316 [PMID: 25071777 DOI: 10.3389/fimmu.2014.00316]
- Lester SN, Li K. Toll-like receptors in antiviral innate immunity. J Mol Biol 2014; 426: 1246-1264 [PMID: 24316048 86 DOI: 10.1016/j.jmb.2013.11.024]
- Zhang XS, Li W, Wu Q, Wu LY, Ye ZN, Liu JP, Zhuang Z, Zhou ML, Zhang X, Hang CH. Resveratrol Attenuates Acute 87 Inflammatory Injury in Experimental Subarachnoid Hemorrhage in Rats via Inhibition of TLR4 Pathway. Int J Mol Sci 2016; 17 [PMID: 27529233 DOI: 10.3390/ijms17081331]
- Chaurasiya V, Kumari S, Onteru SK, Singh D. Up-regulation of miR-326 regulates pro-inflammatory cytokines targeting 88 TLR-4 in buffalo granulosa cells. Mol Immunol 2020; 119: 154-158 [PMID: 32035362 DOI: 10.1016/j.molimm.2020.01.019]
- 89 Qiao H, Zhang X, Zhu C, Dong L, Wang L, Xing Y, Wang C, Ji Y, Cao X. Luteolin downregulates TLR4, TLR5, NF-κB and p-p38MAPK expression, upregulates the p-ERK expression, and protects rat brains against focal ischemia. Brain Res 2012; 1448: 71-81 [PMID: 22377454 DOI: 10.1016/j.brainres.2012.02.003]
- Gu L, Huang J, Tan J, Wei Q, Jiang H, Shen T, Liang B, Tang N. Impact of TLR5 rs5744174 on stroke risk, gene 90 expression and on inflammatory cytokines, and lipid levels in stroke patients. Neurol Sci 2016; 37: 1537-1544 [PMID: 27262705 DOI: 10.1007/s10072-016-2607-9]
- Dabrowska S, Andrzejewska A, Strzemecki D, Muraca M, Janowski M, Lukomska B. Human bone marrow mesenchymal stem cell-derived extracellular vesicles attenuate neuroinflammation evoked by focal brain injury in rats. J Neuroinflammation 2019; 16: 216 [PMID: 31722731 DOI: 10.1186/s12974-019-1602-5]
- Zhang L, Yu D. Exosomes in cancer development, metastasis, and immunity. Biochim Biophys Acta Rev Cancer 2019; 92 1871: 455-468 [PMID: 31047959 DOI: 10.1016/j.bbcan.2019.04.004]
- 93 Jiang CT, Wu WF, Deng YH, Ge JW. Modulators of microglia activation and polarization in ischemic stroke (Review). Mol Med Rep 2020; 21: 2006-2018 [PMID: 32323760 DOI: 10.3892/mmr.2020.11003]
- 94 Yang H, Tu Z, Yang D, Hu M, Zhou L, Li Q, Yu B, Hou S. Exosomes from hypoxic pre-treated ADSCs attenuate acute ischemic stroke-induced brain injury via delivery of circ-Rps5 and promote M2 microglia/macrophage polarization. Neurosci Lett 2022; 769: 136389 [PMID: 34896256 DOI: 10.1016/j.neulet.2021.136389]
- Wang J, Xing H, Wan L, Jiang X, Wang C, Wu Y. Treatment targets for M2 microglia polarization in ischemic stroke. 95 Biomed Pharmacother 2018; 105: 518-525 [PMID: 29883947 DOI: 10.1016/j.biopha.2018.05.143]
- Hu X, Li P, Guo Y, Wang H, Leak RK, Chen S, Gao Y, Chen J. Microglia/macrophage polarization dynamics reveal novel 96



mechanism of injury expansion after focal cerebral ischemia. Stroke 2012; 43: 3063-3070 [PMID: 22933588 DOI: 10.1161/STROKEAHA.112.659656]

- Huang S, Ge X, Yu J, Han Z, Yin Z, Li Y, Chen F, Wang H, Zhang J, Lei P. Increased miR-124-3p in microglial exosomes following traumatic brain injury inhibits neuronal inflammation and contributes to neurite outgrowth via their transfer into neurons. FASEB J 2018; 32: 512-528 [PMID: 28935818 DOI: 10.1096/fj.201700673R]
- Domenis R, Cifù A, Quaglia S, Pistis C, Moretti M, Vicario A, Parodi PC, Fabris M, Niazi KR, Soon-Shiong P, Curcio F. 98 Pro inflammatory stimuli enhance the immunosuppressive functions of adipose mesenchymal stem cells-derived exosomes. Sci Rep 2018; 8: 13325 [PMID: 30190615 DOI: 10.1038/s41598-018-31707-9]
- Duan S, Wang F, Cao J, Wang C. Exosomes Derived from MicroRNA-146a-5p-Enriched Bone Marrow Mesenchymal 99 Stem Cells Alleviate Intracerebral Hemorrhage by Inhibiting Neuronal Apoptosis and Microglial M1 Polarization. Drug Des Devel Ther 2020; 14: 3143-3158 [PMID: 32821084 DOI: 10.2147/DDDT.S255828]
- 100 Liu W, Rong Y, Wang J, Zhou Z, Ge X, Ji C, Jiang D, Gong F, Li L, Chen J, Zhao S, Kong F, Gu C, Fan J, Cai W. Exosome-shuttled miR-216a-5p from hypoxic preconditioned mesenchymal stem cells repair traumatic spinal cord injury by shifting microglial M1/M2 polarization. J Neuroinflammation 2020; 17: 47 [PMID: 32019561 DOI: 10.1186/s12974-020-1726-7]
- 101 Zha Z, Gao YF, Ji J, Sun YQ, Li JL, Qi F, Zhang N, Jin LY, Xue B, Yang T, Fan YP, Zhao H, Wang L. Bu Shen Yi Sui Capsule Alleviates Neuroinflammation and Demyelination by Promoting Microglia toward M2 Polarization, Which Correlates with Changes in miR-124 and miR-155 in Experimental Autoimmune Encephalomyelitis. Oxid Med Cell Longev 2021; 2021: 5521503 [PMID: 33815654 DOI: 10.1155/2021/5521503]
- Yang J, Chen Y, Jiang K, Zhao G, Guo S, Liu J, Yang Y, Deng G. MicroRNA-182 supplies negative feedback regulation 102 to ameliorate lipopolysaccharide-induced ALI in mice by targeting TLR4. J Cell Physiol 2020; 235: 5925-5937 [PMID: 32003008 DOI: 10.1002/jcp.29504]
- 103 Li Y, Guo W, Cai Y. NEAT1 Promotes LPS-induced Inflammatory Injury in Macrophages by Regulating MiR-17-5p/ TLR4. Open Med (Wars) 2020; 15: 38-49 [PMID: 32099901 DOI: 10.1515/med-2020-0007]
- 104 Zhang Q, Bian G, Chen P, Liu L, Yu C, Liu F, Xue Q, Chung SK, Song B, Ju G, Wang J. Aldose Reductase Regulates Microglia/Macrophages Polarization Through the cAMP Response Element-Binding Protein After Spinal Cord Injury in Mice. Mol Neurobiol 2016; 53: 662-676 [PMID: 25520004 DOI: 10.1007/s12035-014-9035-8]
- Lin L, Yihao T, Zhou F, Yin N, Qiang T, Haowen Z, Qianwei C, Jun T, Yuan Z, Gang Z, Hua F, Yunfeng Y, Zhi C. 105 Inflammatory Regulation by Driving Microglial M2 Polarization: Neuroprotective Effects of Cannabinoid Receptor-2 Activation in Intracerebral Hemorrhage. Front Immunol 2017; 8: 112 [PMID: 28261199 DOI: 10.3389/fimmu.2017.00112]
- 106 Zhang Y, Xu N, Ding Y, Zhang Y, Li Q, Flores J, Haghighiabyaneh M, Doycheva D, Tang J, Zhang JH. Chemerin suppresses neuroinflammation and improves neurological recovery via CaMKK2/AMPK/Nrf2 pathway after germinal matrix hemorrhage in neonatal rats. Brain Behav Immun 2018; 70: 179-193 [PMID: 29499303 DOI: 10.1016/j.bbi.2018.02.015
- 107 Coulibaly AP, Provencio JJ. Aneurysmal Subarachnoid Hemorrhage: an Overview of Inflammation-Induced Cellular Changes. Neurotherapeutics 2020; 17: 436-445 [PMID: 31907877 DOI: 10.1007/s13311-019-00829-x]
- Wang M, Thomson AW, Yu F, Hazra R, Junagade A, Hu X. Regulatory T lymphocytes as a therapy for ischemic stroke. 108 Semin Immunopathol 2022 [PMID: 36469056 DOI: 10.1007/s00281-022-00975-z]
- Ruhnau J, Schulze J, von Sarnowski B, Heinrich M, Langner S, Pötschke C, Wilden A, Kessler C, Bröker BM, 109 Vogelgesang A, Dressel A. Reduced Numbers and Impaired Function of Regulatory T Cells in Peripheral Blood of Ischemic Stroke Patients. Mediators Inflamm 2016; 2016: 2974605 [PMID: 27073295 DOI: 10.1155/2016/2974605]
- Hu Y, Zheng Y, Wu Y, Ni B, Shi S. Imbalance between IL-17A-producing cells and regulatory T cells during ischemic 110 stroke. Mediators Inflamm 2014; 2014: 813045 [PMID: 24991091 DOI: 10.1155/2014/813045]
- Zhu D, Johnson TK, Wang Y, Thomas M, Huynh K, Yang Q, Bond VC, Chen YE, Liu D. Macrophage M2 polarization 111 induced by exosomes from adipose-derived stem cells contributes to the exosomal proangiogenic effect on mouse ischemic hindlimb. Stem Cell Res Ther 2020; 11: 162 [PMID: 32321589 DOI: 10.1186/s13287-020-01669-9]
- Okoye IS, Coomes SM, Pelly VS, Czieso S, Papayannopoulos V, Tolmachova T, Seabra MC, Wilson MS. MicroRNA-112 containing T-regulatory-cell-derived exosomes suppress pathogenic T helper 1 cells. Immunity 2014; 41: 89-103 [PMID: 25035954 DOI: 10.1016/j.immuni.2014.05.019]
- Blazquez R, Sanchez-Margallo FM, de la Rosa O, Dalemans W, Alvarez V, Tarazona R, Casado JG. Immunomodulatory 113 Potential of Human Adipose Mesenchymal Stem Cells Derived Exosomes on in vitro Stimulated T Cells. Front Immunol 2014; 5: 556 [PMID: 25414703 DOI: 10.3389/fimmu.2014.00556]
- 114 Zhang B, Yin Y, Lai RC, Tan SS, Choo AB, Lim SK. Mesenchymal stem cells secrete immunologically active exosomes. Stem Cells Dev 2014; 23: 1233-1244 [PMID: 24367916 DOI: 10.1089/scd.2013.0479]
- Bian S, Zhang L, Duan L, Wang X, Min Y, Yu H. Extracellular vesicles derived from human bone marrow mesenchymal 115 stem cells promote angiogenesis in a rat myocardial infarction model. J Mol Med (Berl) 2014; 92: 387-397 [PMID: 24337504 DOI: 10.1007/s00109-013-1110-5]
- Wang C, Börger V, Mohamud Yusuf A, Tertel T, Stambouli O, Murke F, Freund N, Kleinschnitz C, Herz J, Gunzer M, 116 Popa-Wagner A, Doeppner TR, Giebel B, Hermann DM. Postischemic Neuroprotection Associated With Anti-Inflammatory Effects by Mesenchymal Stromal Cell-Derived Small Extracellular Vesicles in Aged Mice. Stroke 2022; 53: e14-e18 [PMID: 34847707 DOI: 10.1161/STROKEAHA.121.035821]
- 117 Bellon M, Lepelletier Y, Hermine O, Nicot C. Deregulation of microRNA involved in hematopoiesis and the immune response in HTLV-I adult T-cell leukemia. Blood 2009; 113: 4914-4917 [PMID: 19246560 DOI: 10.1182/blood-2008-11-189845]
- Zhang M, Johnson-Stephenson TK, Wang W, Wang Y, Li J, Li L, Zen K, Chen X, Zhu D. Mesenchymal stem cell-118 derived exosome-educated macrophages alleviate systemic lupus erythematosus by promoting efferocytosis and recruitment of IL-17(+) regulatory T cell. Stem Cell Res Ther 2022; 13: 484 [PMID: 36153633 DOI: 10.1186/s13287-022-03174-7



119 Chen J, Jin J, Li K, Shi L, Wen X, Fang F. Progresses and Prospects of Neuroprotective Agents-Loaded Nanoparticles and Biomimetic Material in Ischemic Stroke. Front Cell Neurosci 2022; 16: 868323 [PMID: 35480961 DOI: 10.3389/fncel.2022.868323]





# Published by Baishideng Publishing Group Inc 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA Telephone: +1-925-3991568 E-mail: bpgoffice@wjgnet.com Help Desk: https://www.f6publishing.com/helpdesk https://www.wjgnet.com

