Review paper

Folia Neuropathologica

Cerebral ischemia reperfusion injury: from public health perspectives to mechanisms

Gulnara Kapanova[1,2], Gulnara Tashenova[3,4], Aida Akhenbekova[3], Adem Tokpınar[5], Seher Yılmaz[5]

[1]Al-Farabi Kazakh National University, Almaty 050040, Kazakhstan, [2]Scientific Center of Anti-Infectious Drugs, Almaty 050040, Kazakhstan, [3]Asfendiyarov Kazakh National Medical University, Almaty 050040, Kazakhstan, [4]JCS "Scientific Center of Pediatrics and Children Surgery", Kazakhstan, [5]Department of Anatomy, Faculty of Medicine, Yozgat Bozok University, Yozgat, Turkey

Folia Neuropathol 2022; 60 (4): 384-389 *DOI: https://doi.org/10.5114/fn.2022.120101*

Abstract

Cerebral ischemia/reperfusion injury has emerged as an intricate mechanism. However, identification of wide-ranging mechanisms which mechanistically regulate reperfusion injuries have significantly improved our understanding. Recent advancements in our knowledge about the molecular consequences of ischemia and reperfusion might be advantageous in the development of innovative therapeutic strategies for the treatment of patients with ischemia and reperfusion-associated organ dysfunction and tissue inflammation. Some of the extensively studied mechanisms of reperfusion injury consist of oxidative stress, mitochondrial mechanisms, infiltration of leukocytes, activation/aggregation of the platelets, complement activation, and disruption of the blood-brain-barrier (BBB), which eventually results in the brain oedema or haemorrhagic transformations. In this review, we have attempted to provide a review of the protein networks involved in the regulation of cerebral ischemia reperfusion injury and how different natural products have shown potential in the amelioration of reperfusion induced injuries.

Key words: *mTOR, PI3K/AKT, cerebral ischemia, stroke.*

Introduction

Stroke, including haemorrhagic stroke and ischemic stroke, is an important cause of death worldwide. Cerebral ischemia may be clinically viewed as a major type of stroke. Restoration of blood supply is termed as "reperfusion" and has attracted widespread appreciation and remains an overarching goal for the treatment of acute stroke. Intravenously administered recombinant tissue plasminogen activator (r-tPA) is an Food and Drug Administration (FDA)-approved thrombolytic therapy for the treatment of acute ischemic stroke. Ever since the approval of intravenous administration of r-tPA for treatment of acute stroke, undesired and off-target effects of rapid reperfusion on brain functionality have been reported in different scientific reports. Additionally, underlying mechanisms of reperfusion injury are being unveiled by emerging experimental and clinical findings, part of which are gained from ischemia-reperfusion injuries in the liver and heart. Some of the extensively studied mechanisms of reperfusion injury consist of oxidative stress, mitochondrial mechanisms, infiltration of leukocytes, activation/aggregation of the platelets, complement activation, and disruption of the blood-brain-barrier (BBB), which eventually results in the brain oedema or haemorrhagic transformations. These damages ultimately cause significant neuronal death and neurological dysfunctions.

Recent advancements in our knowledge about the molecular consequences of ischemia and reperfusion might be advantageous in the development of innovative therapeutic strategies for the treatment of patients with ischemia and reperfusion-associated organ dysfunction and tissue inflammation [15,16,43].

Communicating author:
Dr. Seher Yılmaz, Department of Anatomy, Faculty of Medicine, Yozgat Bozok University, Yozgat, Turkey, e-mail: sehery38@hotmail.com

There are some good reviews which have comprehensively analysed different mechanisms which play a critical role in the pathogenesis of cerebral ischemia/reperfusion injury [3,26,28,29,31,37,46]. In this review, we have summarized pioneering research works which greatly enhanced our understanding about underlying causes of cerebral ischemia/reperfusion injury.

Involvement of mTORC1 in cerebral ischemia/reperfusion injuries

Zinc and ring finger 2 (ZNRF2) is an E3 ubiquitin ligase reportedly involved in different pathologies [14]. Overexpression of ZNRF2 considerably reduced the neurological deficits, brain infarct volume and histopathological damages of cortex in the MCAO model. ZNRF2 overexpression decreased the neuronal apoptotic death induced by OGD/R. ZNRF2 overexpression inhibited the hyperactivation of autophagy induced by OGD/R which was abolished by rapamycin (mTORC1 inhibitor) [14].

Autophagy played an essential role in different pathological conditions. Autophagy induced apoptotic cell death, whereas inhibition of autophagy not only enhanced the neuronal survival rate, but also provided protection against ischemic injuries. Pioneering research works have shown that mTOR centrally regulates initiation and termination of control of autophagy. Reactivation of mTOR caused blockade of autophagic flux in the primary cortical neurons exposed to OGD/R [17]. Likewise, inhibition of autophagic flux has also been reported in neurons of ischemia-reperfusion animal models. Furthermore, ischemia-reperfusion injury triggered phosphorylation of mTOR at Serine-2448 and Serine-2481 in the cortical neurons of MCAO mice. mTOR forms discrete complexes which transduce the signals to the downstream effectors. In the past decades, cutting-edge structural studies have shed substantial light on the catalysis and assembly of mTORC1. Comprehensive investigation of structural components of mTORC1 in the presence of its substrates and regulators have enabled the researchers to gain detailed insights into the mechanism and functions of mTORC1. S6K1 is a downstream substrate of mTORC1. Importantly, mTORC1 phosphorylated S6K1 at threonine-389 and further activated ribosomal protein S6. mTORC1 inhibitors caused reversal of increased phosphorylated levels of S6K1 in OGD/R exposed neurons. Reactivated mTORC1 suppressed the transcriptional levels of autophagy-related genes. Collectively, these findings suggested that mTOR played a pivotal role in the negative regulation of autophagy at transcriptional and post-translational levels in the neurons [17].

ZSTK474 treatment reduced the levels of phosphorylated AKT [35]. ZSTK474 markedly reduced the phosphorylated levels of p70S6k at threonine-389. Because of reperfusion, the resultant restoration of blood flow not only triggered the activation of microglia/macrophages as well as severely harmful effects exerted by pro-inflammatory cytokines. Microglia/macrophages transformed to a dangerous version in the absence of ZSTK474 but shifted from the lethal version to a restorative state after treatment with ZSTK474 in the MCAO rodent model. ZSTK474 effectively minimized neurological defects, prevented histopathological changes and reduced infarct volume [35].

In the upcoming section, we will briefly summarize recently available evidence related to the role of non-coding RNAs in cerebral ischemia/reperfusion injury.

Regulatory role of long non-coding RNAs and circular RNAs

Discovery of non-coding RNAs has splendidly transformed the field of molecular oncology. High-throughput technologies have enabled researchers to characterize different types of non-coding RNAs. Accordingly, microRNAs (miRNAs) [7-9,11,13,25,32,36], long non-coding RNAs (LncRNAs) [1,21], circular RNAs (CircRNAs) have been reported to play an instrumental role in development and pathologies.

Long non-coding RNAs

Levels of miR-200a-3p were noted to be reduced upon I/R injury. However, there was an evident increase in the levels of NLRP3 and TET2 [41]. TUG1 knockdown alleviated OGD/R-mediated inflammatory responses through downregulation of NLRP3 along with different pro-inflammatory molecules. Importantly, inhibition of miR-200a-3p caused partial reversal of the effects exerted by silencing of TUG1. TUG1 interfered with miRNA-200a-3p-mediated targeting of NLRP3. TET2 knockdown resulted in low expression of TUG1 and higher expression of miR-200a-3p in SH-SY5Y and SK-N-SH cells. Importantly, there was a marked reduction in the levels of interleukin 1β, interleukin 18, NLRP3 and caspase-1 in OGD/R-induced SH-SY5Y and SK-N-SH cells upon the knockdown of TET2. On the contrary, TUG1 overexpression reversed these effects. TET2 demethylated TUG1 and contributed to the inflammatory responses. It was found that TET2 knockdown reduced I/R-mediated inflammatory responses and injuries of the brain in the MCAO mice model mainly through downregulation of TUG1 and upregulation of miRNA-200a-3p to inhibit NLRP3 [41].

Upregulation of FOXD3-AS1 and downregulation of miR-765 were reported after cerebral ischemia/reperfusion within the brain tissues [24]. Moreover, miR-765 overexpression reduced apoptotic death of N2a cells caused by OGD/R. microRNA-765 directly targeted BCL2L13.

In addition, FOXD3-AS1 antagonized miR-765 mediated inhibition of BCL2L13. FOXD3-AS1 overexpression interfered with the inhibitory effects of miR-765 on BCL2L13 and the apoptotic death of OGD/R-treated N2a cells, whereas FOXD3-AS1 knockdown promoted the inhibitory effects of miR-765 on BCL2L13 and the apoptotic death of OGD/R-treated N2a cells [24].

Overexpression of miR-650 reduced apoptotic death of OGD/R-treated N2a cells [2]. MiR-650 directly targeted APAF1. TALNEC2 played a pivotal role as a ceRNA for miR-650 and relieved the repressive effects of miR-650 on APAF1. TALNEC2 overexpression antagonized the repressive effects of miR-650 on APAF1 and apoptotic death of OGD/R-treated N2a cells, whereas TALNEC2 knockdown aggravated the effects. Moreover, the knockdown of TALNEC2 led to reversal of brain injuries and neurological deficits induced by I/R in a rodent model [2].

Mesenchymal stem cells (MSCs) have been shown to ameliorate ischemia/reperfusion injuries. SNHG12 inhibition led to an increase in the efficacy of MSCs in the amelioration of ischemia/reperfusion injuries [19]. MSCs markedly reduced the infarct areas as well as the rate of neuronal apoptotic death in MCAO rats. MSCs also decreased the phosphorylated levels of PI3K, AKT and mTOR proteins. Additionally, SNHG12 inhibition increased the ameliorative effects of MSCs in the treatment of brain injuries in MCAO rats [19].

H19 caused aggravation of I/R or OGD/R-driven neuronal apoptotic death and oxidative stress *via* PTEN/AKT transduction cascade [12]. H19 acted as a sponge for miR-19a-3p and inhibited PI3K/AKT pathway. miRNA-19a-3p directly targeted PTEN and promoted PI3K/AKT signalling. Importantly, knockdown of H19 and overexpression of miR-19a-3p effectively reduced I/R or OGD/R-mediated apoptotic death and oxidative stress. The H19/miRNA-19a-3p/PTEN axis played a central role in the regulation of cerebral I/R injuries through the PI3K/AKT axis [12].

Circular RNAs

Expression levels of circ-HECTD1 and TRAF3 (tumour necrosis factor receptor-associated factor 3) were noted to be upregulated, however miRNA-133b was downregulated in oxygen-glucose deprivation (OGD)-induced HT22 cells and MCAO models [5]. Knockdown of circ-HECTD1 relieved OGD-induced neuronal cell death. Moreover, knockdown of circ-HECTD1 not only ameliorated infarction volume in the cerebrum, but also inhibited neuronal apoptosis in MCAO mice. Data clearly indicated that circ-HECTD1 interfered with miR-133b-mediated targeting of TRAF3. miR-133b upregulation caused inhibition of TRAF3 in OGD-stimulated cells, while upregulation of circ-HECTD1 reversed these effects [5].

Levels of circUCK2 were reported to be reduced in brain tissues of a rodent model of focal cerebral ischemia and reperfusion [4]. However, increase in the levels of circUCK2 led to a significant reduction in the infarct

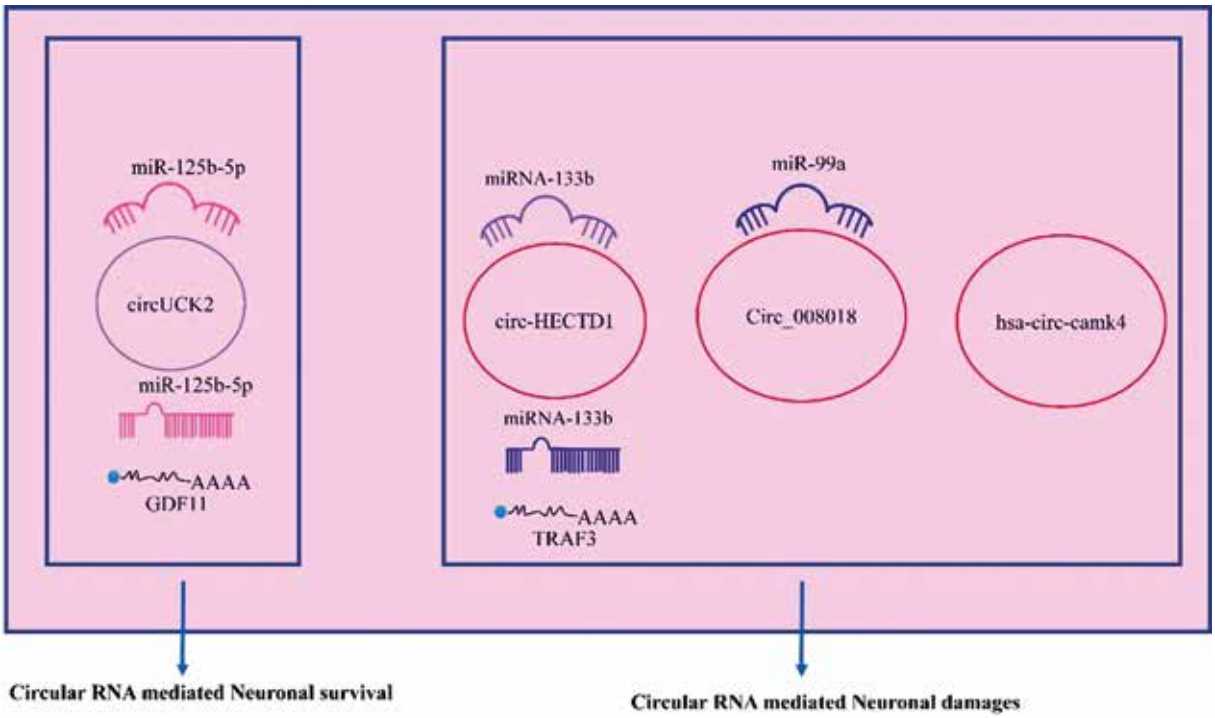

Fig. 1. Interplay between circular RNAs and miRNAs for the regulation of target genes.

volumes, markedly reduced neuronal injuries and improved neurological deficits. Importantly, circUCK2 notably reduced OGD-induced cell apoptosis by regulation of TGF-β/SMAD3 transduction. CircUCK2 antagonized miR-125b-5p mediated targeting of GDF11 (growth differentiation factor 11) and ameliorated neuronal injury [4].

Levels of hsa-circ-camk4 are upregulated in OGD/R treated-SH-SY5Y cells [44]. hsa-circ-camk4 overexpression caused a significant increase in the rate of cell death after OGD/R. These findings highlighted that circ-camk4 played a pivotal role in the progression of cerebral ischemia-reperfusion injury [44].

Circ_008018 knockdown caused reduction in cerebral I/R-induced damage to the brain tissues and neurological deficits in mice [39]. There was an evident decrease in the phosphorylated levels of AKT and GSK3β caused by I/R. However, levels of p-AKT and p-GSK3β were reversed partly by circ_008018 silencing or overexpression of miR-99a. Collectively, these findings suggested that inhibition of circ_008018 protected against neurological damages [39] (Fig. 1).

Inhibition of apoptotic cell death

Ischemia/reperfusion promoted the binding of CDC42 to MLK3 and consequent autophosphorylation of MLK3 in the hippocampal region CA1 [45]. CDC42 silencing significantly impaired the binding of CDC42 to MLK3 during reperfusion. Knockdown of CDC42 blocked ischemia/reperfusion-mediated selective activation of MLK3/MKK7/JNK3 signalling. A notable increase in the caspase-3 activity in the hippocampal region CA1 promoted apoptosis after cerebral ischemia. CDC42 silencing caused a marked reduction in the activation of caspase-3 [45].

NADPH oxidases (NOX) are the primary enzymes involved in ROS generation and responsible for ROS production in brain tissues in the rat ischemic stroke models [23]. I/R injury induced ROS generation and apoptotic death in brain tissues. I/R injury led to a significant rise in mRNA and protein levels of ALK5 and phosphorylation of SMAD2/3. Moreover, I/R injury significantly enhanced the expression and activity of NOX2 and NOX4. ROS generation was reported to be significantly reduced in ALK5-silenced PC-12 cells. Additionally, caspase-3 activity was also found to be reduced in ALK5-silenced PC-12 cells [22].

Use of natural products in the treatment of cerebral/ischemia reperfusion injuries

Natural product research has generated wealth of information about significance of pharmacologically active compounds from natural sources [10,20,27,34,38,47]. In this section we have summarized interesting research works which provided compelling evidence about the important role of natural products in amelioration of pathogenesis associated with cerebral ischemia/reperfusion injuries.

Trametenolic acid B is a lanostane-type triterpenoid. It is obtained from trametes lactinea (Berk.) Pat [33]. Trametenolic acid B significantly reduced neuronal cell loss, ameliorated cerebral oedema and suppressed cerebral infarction volume of cerebral I/R injury animal models. Trametenolic acid B efficiently downregulated cytochrome C, Bax, cleaved-caspase-9 and cleaved-caspase-3. Trametenolic acid B exhibited neuroprotective properties against ODG/R and I/R injury by activation of PI3K/AKT/mTOR signalling cascade and suppression of mitochondrial-mediated apoptosis [33].

Xiao-Xu-Ming decoction increased Bcl-2 levels and simultaneously reduced p53 and Bax levels in mitochondrial fractions [18]. Xiao-Xu-Ming decoction caused significant blockade of the mitochondrial release of SMAC/DIABLO and cytochrome c. Xiao-Xu-Ming decoction also inhibited caspase-9 and caspase-3 [18].

Gallic acid has also been shown to inhibit mitochondrial release of cytochrome c [30].

Astragaloside IV efficiently blocked ischemia reperfusion-induced neuronal apoptotic death by interfering with the activation of signalling cascades in the death receptor pathway and mitochondrial pathway [40].

Picroside II is biologically active component of Picrorhiza and effectively reduces the cerebral infarction volume and neuronal apoptosis [42].

Ligustrazine or tetramethylpyrazine (TMP) is a traditional Chinese medicine with the functions of improving the circulation of blood, expanding blood vessels and inhibitory effects on the aggregation of platelets [6]. Transient focal cerebral ischemia Wistar rat model was established through occlusion of the middle cerebral artery. Ligustrazine was intraperitoneally injected into the cerebral I/R injury rats. Ligustrazine not only improved the pathological morphology but also reduced oedema of cells [6].

Concluding remarks

In this mini-review we have presented an integrated overview of different molecular pathogenic mechanisms underlying ischemic damage in the brain, and how our highly refined knowledge of these mechanisms will pave the way for the identification of new targets for therapy.

Over the past few decades, a significant amount of attention has been given to the development of efficient pharmacological combinations that can be administered after acute ischemic insults to minimize adverse cerebral damages. Emerging results obtained

from animal stroke models are indeed encouraging. However, there is still a dire need to further dissect most critical pathways which regulate the pathogenicity of cerebral ischemia/reperfusion injury. Therefore, further investigation of the pharmacological targets of natural compounds and effects of these compounds on critical signalling cascades and disease progression require detailed research.

Disclosure

The authors report no conflict of interest.

References

1. Adylova A, Mukhanbetzhanovna AA, Attar R, Yulaevna IM, Farooqi AA. Regulation of TGFβ/SMAD signaling by long non-coding RNAs in different cancers: Dark Knight in the Castle of molecular oncology. Noncoding RNA Res 2021; 6: 23-28.
2. Cao Y, Gao W, Tang H, Wang T, You C. Long Non-coding RNA TALNEC2 aggravates cerebral ischemia/reperfusion injury via acting as a competing endogenous RNAs for miR-650 to target apoptotic peptidase activating factor 1. Neuroscience 2021; 458: 64-76.
3. Chen HS, Chen X, Li WT, Shen JG. Targeting RNS/caveolin-1/MMP signaling cascades to protect against cerebral ischemia-reperfusion injuries: potential application for drug discovery. Acta Pharmacol Sin 2018; 39: 669-682.
4. Chen W, Wang H, Feng J, Chen L. Overexpression of circRNA circUCK2 attenuates cell apoptosis in cerebral ischemia-reperfusion injury via miR-125b-5p/GDF11 signaling. Mol Ther Nucleic Acids 2020; 22: 673-683.
5. Dai Q, Ma Y, Xu Z, Zhang L, Yang H, Liu Q, Wang J. Downregulation of circular RNA HECTD1 induces neuroprotection against ischemic stroke through the microRNA-133b/TRAF3 pathway. Life Sci 2021; 264: 118626.
6. Ding Y, Du J, Cui F, Chen L, Li K. The protective effect of ligustrazine on rats with cerebral ischemia-reperfusion injury via activating PI3K/Akt pathway. Hum Exp Toxicol 2019; 38: 1168-1177.
7. Ekmekci CG, Coskunpinar E, Avci H, Farooqi AA, Orhan KS, Akbas F. Integrative analysis of mRNA and microRNA expression profiles in laryngeal squamous cell carcinoma. J Cell Biochem 2019; 120: 3415-3422.
8. Farhan M, Malik A, Ullah MF, Afaq S, Faisal M, Farooqi AA, Biersack B, Schobert R, Ahmad A. Garcinol sensitizes NSCLC cells to standard therapies by regulating EMT-modulating miRNAs. Int J Mol Sci 2019; 20: 800.
9. Farooqi AA, Fayyaz S, Shatynska-Mytsyk I, Javed Z, Jabeen S, Yaylim I, Gasparri ML, Panici PB. Is miR-34a a well-equipped swordsman to conquer temple of molecular oncology? Chem Biol Drug Des 2016; 87: 321-334.
10. Farooqi AA. Regulation of deregulated cell signaling pathways by pomegranate in different cancers: Re-interpretation of knowledge gaps. Semin Cancer Biol 2021; 73: 294-301.
11. Fayyaz S, Javed Z, Attar R, Farooqi AA, Yaylim I, Ahmad A. MicroRNA regulation of TRAIL mediated signaling in different cancers: Control of micro steering wheels during the journey from bench-top to the bedside. Semin Cancer Biol 2019; 58: 56-64.
12. Gao N, Tang H, Gao L, Tu GL, Luo H, Xia Y. LncRNA H19 aggravates cerebral ischemia/reperfusion injury by functioning as a ceRNA for miR-19a-3p to target PTEN. Neuroscience 2020; 437: 117-129.
13. Gasparri ML, Besharat ZM, Farooqi AA, Khalid S, Taghavi K, Besharat RA, Sabato C, Papadia A, Panici PB, Mueller MD, Ferretti E. MiRNAs and their interplay with PI3K/AKT/mTOR pathway in ovarian cancer cells: a potential role in platinum resistance. J Cancer Res Clin Oncol 2018; 144: 2313-2318.
14. Gu C, Yang J, Luo Y, Ran D, Tan X, Xiang P, Fei H, Lu Y, Guo W, Tu Y, Liu X, Wang H. ZNRF2 attenuates focal cerebral ischemia/reperfusion injury in rats by inhibiting mTORC1-mediated autophagy. Exp Neurol 2021; 342: 113759.
15. Hong T, Zhou Y, Peng L, Wu X, Li Y, Li Y, Zhao Y. Knocking down peroxiredoxin 6 aggravates cerebral ischemia-reperfusion injury by enhancing mitophagy. Neuroscience 2021; S0306-4522(21)00610-2.
16. Hou JB, Shen QN, Wan X, Liu XK, Yu Y, Li M, Gao WW, Zhao B. Ubiquitin-specific protease 29 exacerbates cerebral ischemia-reperfusion injury in mice. Oxid Med Cell Longev 2021; 6955628.
17. Hua R, Wei H, Liu C, Shi Z, Xing Y. Phosphorylated mTORC1 represses autophagic-related mRNA translation in neurons exposed to ischemia-reperfusion injury. J Cell Biochem 2019; 120: 15915-15923.
18. Lan R, Zhang Y, Xiang J, Zhang W, Wang GH, Li WW, Xu LL, Cai DF. Xiao-Xu-Ming decoction preserves mitochondrial integrity and reduces apoptosis after focal cerebral ischemia and reperfusion via the mitochondrial p53 pathway. J Ethnopharmacol 2014; 151: 307-316.
19. Li Y, Guo S, Liu W, Jin T, Li X, He X, Zhang X, Su H, Zhang N, Duan C. Silencing of SNHG12 enhanced the effectiveness of MSCs in alleviating ischemia/reperfusion injuries via the PI3K/AKT/mTOR signaling pathway. Front Neurosci 2019; 13: 645.
20. Lin X, Attar R, Mobeen I, Yulaevna IM, Aras A, Butt G, Farooqi AA. Regulation of cell signaling pathways by Schisandrin in different cancers: Opting for "Swiss Army Knife" instead of "Blunderbuss". Cell Mol Biol (Noisy-le-grand) 2021; 67: 25-32.
21. Liu PF, Farooqi AA, Peng SY, Yu TJ, Dahms HU, Lee CH, Tang JY, Wang SC, Shu CW, Chang HW. Regulatory effects of noncoding RNAs on the interplay of oxidative stress and autophagy in cancer malignancy and therapy. Semin Cancer Biol 2022; 83: 269-282.
22. Lou Z, Wang AP, Duan XM, Hu GH, Song GL, Zuo ML, Yang ZB. Upregulation of NOX2 and NOX4 mediated by TGF-β signaling pathway exacerbates cerebral ischemia/reperfusion oxidative stress injury. Cell Physiol Biochem 2018; 46: 2103-2113.
23. Lou Z, Wang AP, Duan XM, Hu GH, Zuo ML, Yang ZB. Role of ALK5/SMAD2/3 signaling in the regulation of NOX expression in cerebral ischemia/reperfusion injury. Exp Ther Med 2018; 16: 1671-1678.
24. Lu Y, Han Y, He J, Zhou B, Fang P, Li X. LncRNA FOXD3-AS1 knockdown protects against cerebral ischemia/reperfusion injury via miR-765/BCL2L13 axis. Biomed Pharmacother 2020; 132: 110778.
25. Mytsyk Y, Dosenko V, Borys Y, Kucher A, Gazdikova K, Busselberg D, Caprnda M, Kruzliak P, Farooqi AA, Lubov M. MicroRNA-15a expression measured in urine samples as a potential biomarker of renal cell carcinoma. Int Urol Nephrol 2018; 50: 851-859.
26. Patel AMR, Apaijai N, Chattipakorn N, Chattipakorn SC. The protective and reparative role of colony-stimulating factors in the brain with cerebral ischemia/reperfusion injury. Neuroendocrinology 2021; 111: 1029-1065.

27. Peng SY, Lin LC, Chen SR, Farooqi AA, Cheng YB, Tang JY, Chang HW. Pomegranate extract (POMx) induces mitochondrial dysfunction and apoptosis of oral cancer cells. Antioxidants (Basel) 2021; 10: 1117.
28. Shvedova M, Anfinogenova Y, Atochina-Vasserman EN, Schepetkin IA, Atochin DN. c-Jun N-Terminal Kinases (JNKs) in myocardial and cerebral ischemia/reperfusion injury. Front Pharmacol 2018; 9: 715.
29. Stegner D, Klaus V, Nieswandt B. Platelets as modulators of cerebral ischemia/reperfusion injury. Front Immunol 2019; 10: 2505.
30. Sun J, Li YZ, Ding YH, Wang J, Geng J, Yang H, Ren J, Tang JY, Gao J. Neuroprotective effects of gallic acid against hypoxia/reoxygenation-induced mitochondrial dysfunctions in vitro and cerebral ischemia/reperfusion injury in vivo. Brain Res 2014; 1589: 126-139.
31. Vongsfak J, Pratchayasakul W, Apaijai N, Vaniyapong T, Chattipakorn N, Chattipakorn SC. The alterations in mitochondrial dynamics following cerebral ischemia/reperfusion injury. Antioxidants (Basel) 2021; 10: 1384.
32. Wallace DR, Taalab YM, Heinze S, Tariba Lovaković B, Pizent A, Renieri E, Tsatsakis A, Farooqi AA, Javorac D, Andjelkovic M, Bulat Z, Antonijević B, Buha Djordjevic A. Toxic-metal-induced alteration in miRNA expression profile as a proposed mechanism for disease development. Cells 2020; 9: 901.
33. Wang J, Wang A, He H, She X, He Y, Li S, Liu L, Luo T, Huang N, Luo H, Zou K. Trametenolic acid B protects against cerebral ischemia and reperfusion injury through modulation of microRNA-10a and PI3K/Akt/mTOR signaling pathways. Biomed Pharmacother 2019; 112: 108692.
34. Wang L, Cheng L, Ma L, Ahmad Farooqi A, Qiao G, Zhang Y, Ye H, Liu M, Huang J, Yang X, Lin X, Cao S. Alnustone inhibits the growth of hepatocellular carcinoma via ROS- mediated PI3K/Akt/mTOR/p70S6K axis. Phytother Res 2022; 36: 525-542.
35. Wang P, He Y, Li D, Han R, Liu G, Kong D, Hao J. Class I PI3K inhibitor ZSTK474 mediates a shift in microglial/macrophage phenotype and inhibits inflammatory response in mice with cerebral ischemia/reperfusion injury. J Neuroinflammation 2016; 13: 192.
36. Wen R, Umeano AC, Essegian DJ, Sabitaliyevich UY, Wang K, Farooqi AA. Role of microRNA-410 in molecular oncology: A double edged sword. J Cell Biochem 2018; 119: 8737-8742.
37. Wong CH, Crack PJ. Modulation of neuro-inflammation and vascular response by oxidative stress following cerebral ischemia-reperfusion injury. Curr Med Chem 2008; 15: 1-14.
38. Xu B, Guo M, Ma L, Farooqi AA, Wang L, Qiao G, Liu M, Zuo L, Ye H, Lin X, Cao S. Mere15, a novel polypeptide from Meretrix meretrix, inhibits proliferation and metastasis of human non-small cell lung cancer cells through regulating the PI3K/Akt/mTOR signaling pathway. Neoplasma 2021; 68: 1181-1189.
39. Yang X, Ji H, Yao Y, Lai X, Jiang Y, Wu D, Cai L, Zhu W, Gu X, Hu R, Li L, Xu L, Jiang M. Downregulation of circ_008018 protects against cerebral ischemia-reperfusion injury by targeting miR-99a. Biochem Biophys Res Commun 2018; 499: 758-764.
40. Yin F, Zhou H, Fang Y, Li C, He Y, Yu L, Wan H, Yang J. Astragaloside IV alleviates ischemia reperfusion-induced apoptosis by inhibiting the activation of key factors in death receptor pathway and mitochondrial pathway. J Ethnopharmacol 2020; 248: 112319.
41. Yin M, Chen WP, Yin XP, Tu JL, Hu N, Li ZY. LncRNA TUG1 Demethylated by TET2 promotes NLRP3 expression, contributes to cerebral ischemia/reperfusion inflammatory injury. ASN Neuro 2021; 13: 17590914211003247.
42. Zhang H, Zhai L, Wang T, Li S, Guo Y. Picroside II exerts a neuroprotective effect by inhibiting the mitochondria cytochrome C signal pathway following ischemia reperfusion injury in rats. J Mol Neurosci 2017; 61: 267-278.
43. Zhang Z, Ma T, Fu Z, Feng Y, Wang Z, Tian S, Liu Z, Wei W, Li X, Chen J, Zhao W. TBC1Domain Family Member 25 deficiency aggravates cerebral ischemia-reperfusion injury via TAK1-JNK/p38 pathway. J Neurochem 2022; 160: 392-411.
44. Zhang ZH, Wang YR, LiF, Liu XL, Zhang H, Zhu ZZ, Huang H, Xu XH. Circ-camk4 involved in cerebral ischemia/reperfusion induced neuronal injury. Sci Rep 2020; 10: 7012.
45. Zhao J, Pei DS, Zhang QG, Zhang GY. Down-regulation Cdc42 attenuates neuronal apoptosis through inhibiting MLK3/JNK3 cascade during ischemic reperfusion in rat hippocampus. Cell Signal 2007; 19: 831-843.
46. Zhong Y, Yin B, Ye Y, Dekhel OYAT, Xiong X, Jian Z, Gu L. The bidirectional role of the JAK2/STAT3 signaling pathway and related mechanisms in cerebral ischemia-reperfusion injury. Exp Neurol 2021; 341: 113690.
47. Zhou Y, Farooqi AA, Xu B. Comprehensive review on signaling pathways of dietary saponins in cancer cells suppression. Crit Rev Food Sci Nutr 2021: 1-26.