European Review for Medical and Pharmacological Sciences 2020; 24: 4971-4978

# MiR-210 suppresses neuronal apoptosis in rats with cerebral infarction through regulating VEGF-notch signaling pathway

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**Abstract. – OBJECTIVE:** The aim of this study was to explore the effect of micro ribonucleic acid (miR)-210 on neuronal apoptosis in rats with cerebral infarction (CI) by regulating the vascular endothelial growth factor (VEGF)-Notch signaling pathway.

**MATERIALS AND MATERIALS:** A total of 30 clean healthy male Sprague-Dawley rats weighing 200-300 g were selected and randomly divided into Sham group (n=10), CI model group (CIM group, n=10), and CIM + miR-210 Mimic group (n=10). The protein expression levels of VEGF, Notch1, cleaved-Caspase3 (c-Caspase3), lymphoma-2 (Bcl-2), and tubulin were d[illegible] *via* Western blotting. The messenger RNA[illegible]R-NA) levels of VEGF and Notch1 were dete[illegible] *via* quantitative Polymerase Chain Reaction ([illegible]CR). Meanwhile, the expression l[illegible]ls of VEG[illegible] and Notch1 in tissues were [illegible]d using immunohistochemistry. Fur[illegible]more[illegible]e apoptosis of tissues was de[illegible]ined w[illegible]Annexin V-FITC, propidium iodi[illegible]) dou[illegible] and flow cytometry.

**RESULTS:** The l[illegible]s of [illegible]and Notch1 increased signifi[illegible]y in the C[illegible]oup when compared with t[illegible]the Sham g[illegible]p<0.01). However, thei[illegible]p[illegible]ns decreas[illegible]remarkably in CIM +[illegible]iR-210[illegible]c group when compared wit[illegible]M group ([illegible]). The mRNA expressio[illegible]f VEGF and No[illegible]were evidently upreg[illegible]ed in t[illegible]e CIM group when compared with[illegible]e Sha[illegible]oup ($p<0.01$), whereas they we[illegible]ar[illegible]y dow[illegible]egulated in the CIM + miR-2[illegible]group[illegible]n CIM group ($p<0.05$). [illegible]uno[illegible]hem[illegible]y results indicated that [illegible]pres[illegible]s of VEGF and Notch1 in tiss[illegible]were[illegible]stent with Western blotting res[illegible]. Besides, the protein expressions of c[illegible]d Bcl-2 were remarkably higher [illegible]e CI[illegible]roup than Sham group ($p<0.01$). [illegible]owever, they were significantly lower in the [illegible]+ miR-210 Mimic group than those in the C[illegible]oup ($p<0.05$). In addition, flow cytometry results demonstrated that the apoptosis level increased significantly in CIM group when compared with the Sham group ($p<0.05$), while it was [illegible]arkably inh[illegible]he CIM + miR-210 M[illegible]up ($p<0.05$).

**CONC[illegible]ON[illegible]-210 can re[illegible]duce the protein expressions of [illegible]and Notch1, inhibit the VEGF[illegible]h signaling[illegible]hway, decrease the ex[illegible]of pro-apopt[illegible]factor c-Caspase3 a[illegible]increase the expression of anti-apoptotic [illegible]or Bcl-2, the[illegible]y suppressing cerebral neu-[illegible]l apoptosis[illegible]preventing CI-induced neu-r[illegible]apoptosis.

*Key w[illegible]*
MiR-210, VEGF-Notch signaling pathway, Cerebral [illegible]farction.



## Introduction

Micro ribonucleic acids (miRNAs) are a kind of endogenous non-coding single-stranded small-molecule RNAs with 19-22 nt in length. They can regulate the expression of target genes at the transcriptional level[1]. MiRNAs were first discovered in the *Caenorhabditis elegans* in 1993. Since then, various miRNAs were found in the fruit flies, zebrafish, and mammals, as well as human body. MiRNAs mainly bind to the 3'-untranslated region (3'-UTR) of target genes, thereby leading to direct degradation or inhibition on translation of messenger RNAs (mRNAs) and regulating the gene expression at the transcriptional level. MiRNAs play extremely important roles in many biological processes, such as cell proliferation, differentiation, and apoptosis[2-4].

As a member of the miRNA family, miR-210 is recognized as a small RNA molecule associated with hypoxia[5,6]. In cerebral infarction (CI), hypoxia can induce the high expression of hypoxia-inducible factor (HIF). Meanwhile, the expression level of miR-210 is also significantly upregulated. Therefore, miR-210 plays an important role

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in resisting CI-induced apoptosis[7]. In addition, miR-210 has been confirmed associated with cell proliferation and migration and drug sensitivity in breast cancer, serving as a marker for early detection and diagnosis of malignant tumors.

Clinically, severe infection, poisoning, shock, and surgery can cause acute insufficient blood supply in brain tissues. This may ultimately lead to CI, which is a major disease seriously threatening human health. In the vascular endothelial growth factor (VEGF)-Notch signaling pathway, VEGF is an important regulator of angiogenesis[8]. The activation of VEGF-Notch promote vascular proliferation and alleviate cardiovascular diseases, such as vascular dysfunction. Therefore, the VEGF-Notch signaling pathway is of great importance in regulating insufficient cerebral blood supply and CI. In the present study, we aimed to investigate whether increased miR-210 caused by insufficient cerebral oxygen supply could improve CI by regulating the VEGF-Notch pathway.

## Materials and Methods

### Animal Feeding, Treatment and Grouping

The Sprague-Dawley (SD) rats purchased [from] Shanghai Bioray Laboratory Co., Ltd. (Shangh[ai], China) were fed in the specific p[athogen]-free an[d] mal room under the temperat[ure] humidity of 45% and 12/12 h lig[ht] ark cyc[le]. All rats were given free access t[o] and w[ater]. After 1 week, SD rats were ra[ndo]vi[de]d into groups, including: S[ham] grou[p] 0), CI model group (CIM gr[oup] treated wi[th] operation, n=10), and CIM[-]210 Mimic g[roup] (treated with miR-21[0] mic, [n=10]). After routine feeding for an[other] 3 d, the [rats] were sacrificed *via* cervical [dis]location, and br[ain] ssues were collected. [All] animal operations conformed to the reg[ulati]on in the Guidelines for laboratory animal care [and] use of the Nat[ional] Institute. This study was ap[proved] by the Animal Ethics Committee [of] Kunmin[g] Medical University Animal Center.

### Establishment of CIM Model in Rats

[Blood] first taken from the heart of rats in [eit]her gender and placed at room temperature for [1] h to form thrombus. Subsequently, blood clot was aspirated using the syringe into normal saline repeatedly for 3 times, thereby forming the small embolus suspension. Next, 0.2 mL of suspension (100-250 μm of embolus) was aspirated into the common carotid artery (CCA) to induce multiple CI. Finally, the rat model of CIM was successfully established.

### Detection of Protein in Brain [Nerve] Tissues Via Western Blotting

Brain nerve tissues were cut [into] pieces, homogenized, and added with l[y]sis bu[ffer] llowed by centrifugation at 20,000 [rpm] d 4°C f[or] in. The concentration of th[e] tracted total p[rotein] was measured using th[e] Bicinchon[inic] acid (BC[A]) protein assay kit (Pie[rce] ockf[ord], IL, USA). The protein samples [were] s[eparated] by so[dium] dodecyl sulphate-[polya]crylam[ide] el[ectr]ophoresis (SDS-PAGE) [and] transferred [onto] vinylidene difluoride [PVDF] embranes (H[V]00010; Millipore, Bi[llerica], M[A], USA). The membranes were then incubated with p[rimary] antibodies of VEGF, Not[ch1], Cleaved-Caspas[e]-Caspase3), B-cell l[ymp]homa-2 (Bcl-2), and tubulin (CST, Danvers, [MA], USA) at 4[°C] overnight. After washing, the [mem]branes were [in]cubated again with horseradish [pe]roxidase-[con]jugated secondary antibodies (CS[T], USA) for 1 h. Immuno-reactive ban[ds] were finally exposed by the enhanced chemiluminescence (ECL) technique.

### Detection of mRNA Expression Levels of VEGF and Notch1 Via Quantitative Polymerase Chain Reaction (qPCR)

The mRNAs in brain nerve tissues were first extracted using the TRIzol reagent (Invitrogen, Carlsbad, CA, USA). Subsequently, extracted RNA was reversely transcribed into complementary deoxyribose nucleic acid (cDNA) according to the instructions. Next, 500 ng of RNAs were added with 2 μL of 5 × PrimeScript RT Master Mix, followed by PCR amplification. The reaction system (20 μL in total) was prepared, including 2 μL of cDNA, 10 μL of SYBR Premix Ex Taq II (Tli RNaseH Plus) (2×), 0.8 μL of forward primers, 0.8 μL of reverse primers, 0.4 μL of ROX Reference Dye II (50×), and deionized water was added till the total volume was 20 μL. The mRNA expression levels were calculated, with β-actin as an internal reference. Primer sequences used in this study were shown in Table I.

### Immunohistochemistry of Brain Tissues

Paraffin sections were routinely prepared, deparaffinized, and incubated with 3% $H_2O_2$-60% methanol at room temperature for 30 min. After washing with phosphate-buffered saline (PBS) for

**Table I.** Primer sequences of genes.

| Gene | Forward primer (5'-3') | Reverse primer (5'-3') |
|---|---|---|
| VEGF | AAGGGAGAGGAGCCCGCCAAG | TTTCTGCTCCCTTCTGTCGTG |
| Notch1 | AGAACTGTGAAGAAAATGTGG | GCCACCGTGGGAGTTGTGGC |
| β-actin | GCAGAAGGAGATTACTGCCCT | GCTGATCCACATCTGCTGGAA |

3 times, the sections were transparentized with 0.1% Triton X 100 + PBS for 20 min and incubated with 5% normal goat serum at room temperature for 20 min. Subsequently, the sections were added with rabbit anti-mouse VEGF and Notch1 polyclonal antibodies (1:200) at 4°C overnight. On the next day, the sections were added dropwise with biotinylated goat anti-rabbit IgG secondary antibody for 1 h of incubation at 37°C. Then, they were washed with PBS for 3 times, and added dropwise with horseradish peroxidase-labeled streptomycin antibody for 30 min of incubation at 37°C. After that, the sections were stained with diaminobenzidine (DAB) in the dark at room temperature, followed by hematoxylin counterstaining for 30 min, dehydration with ethanol in conventional gradient, transparentizing with xylene, and sealing with neutral balsam. Finally, the sections were photographed under the inverted fluorescence microscope.

Dark brown particles in brain nerve tissues indicated positive expression. The mean optical density (OD) value of immunohistochemistry positive particles was determined using the ImageJ professional image analysis system, followed by semi-quantitative analysis of VEGF and Notch1 protein expressions.

### Detection of Apoptosis Via Flow Cytometry

The tissues were resuspended, directly centrifuged at 1000 rpm for 5 min and collected. Adherent cells were digested with trypsin containing ethylenediaminetetraacetic acid (EDTA/9 for an appropriate time and the digestion was terminated using complete medium. Subsequently, the cells were washed with PBS once and counted, followed by centrifugation at 1000 rpm for 5 min. A total of 1-5 × 10⁵ cells were collected and resuspended with 500 μL of binding buffer. After mixing evenly with 5 μL Annexin V-Light 650 and 10 μL of propidium iodide (PI), the mixture was incubated at room temperature in the dark for 5-15 min. Flow cytometry was then performed within 1 h. The Annexin V-Light 650 fluorescence signal was determined through the FL4 channel, while the PI fluorescence signal was detected through the FL2 or FL3 channel. Finally, Annexin V-Light 650 and PI single positive tubes were determined simultaneously to determine the fluorescence compensation values and the proportion of the cross-quadrate.

### Statistical Analysis

GraphPad Prism 6.0 (La Jolla, USA) was used for all statistical analysis. Experimental data were expressed as mean ± SD. *t*-test was performed to compare the differences between the two groups. $p<0.05$ was considered statistically significant.

## Results

### Effects of MiR-210 on Protein Levels of VEGF and Notch1 in VEGF-Notch Signaling Pathway

The proteins were extracted from brain nerve tissues and detected *via* Western blotting. The results showed that the levels of VEGF and Notch1 increased significantly in CIM group when compared with Sham group ($p<0.01$). However, they were remarkably downregulated in CIM + miR-210 Mimic group than CIM group ($p<0.05$). These findings indicated that CIM could activate the VEGF-Notch signaling pathway by elevating the protein expression levels of VEGF and Notch1, while miR-210 could inhibit CIM-induced activation of the VEGF-Notch signaling pathway (Figure 1).

### Effects of MiR-210 on mRNA Levels of VEGF and Notch1 in VEGF-Notch Signaling Pathway

The mRNA levels of VEGF and Notch1 in brain tissues were determined *via* qPCR. It was found that the mRNA expressions of VEGF and Notch1 were significantly upregulated in CIM group compared with those in the Sham group ($p<0.01$). However, they decreased significantly in CIM + miR-210 Mimic group than CIM group ($p<0.05$). These results suggested that CIM could increase, while miR-210 could decrease the mRNA levels of VEGF and Notch1 (Figure 2).

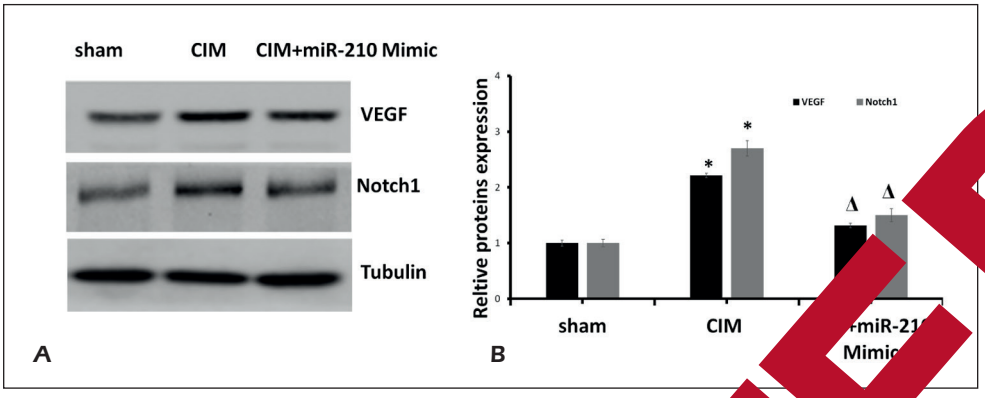


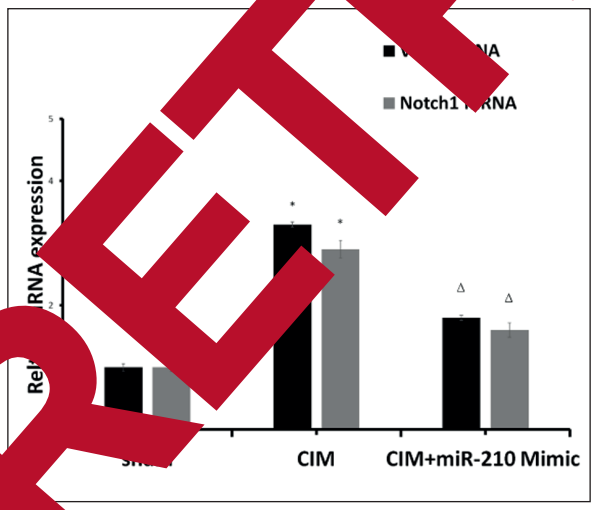

**Figure 1.** Effects of miR-210 on protein levels of VEGF and Notch1 in VEGF-Notch signaling pathway. **A**, Protein levels of VEGF, Notch1, and tubulin detected via Western blot. **B**, Quantitative diagram of Figure 1A. *$p$<0.01: CIM group *vs.* Sham group, $^{\Delta}p$<0.05: CIM + miR-210 Mimic group *vs.* CIM group.

### *Expression Levels of VEGF and Notch1 in VEGF-Notch Signaling Pathway Detected Via Immunohistochemistry*

The expression levels of VEGF and Notch1 in brain tissues were then detected *via* immunohistochemistry. Similarly, the results were consistent with those determined by Western blotting (Figure 2

### *Effects of MiR-210 on Expression Levels of Apoptosis-Related Factors c-Caspase3 and Bcl-2 in Each Group*

In addition, the expressi tosis-related factors were detected estern ting revealed that the protein e ions o




**Fi 2.** Effects of miR-210 on mRNA levels of VEGF and Notch1 in VEGF-Notch signaling pathway. *p<0.01: CIM group vs. Sham group, $^{\Delta}p$<0.05: CIM + miR-210 Mimic group *vs.* CIM group.

and were remarka gher in CIM group t Sham group ($p$<0.01). However, they were arkably low in CIM + miR-210 Mimic p than CIM up ($p$<0.05), demonstrating t iR-210 co nhibit apoptosis (Figure 4).

### *Effect -210 on Apoptosis Level in Each Group*

apoptosis of brain nerve tissues was de- *a* Annexin V-FITC and PI double labeling and flow cytometry. The results showed that the apoptosis level was significantly elevated in CIM group compared with Sham group ($p$<0.05). However, it was remarkably inhibited in CIM + miR-210 Mimic group, suggesting that miR-210 could suppress apoptosis (Figure 5).

### *Diagram of Mechanism of Action of MiR-210*

The diagram of mechanism of action of miR-210 was finally plotted. The results demonstrated that miR-210 could reduce the protein expressions of VEGF and Notch1, inhibit the VEGF-Notch signaling pathway, decrease the expression of pro-apoptotic factor c-Caspase3, and increase the expression of anti-apoptotic factor Bcl-2, thereby suppressing cerebral neuronal apoptosis and preventing CI-induced neuronal apoptosis (Figure 6).

## Discussion

MiRNAs are short non-coding RNAs (19-22 nt in length) involved in post-transcriptional regulation of multiple gene expressions by affecting the stability and translation of mRNA[9-11]. MiR-

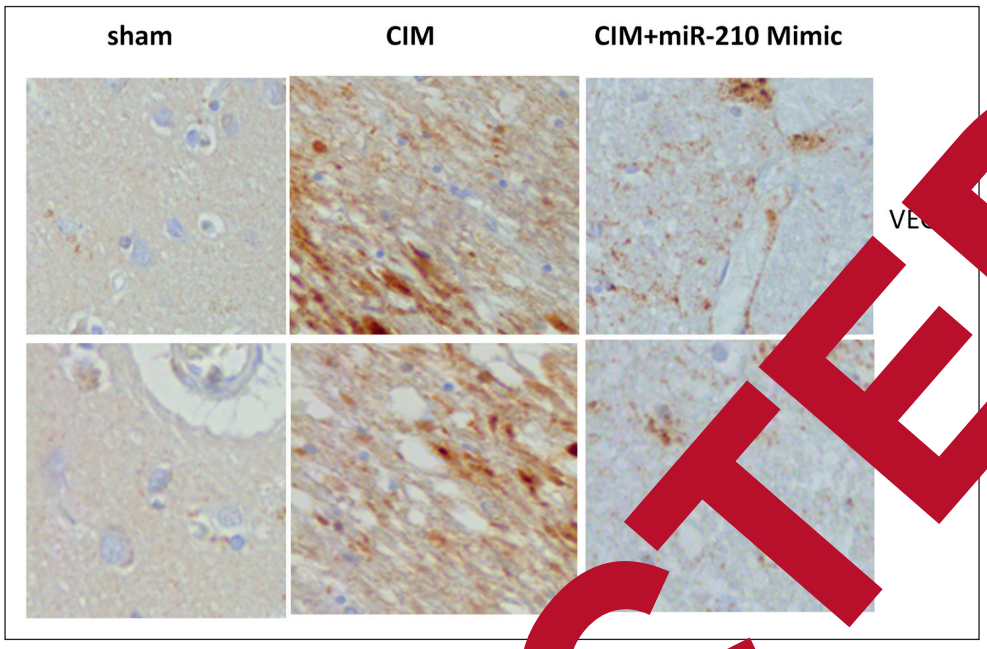



**Figure 3.** Expression levels of VEGF and Notch1 in VEGF-Notch ling pathway i ues detected via immunohistochemistry. The expression levels of VEGF and Notch1 in brain tissues ar cted via immu stochemistry (magnification: 400×).

NAs are transcribed by RNA polymerase I d original transcripts pri-miRNAs are a non-coding RNAs. Original transcripts c be cleaved by the Drosha ribonuclease III enz The stem-loop precursor miRNA (pre-miR (about 70 nt) is produced and c by the c toplasmic ribonuclease Dic produc- ing mature miRNAs and ense n NA star (miRNA*). Mature mi are into the RNA-induced ex

that ca ize target mRNAs through incomplete base pairing with miRNA. Meanwhile, the mmon results are inhibited translation or n of target mRNAs.

As a member of the miRNA family, miR-210 is currently recognized as a small RNA molecule associated with hypoxia[12]. It has been reported[13,14] that after silencing the expression of miR-210 in liver cancer tissues using the anti-nucleotide technique, the proliferation ability of the liver

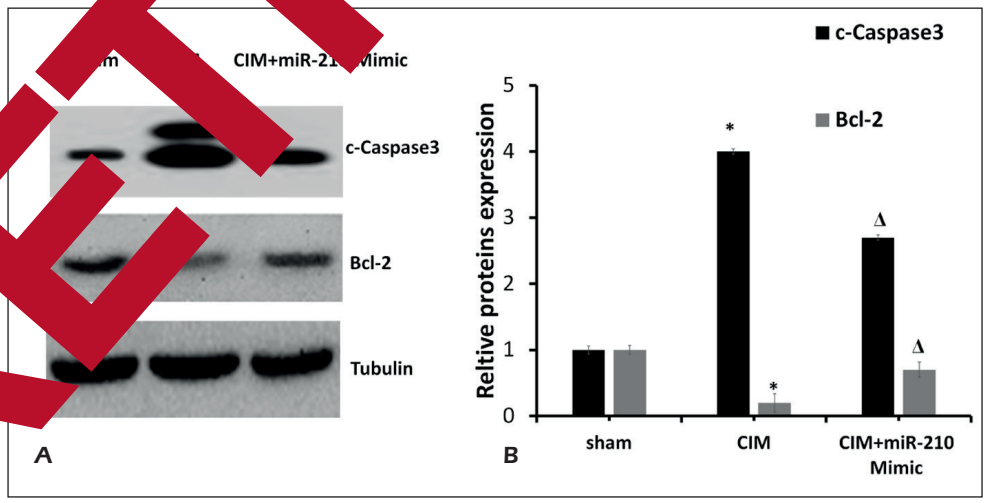



**Figure 4.** Effects of miR-210 on expression levels of apoptosis-related factors c-Caspase3 and Bcl-2 in each group. A, Protein expression levels of c-Caspase3 and Bcl-2 detected via Western blotting. B, Quantitative diagram of Figure 4A. *$p$<0.01: CIM group *vs.* Sham group, $^{\Delta}p$<0.05: CIM + miR-210 Mimic group *vs.* CIM group.

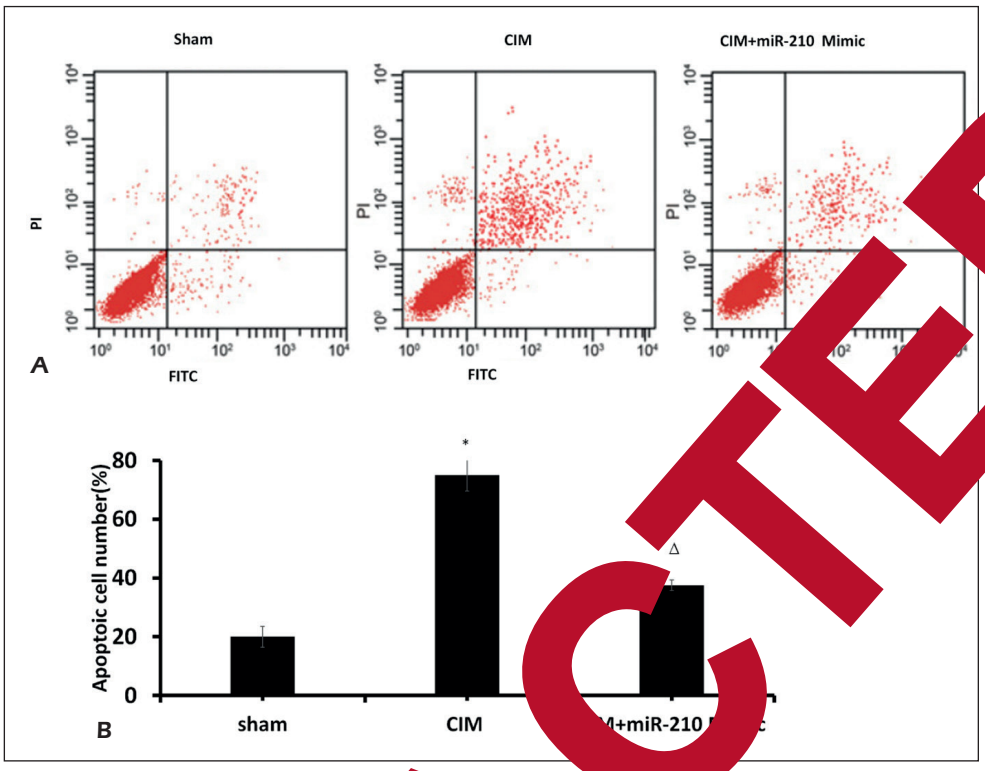



**Figure 5.** Effect of miR-210 on apoptosis level i[n]. **A**, Apoptosis detected via Annexin V-FITC and PI double labeling. **B**, Quantitative diagram of Figure 4A. *$p$ [illegible] vs.* Sham group, $^{\Delta}p<0.05$: CIM + miR-210 Mimic group *vs.* CIM group.



cancer cells is remarkably in[creased]. Meanwhile, the sensitivity of liver can[cer] cells t[o] diotherapy is remarkably enha[nced]. This i[s] that miR-210 plays an impo[rtant] [role] proliferation and ap[optos]is, a[s well] as drug sensitivity and angio[genes]is. In addi[tion], miR-210 is positively asso[ciated] h hypoxia i[n] ast cancer cells. Hyp[oxia] ca[n] ase the expression of miR-210 a[nd] he migratio[n] ity of breast cancer MCF-7 [cells], serving as a [potential] therapeutic target [for] malign[ant] tumors[15].

ogene[sis] lays an important role in tissue [repair], an[d] e occurrence and development [of] ischem[ic] ardiovascular and cerebrovascular [diseases] and malignant tumors[16-18]. Th[e] otch si[gnaling] pathway, highly conserved in e[volu]tion, is widely existed in vertebrates and in[vertebrates]. The changes in Notch signals are closely related to the occurrence and development of diseases, including tumors, hereditary diseases, neurodegenerative diseases and cardiovascular and cerebrovascular diseases. VEGF acts as an important regulator of angiogenesis, and the activation of VEGF-Notch can promote vascular

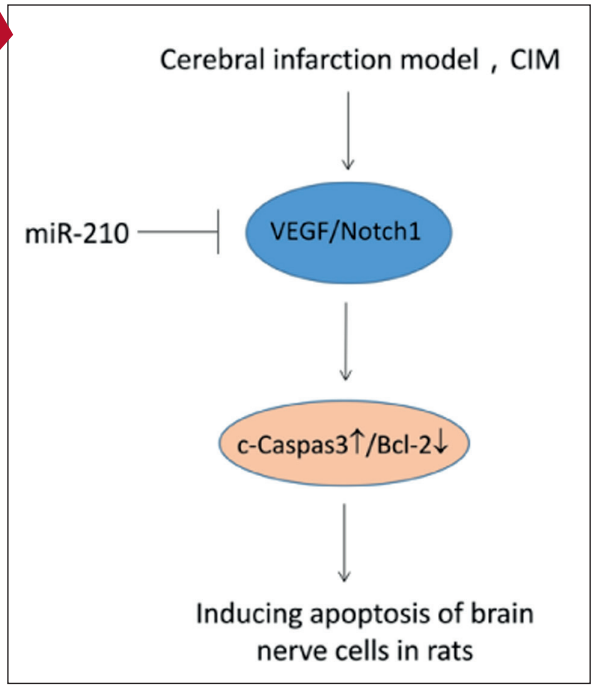



**Figure 6.** Diagram of mechanism of action of miR-210 in regulating VEGF-Notch signaling pathway.

proliferation. Moreover, miR-210 improves cell hypoxia in CI through targeting the VEGF-Notch signaling pathway.

In the present study, SD rats were divided into Sham group, CIM group, and CIM + miR-210 Mimic group. Western blotting results indicated that the protein expression levels of VEGF and Notch1 were significantly upregulated in CIM group when compared with Sham group. However, they significantly declined in CIM + miR-210 Mimic group. The results of qPCR manifested that the mRNA expressions of VEGF and Notch1 were evidently upregulated in CIM group, whereas were downregulated in CIM + miR-210 Mimic group. Immunohistochemical results were consistent with Western blotting results. All these findings indicated that CIM could activate the VEGF-Notch signaling pathway, while miR-210 Mimic could inhibit it. Furthermore, flow cytometry results demonstrated that the apoptosis level increased significantly in CIM group when compared with Sham group, while it was remarkably inhibited in CIM + miR-210 Mimic group.

## Conclusions

Briefly, miR-210 can reduce the protein pressions of VEGF and Notch1, inhibit the VEG Notch signaling pathway, decrea expressio of pro-apoptotic factor c-Cas increase the expression of anti-ap tic fa Bcl-2, thereby suppressing cer neuron and preventing CI-ind ed opt

### Conflict of Int

The authors dec that th no conflict of interest.

### eferences


1) L MicroR genomics, biogenesis, me , and f on. Cell 2004; 116: 281-297.
2) EHME B. Onset and progression human rthritis-can growth factors, inmmatory okines, or differential miRNA exoncomitantly induce proliferation, ECM deg n, and inflammation in articular cartilage? Int J Mol Sci 2018; 19: 2282.
3) Guo J, Zeng X, Miao J, Liu C, Wei F, Liu D, Zheng Z, K, Wang C, Liu Y. MiRNA-218 regulates osteoast differentiation and inflammation response in periodontitis rats through Mmp9. Cell Microbiol 2019; 21: e12979.
4) Sun Y, An N, Li J, Xia J, Tian Y, Zhao P, Liu X, Huang H, Gao J, Zhang X. MiRNA-206 regulates human pulmonary microvascular endothelial cell apoptosis via targeting in chronic obstructive pul ary disease. J Cell Biochem 2019; 120: 6
5) Zhang Y, Yan J, Wang L, Dai H, Li N, H ai H. Hi 1α promotes breast cancer cell M proliferation and invasion through regulating 10. Cancer Biother Radiopharm 2017; 32: 297-
6) Corn PG. Hypoxic regula of miR- rinking targets expand HIF fluence. Ca Ther 2008; 7: 265-26
7) Chang Z, Huo L, W hang P 1 α had pivotal effects on downreg -210 d asing viability and in g a n hypo ondrocytes. Scien WorldJou 14; 2 376363.
8) Deng S, Wu L, Hu Z, hen Y, Shen Y, Zho Lin S. The r atory roles of VEG tch s g pathway on aplastic anemia with kidney ncy and blood stasis. J C hem 2018. 1002/jcb.27516. [Epub of print].
9) Moraes LN, Fernandez GJ, Vechetti-Junior IJ, Freire PP, Souza R, acis R, Rogatto SR, Reis PP, Dal-Pai-Silva M, alho RF. Integration of miRNA d mRNA ession profiles reveals microR- egulat etworks during muscle wasting in c xia. Sci Rep 2017; 7: 6998.
10) Bao H, Kommadath A, Liang G, Sun X, Arantes AS, Tuggle CK, Bearson SM, Plastow GS, Stothard P, LL. Genome-wide whole blood microR- me and transcriptome analyses reveal miRNA-mRNA regulated host response to foodborne pathogen Salmonella infection in swine. Sci Rep 2015; 5: 12620.
11) Li J, Li C, Han J, Zhang C, Shang D, Yao Q, Zhang Y, Xu Y, Liu W, Zhou M, Yang H, Su F, Li X. The detection of risk pathways, regulated by miRNAs, via the integration of sample-matched miRNA-mRNA profiles and pathway structure. J Biomed Inform 2014; 49: 187-197.
12) Tonevitsky AG, Maltseva DV, Abbasi A, Samatov TR, Sakharov DA, Shkurnikov MU, Lebedev AE, Galatenko VV, Grigoriev AI, Northoff H. Dynamically regulated miRNA-mRNA networks revealed by exercise. BMC Physiol 2013; 13: 9.
13) de Souza MG, de Jesus SF, Santos EM, Gomes E, de Paulo SFA, Santos E, Da SL, Santos S, de Paula A, Farias LC, Guimaraes A. Radiation therapy reduced blood levels of LDH, HIF-1alpha, and miR-210 in OSCC. Pathol Oncol Res 2018. doi: 10.1007/s12253-018-0517-2. [Epub ahead of print].
14) Zhang H, Wu J, Wu J, Fan Q, Zhou J, Wu J, Liu S, Zang J, Ye J, Xiao M, Tian T, Gao J. Exosome-mediated targeted delivery of miR-210 for angiogenic therapy after cerebral ischemia in mice. J Nanobiotechnology 2019; 17: 29.
15) Muller V, Gade S, Steinbach B, Loibl S, von Minckwitz G, Untch M, Schwedler K, Lubbe K, Schem C, Fasching PA, Mau C, Pantel K, Schwarzenbach H. Changes in serum levels of miR-21, miR-210,

and miR-373 in HER2-positive breast cancer patients undergoing neoadjuvant therapy: a translational research project within the Geparquinto trial. Breast Cancer Res Treat 2014; 147: 61-68.

16) Alhasan L. MiR-126 modulates angiogenesis in breast cancer by targeting VEGF-A-mRNA. Asian Pac J Cancer Prev 2019; 20: 193-197.

17) Dewangan J, Srivastava S, Mishra S, Divakar A, Kumar S, Rath SK. Salinomycin inhibits breast cancer progression via targeting HIF-1alpha/VEGF mediated tumor angiogenesis in vitro and in vivo. Biochem Pharmacol 2019; 164: 326-3

18) Tang E, Wang Y, Liu T, Yan B. Gastri notes a giogenesis by activating HIF-1 tenin/VEGF signaling in gastric cancer. Gene 704: 42-48.