MiR-518a-5p Targets GZMB to Extenuate Vascular Endothelial Cell Injury Induced by Hypoxia-Reoxygenation and Thereby Improves Myocardial Ischemia

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Summary
To probe the function of miR-518a-5p/Granzyme B (GZMB) in hypoxia/reoxygenation (H/R)-induced vascular endothelial cell injury.

The key genes of myocardial infarction were screened by bioinformatic methods. The upstream micro RNAs (miRNAs) of GZMB were predicted by TargetScan. The binding of miR-518a-5p to GZMB was verified with luciferase reporter assay. The H/R model was constructed with human vascular endothelial cell (HUVEC) in vitro. Cell Counting Kit-8 (CCK8) assay was performed to detect cell proliferation. Western blot was utilized to evaluate the levels of indicated proteins.

GZMB was up-regulated in patients with myocardial infarction and identified as the key gene by the bioinformatics analysis. Then the prediction from TargetScan indicated that miR-518a-5p, which is down-regulated in myocardial infarction patients, might be the potential upstream miRNA for GZMB. The following experiments verified that miR-518a-5p could bind to the 3'UTR of GZMB and negatively modulates GZMB expression. More importantly, the miR-518a-5p mimic enhanced cell proliferation and repressed apoptosis of H/R-injured HUVEC cells by inhibiting GZMB expression.

We proved that miR-518a-5p could partly attenuate H/R-induced HUVEC cell injury by targeting GZMB, and perhaps the miR-518a-5p/GZMB axis could be potential therapeutic targets for myocardial infarction.

Key words: H/R model, Dual-luciferase reporter gene assay, Proliferation, Apoptosis

Myocardial infarction (MI) refers to myocardial injury caused by myocardial ischemia,1,2 and it is the leading cause of sudden death.2 Myocardial ischemia/reperfusion (I/R), a very intricate process, has been known as a vital mechanism of MI.3 Despite being helpful for offering oxygen as well as nutrients to the ischemic area, reperfusion also causes serious myocardial injury (such as cell apoptosis and necrosis) and conduces to high mortality.4,5 To date, the detailed mechanism of I/R injury is still largely unclear. An in-depth understanding of the molecular mechanism of this process will provide a critical contribution for opening up effective methods to lower myocardial damage.

Granzyme B (GZMB), a member of the granzyme serine protease family, known for its pro-apoptotic function, is the most widely studied granzyme in health and diseases.6 Evidence suggested that GZMB played a vital role in perf-mediated induction of apoptosis by ex vivo virus-immune cytotoxic T cells.7,8 Zou, et al found that recombinant human growth hormone therapy inhibited the apoptosis of airway epithelial cells and airway remodeling by reducing the expression of GZMB in the lungs of asthmatic rats.9,10 In view of the important role of GZMB in apoptosis, and the important position of apoptosis in I/R injury, we wonder whether GZMB is also involved in I/R injury, and if yes, what is its regulatory mechanism?

MicroRNAs (miRNAs) are small, non-coding RNA molecules consisting of 21-25 nucleotides. Through translational repression, they can decrease the expression of their target genes.11 Some researches have shown that miRNAs play a pivotal part in the pathogenesis of cardiovascular diseases as well as cardiovascular physiology.12,13 Recently, Xie, et al. illustrated that as a protective agent, miR-451 partially attenuate s the hypoxia/reoxygenation (H/R)-induced myocardial cell injury by repressing high mobility group box 1 (HMGB1) expression.14 Furthermore, miR-320, miR-208a, and miR-1 were considered as the regulators in the process of IR injury.15-17 The regulatory role of miR-518A-5p has been reported in immunological diseases and cancers. A study has found that miR-518a-5p was negatively modulated by cysteine-rich protein 61 (CCN1) through the MAPK signaling and it

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could negatively regulate chemokine ligand 2 (CCL2) expression in osteoblasts, which provided a new insight for the treatment of rheumatoid arthritis.\textsuperscript{15} The study of Rubie, et al. reported that miR-518a-5p regulating CCR6 expression might be one of the regulatory mechanisms in colorectal cancer pathogenesis.\textsuperscript{19} Yet there has been no relevant research on the role of miR-518a-5p in myocardial disease. Through bioinformatics analysis, we discovered that miR-518a-5p expression was prominently downregulated in patients with MI and is predicted as a regulator of GZMB, implying that it may regulate myocardial cell function.

Ischemia-related vascular endothelial injury causes oxidative stress and apoptotic cell death.\textsuperscript{20} A study has shown that different types of cells undergo apoptosis at different times during myocardial IR, but endothelial cells are first affected.\textsuperscript{20} Meanwhile, there is increasing evidence that endothelial apoptosis plays an important role in the progression of ischemic injury and the radial diffusion of apoptosis to surrounding cardiomyocytes.\textsuperscript{21,22} In our present work, we explored the effects of miR-518a-5p/GZMB on H/R-induced human vascular endothelial cell (HUVEC) injury. The data evidenced that miR-518a-5p participated in the regulation of H/R-induced HUVEC damage through targeting GZMB. The results provided new insight for understanding the molecular mechanism of I/R injury.

**Methods**

**Data:** The Gene Expression Omnibus (GEO) datasets GSE66360 and GSE61741 were obtained from the National Center for Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov/). The GSE66360 dataset contains the expression profiling data of circulating endothelial cells from 49 MI and 50 control samples. The GSE 61741 dataset is composed of the non-coding RNA profiling of peripheral blood from 62 MI samples and 94 control samples.

**Construction of an H/R model:** HUVECs were purchased from American Type Culture Collection and maintained in Kaighn’s modification of Ham’s F-12 (F12K) medium containing 15% FBS, 100 g/mL streptomycin, and 100 U/mL penicillin. To construct the H/R model, the cells that were pre-transferred to serum-free medium were maintained at 37°C in the hypoxia incubator with 95% N\textsubscript{2} and 5% CO\textsubscript{2}. After 6 hours, the cells were moved to a normal incubator with 95% atmosphere and 5% CO\textsubscript{2} at 37°C for reoxygenation for 24 hours.

**Transfection:** miR-518a mimic, miR-518a inhibitor, negative control (NC), si-GZMB (5’-AUUGUCUCUACUGAGA CGAAA-3’), and scrambled control (si-con; 5’-AAUUUC CCGAAGUGUCAGCUU-3’) were synthesized by GenePharma Co. (Shanghai, China). On the basis of the specifications, Lipofectamine 3000 reagent (Invitrogen, Carlsbad, CA, USA) was used to do transfection experiments.

**Dual-luciferase reporter gene assay:** The GZMB-WT (wide type) and GZMB-Mut (mutant type) were cloned into a PGL3 firefly luciferase reporter vector. Then the primary HUVECs were transfected with the GZMB-WT + miR-518a-5p NC, GZMB-WT + miR-518a-5p mimic, GZMB-WT + miR-518a-5p inhibitor, GZMB-Mut + miR-518a-5p NC, GZMB-Mut + miR-518a-5p mimic, or GZMB-Mut + miR-518a-5p inhibitor, accordingly. Finally, the luciferase activity was measured with the Dual-Luciferase Reporter Assay Kit after cultivation for 48 hours.

**Cell proliferation assay:** We conducted Cell Counting Kit-8 (CCK8) assay to detect cell proliferation. Briefly, we seeded the HUVECs into 96-well plates (1 × 10\textsuperscript{3} cells/well). Then the proliferation rate was detected every 24 hours by adding 10 μL of CCK8 reagent and incubating at 37°C for 1.5 hours. The OD value was detected with a microplate reader at 450 nm.

**qRT-PCR:** cDNA was generated with the PrimeScript RT Reagent Kit (Takara, Japan), and qRT-PCR was conducted using the SYBR Premix Ex Taq II to detect the expression level of mRNA with GAPDH as a reference (Takara, Japan). Reverse transcription of mRNA was carried out with the MiScript Reverse Transcription Kit (Qiagen), and mRNA expression was detected by the MiScript SYBR-Green PCR Kit (Qiagen) using real-time PCR with U6 as a reference. The data were calculated with the 2\textsuperscript{−ΔΔCt} method. The primers used were miR-518a-5p forward: 5’-TGCAAAAGGGAAGCCCTT-3’, miR-518a-5p reverse: 5’-GAACATGCTGCCTATCCTC-3’; U6 forward: 5’-CTCGC TTCGGCGACGACA-3’, U6 reverse: 5’-AACGCTTCACG AATTGCGT-3’; GZMB forward: 5’-CGACAGTACCATC TGAAGTGGCTGC-3’, GZMB reverse: 5’-TCTGTTCCATA GAGACATGGCC-3’; and GAPDH forward: 5’-GTCTC TCTGATCTCAACAGCCG-3’, GAPDH reverse: 5’-ACC ACCCTTGTGCTTAGCCAA-3’.

**Western blot:** Total protein was isolated from cultured cells with radio-immunoprecipitation assay lysis buffer and then subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred on to polyvinylidene fluoride membranes, succes-
GZMB was dysregulated in MI. A: GSEA analysis of the pathway related to the differential genes. \( P = 0.029 \); FDR = 0.081. B: The up-regulation of GZMB in MI (n = 49) compared with the control (n = 50). C: Two common miRNAs were screened out by TargetScan and the GEO dataset (GSE61741). GSE61741 was obtained from NCBI. D: The down-regulation of miR-518a-5p in MI (n = 62) compared with the control (n = 94).

sively. After that, the membrane was blocked by skimmed milk and incubated with primary and secondary antibodies in turn. Finally, enhanced chemiluminescence (ECL) reagent was added to visualize the protein bands. The gray value of the bands were scanned by Image J software, and the relative protein level was calculated on the basis of the gray value by taking GAPDH as the internal reference.

**Statistical analysis:** Data were analyzed with SPSS22.0 and GraphPad Prism 6.0. The \( t \) test and one-way analysis of variance followed by the Dunnett or Tukey post hoc test were used for comparing the difference between groups, as appropriate. The cutoff of statistical significance was \( P < 0.05 \).

**Results**

**Differential gene analysis:** On the basis of the GSE 66360 dataset that contained 49 MI samples and 50 con-
control samples, we investigated the differential genes in MI. A total of 409 differentially expressed genes were obtained, containing 323 up-regulated genes and 86 down-regulated genes. Secondly, Gene Set Enrichment Analysis (GSEA) was performed to enrich and analyze the differential genes by the WebGestalt website. With $P < 0.05$ as the screening condition, we obtained seven significant differential genes (Table). As apoptosis is one of the most critical pathways (Figure 1A; injury caused by I/R), the apoptosis pathway attracted our attention. DDIT3, FOS, GADD45A, GADD45B, GZMB, JUN, NFKBIA, PMAIP1, and TNF. Since GZMB is known for its pro-apoptotic function, and combined with its logFC ranking and enrichment score, it is elected for further analysis. We evaluated the GZMB expression with GSE 66360 data, and the results indicated that GZMB expression increased with time. On the contrary, the H/R + inhibitor group was prominently lower than the H/R + NC group from 72 hours, whereas there was no significant difference in the first 48 hours compared to the H/R + NC group (Figure 2B). To sum up, these results intimated that the up-regulation of miR-518a-5p could promote the viability of H/R-damaged HUVECs.

**miR-518a-5p could directly bind to GZMB and reduce its expression:** Previously, it was predicted that miR-518a-5p was the upstream miRNA targeting GZMB through TargetScan software, and the binding sites between them were simultaneously predicted as shown in Figure 3A. The luciferase reporter results illustrated that in the WT groups, the relative luciferase activity was suppressed by miR-518a-5p mimic but increased by miR-518a-5p inhibitor. Nevertheless, the relative luciferase activities of two groups were all recovered in the Mut groups owing to the mutation of the predicted binding sites (Figure 3B). These results proved that there exists a regulatory relationship between miR-518a-5p and GZMB in HUVECs. To be more specific, GZMB was a target of miR-518a-5p and regulated by it.

To detect the regulation of miR-518a-5p on GZMB expression, we designed cotransfection of miR-518a-5p mimic with si-GZMB. As shown in Figure 3C-E, miR-518a-5p mimic and si-GZMB could decrease the mRNA and protein levels of GZMB, respectively. More importantly, the cotransfection with miR-518a-5p mimic and si-GZMB significantly enhanced the reduction effect of si-GZMB, suggesting that miR-518a-5p could weaken GZMB expression in a targeted manner at both the mRNA and protein levels.

**The impact of miR-518a-5p/GZMB on HUVEC apoptosis and proliferation:** To inquire the influence of miR-518a-5p/GZMB on apoptosis of H/R-treated HUVECs, we subsequently evaluated the changes of apoptosis-related proteins (Bcl-2, Bax, caspase-3, and cleaved caspase-3) with Western blot. The results presented in Figure 4 revealed that the expression of GZMB was enhanced in the H/R + NC group compared with the control, whereas it was decreased in the H/R + mimic group and increased in the H/R + inhibitor group relative to the H/R + NC group. In addition, the level of Bcl-2 was decreased but Bax and...
Figure 3. GZMB was a target gene of miR-518a-5p. A: The binding sites between miR-518a-5p and GZMB were predicted by bioinformatics. B: Luciferase reporter assay was performed to detect the targeting relationship between miR-518a-5p and GZMB. C: The mRNA expression of GZMB in HUVECs with different transfections was detected by qRT-PCR. D, E: The GZMB protein expression in HUVECs with different transfections was measured by Western blot. **P < 0.01 versus NC group; ***P < 0.01 versus mimic group; ^^^P < 0.01 versus si-GZMB group.

Active caspase-3 were increased in HUVECs that suffered from H/R compared with the control. Bcl-2 was increased by miR-518a-5p mimic and decreased by miR-518a-5p inhibitor, compared with the H/R + NC group. On the contrary, miR-518a-5p mimic exhibited a repressive effect but miR-518a-5p inhibitor presented a promoting function on the expression of Bax and active caspase-3 in the H/R model (Figure 4A and B). Furthermore, Figure 5 demonstrates that the protein expression of Bcl-2 was remarkably increased after transfection of miR-518a-5p mimic or si-GZMB. Besides, the protein expression of Bcl-2 in the cotransfection group with miR-518a-5p mimic and si-GZMB was further enhanced compared to the H/R + miR-518a-5p mimic and H/R + si-GZMB groups (Figure 5A and B). With regard to the changes of other three apoptosis-related proteins, caspase-3 has no significant difference in different groups, and cleaved caspase-3 presented the same trend with Bax. The protein expression of Bax and cleaved caspase-3 decreased in HUVECs transfected with miR-518a-5p mimic or si-GZMB, respectively. Interestingly, under the joint action of miR-518a-5p mimic and si-GZMB, the protein expression was significantly lower than that under any of them that acted alone. Collectively, these results exhibited that miR-518a-5p played a suppressive role in H/R-induced HUVEC apoptosis by targeting GZMB.

To further probe the impact of miR-518a-5p/GZMB on H/R-injured HUVEC proliferation, we performed CCK8 assay. The result indicated that the cell viability was prominently increased in the H/R + miR-518a-5p mimic and H/R + si-GZMB groups compared to that in the H/R + NC group from 24 hours. More importantly, the cotransfection with miR-518a-5p mimic and si-GZMB significantly accelerated the promoting role of si-GZMB on the HUVEC viability in the H/R model, because the OD value was notably higher than that in the si-GZMB
miR-518a-5p/GZMB INHIBITS H/R-INDUCED CELL INJURY

Discussion

MI is a severe coronary heart disease caused by myocardial ischemia.23 The metabolic alterations caused by myocardial ischemia could lead to irreversible damage and cause apoptosis.24,25 After I/R surgery, changes of wall thickness, injury of endothelial nuclei, and decrease of cell junction were often seen in coronary microcirculation.26 Besides, increasing studies suggested that endothelial apoptosis played an important part in the development of ischemic injury and the radial diffusion of apoptosis to surrounding cardiomyocytes.21,22 Herein, we elaborated the role of miR-518a-5p and GZMB in H/R-induced HUVEC injury and unearthed the targeted relationship between miR-518a-5p and GZMB.

Granzymes are serine proteases that cause cell death, with GZMB as the most well studied one. Current research confirms that GZMB lyses multiple intracellular protein substrates and can induce target cells apoptosis rapidly.27 Numerous studies have shown that human GZMB induced Jurkat cell death by degrading McI-1 and subsequently releasing pro-apoptotic Bim.28,29 A study from Pinkoski indicated that the apoptosis mediated by GZMB was primarily through the mitochondrial pathway inhibited by Bcl-2.30 Furthermore, Goping pointed out that apoptosis induced by GZMB requires both direct activation of caspase and removal of inhibition of caspase.31 Anyhow, these reports provided strong evidence that GZMB promotes apoptosis. However, there was little research exploring the impact of GZMB on myocardial ischemia. Our research revealed for the first time that GZMB expression is up-regulated in MI patients and it inhibited cell proliferation and facilitated apoptosis in H/R-damaged HUVECs, indicating that GZMB might play an aggravating effect in the progression of I/R injury.

In recent years, more and more studies have shown that a series of miRNAs participate in the regulation of MI/R injury.32 It has been revealed that overexpression of miR-126 can alleviate acute myocardial ischemic injury.33 As mentioned in the article, the up-regulation of miR-377 could significantly improve myocardial cell injury by targeting LILRB2 to regulate cell activity and apoptosis.34 In our research, the outcomes illustrated that the miR-518a-5p expression was significantly down-regulated in MI, and we confirmed that the up-regulation of miR-518a-5p weakened GZMB expression by targeting the 3'-UTR of GZMB mRNA. Besides, miR-518a-5p could promote cell proliferation and suppress apoptosis by targeting GZMB so as to ameliorate H/R-induced HUVEC injury. Previous studies have shown that miR-518a-5p may be involved in different diseases. It has been revealed that miR-518a-5p was up-regulated in superimposed pre-eclampsia on chronic hypertension and correlated with pathogenic biochemical pathways specific to superimposed pre-eclampsia.35 Zhang, et al. illustrated that through regulating the miR-518a-5p/Fas signaling pathway, circrnas HSA_circ_0078607 could inhibit ovarian cancer progression.36 Our study revealed the regulating role of miR-518a-5p targeting GZMB in MI for the first time, suggesting that the miR-518a-5p/GZMB axis may be novel targets for the therapy of MI.

In summary, our current study illustrated that miR-518a-5p could facilitate HUVEC proliferation and inhibits...
apoptosis by targeting GZMB to mitigate H/R injury, providing evidence that the miR-518a-5p/GZMB axis may be potential targets for the therapy of MI. In vivo experiments as well as clinical data are required to prove our in vitro discoveries and facilitate the translation of these findings into clinical usage.

Disclosure

Conflicts of interest: None.

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