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Research Progress of Adipocytokines in Myocardial Ischemia/Reperfusion Injury

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Abstract: ***Following myocardial infarction, it is crucial to promptly restore blood and nutrient supply to the ischemic area; however, reperfusion after interrupted blood flow often leads to more severe myocardial damage, known as myocardial ischemia/reperfusion injury (MIRI). The pathological mechanism of MIRI remains incompletely understood, and there are limited therapeutic measures available for practical clinical application. Therefore, further research is needed to explore additional interventions aimed at improving myocardial injury and cardiac function. Adipocytokines are secreted proteins produced by adipose tissue that directly impact MIRI through autocrine, paracrine, or endocrine modes on nearby or remote organs. This review provides a concise overview of the cardioprotective effects and potential mechanisms of adipocytokines in MIRI.***

Keywords: Adipocytokines, Myocardial ischemia/reperfusion injury, Myocardial injury.

1. Introduction

Myocardial infarction is one of the leading causes of death and disability worldwide [1]. Early restoration of blood flow to the ischemic region during acute myocardial infarction, known as reperfusion therapy, can significantly reduce the severity of the infarction [2]. Reperfusion methods primarily include thrombolysis, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), and heart transplantation [3]. However, evidence suggests that both reperfusion therapy and ischemia can exacerbate myocardial injury, further deteriorating the patient's condition. The damage caused by reperfusion is specifically referred to as myocardial ischemia-reperfusion injury [2,3]. This type of injury leads to myocardial cell damage through mechanisms such as arrhythmias, myocardial stunning, microvascular damage, endothelial dysfunction, and irreversible cellular injury or necrosis [4]. Although the pathological mechanisms of myocardial ischemia-reperfusion injury are not yet fully understood, current research indicates that they involve oxidative stress, intracellular calcium overload, energy metabolism disorders, apoptosis, endoplasmic reticulum stress, autophagy, ferroptosis, and necroptosis [5]. Despite advancements in the treatment of myocardial ischemia-reperfusion injury, the damage it causes remains a common cause of mortality in myocardial infarction, cardiovascular surgery, and organ transplantation. Therefore, it is crucial to further improve the clinical cure rate for patients with myocardial ischemia-reperfusion injury. Implementing adjunctive interventions during ischemia/reperfusion injury to limit myocardial cell death has become necessary.

Recent studies have highlighted the significant role of adipokines in cardiac function and myocardial protection. Contrary to the previous belief that adipose tissue primarily serves as an energy storage site, research has shown that it is a significant endocrine and metabolic organ. It secretes and expresses various bioactive peptides, known as adipokines, which function through autocrine, paracrine, or endocrine mechanisms [6]. Adipokines, composed of hormones, cytokines, growth factors, and vasodilators, are crucial signaling molecules involved in various functions. They influence numerous processes, such as energy and appetite regulation, lipid and glucose metabolism, insulin function, endothelial cell function, inflammation, blood pressure, hemostasis, atherosclerosis, and metabolic syndrome [7,8]. Adipokines influence cardiovascular diseases both directly and indirectly by affecting immune responses, angiogenesis, and vascular homeostasis [9]. Adipokines such as adiponectin, C1q/TNF-related protein 9, and fibroblast growth factor 12 have been shown to protect against ischemia-reperfusion-induced myocardial injury. Recently, adipokines have garnered significant attention as key regulators of obesity and obesity-related diseases, which are closely linked to cardiovascular diseases [10]. Research indicates that adipokines possess antioxidant and anti-inflammatory cellular activities, which reduce oxidative stress, improve mitochondrial dysfunction, and inhibit inflammation, potentially alleviating myocardial ischemia/reperfusion injury. Importantly, the functions, molecular targets, and potential clinical relevance of many adipokines remain unclear, representing key areas for future research.

2. Adiponectin

Adiponectin, produced by adipocytes [11,12], features a globular C-terminal domain known as globular adiponectin, which is a biologically active cytokine [13,14]. It offers several beneficial effects on cardiovascular diseases associated with dysregulated glucose and lipid metabolism [14]. These benefits include regulating glucose and lipid metabolism, enhancing insulin sensitivity, reducing oxidative stress and inflammation, protecting cardiomyocytes, and improving endothelial cell function [15]. APN can be used for the diagnosis and prediction of heart failure. APN monomers are found only in adipocytes, but they have also been reported in plasma, where they are secreted after forming multimers [16]. In healthy individuals, plasma APN levels range from 2 to 20 mg/L, accounting for approximately 0.01% of total plasma proteins [17].

Adiponectin plays a crucial role in mitigating myocardial ischemia-reperfusion injury in diabetic patients. A decrease in

adiponectin levels disrupts the cardioprotective effects of ischemic preconditioning in these patients, leading to reduced myocardial p-AKT expression and exacerbated cellular damage [18]. Research has identified a novel therapeutic approach targeting the phosphorylation of adiponectin receptor 1, which is implicated in maladaptive cardiac remodeling post-ischemia. Specifically, the phosphorylation-sensitive site Ser205 of G protein-coupled receptor kinase 2 (GRK2), identified through mass spectrometry, can inhibit the phosphorylation of adiponectin receptor 1, thereby enhancing adiponectin's ability to reverse myocardial remodeling [19]. Another study explored the mechanism of propofol postconditioning in diabetic patients with myocardial ischemia-reperfusion injury, revealing that it suppresses miR-200c-3p expression, upregulates adiponectin receptor 2, activates the STAT3 signaling pathway, and alleviates myocardial ischemia-reperfusion injury [20]. The cardioprotective effects of adiponectin during myocardial ischemia-reperfusion are mediated through the activation of AMPK and SIRT-1 signaling pathways [21]. Furthermore, research has demonstrated that lipid transport proteins can mitigate myocardial ischemia-reperfusion injury via the adiponectin receptor 1/APPL1 signaling pathway, and a reduction in the interaction between adiponectin receptor 1 and APPL1 can also promote myocardial recovery [22]. Zhu Qiqi et al. found that adiponectin exerts cardioprotective effects through AMPK-dependent nuclear and non-dependent mitochondrial STAT3 activation. Ischemic postconditioning (IPO) provides cardiac protection via AMPK-dependent mitochondrial STAT3 activation, and the combined use of adiponectin and IPO induces STAT3 activation through different signaling pathways, protecting the myocardium from ischemia-reperfusion injury [23]. In the context of myocardial ischemia-reperfusion, treatment with globular adiponectin can reduce myocardial cell damage by decreasing oxidative stress and interrupting p38/MAPK signaling, thereby inhibiting ischemia-reperfusion-induced necroptosis and apoptosis, as evidenced by increased cell viability and reduced lactate dehydrogenase release [24]. Adiponectin also partially alleviates myocardial cell damage by inhibiting autophagy through the AMPK/mTOR/ULK1/Beclin-1 signaling pathway [25].

3. Visfatin

Visfatin, also known as pre-B-cell colony-enhancing factor (PBEF) and nicotinamide phosphoribosyltransferase (NAMPT), was first identified in 1994 from a bone marrow cDNA library. It is an adipocytokine produced by visceral fat tissue [26]. It is also expressed in the bone marrow, liver, muscles, heart, placenta, lungs, and kidneys [27]. Nampt exists in different forms intracellularly (iNAMPT) and extracellularly (eNAMPT) [26]. High levels of Nampt in the bloodstream are associated with vascular remodeling, vascular inflammation, and atherosclerosis, thereby increasing the risk of cardiovascular events [28].

Clinical studies have shown that circulating visfatin levels in patients with acute myocardial infarction are associated with epicardial fat thickness, although the specific mechanism remains unclear. Additionally, elevated visfatin levels in these patients may contribute to atherosclerosis [29]. Visfatin may serve as a potential biomarker for risk stratification and personalized treatment in AMI patients, as its peripheral blood levels are closely associated with the severity of AMI, cardiovascular risk factors, and post-PCI atrial fibrillation [30]. In a mouse I/R model, a single intravenous injection of visfatin reduced the infarct size by 50%, demonstrating a direct cardioprotective effect. This mechanism may involve the PI3K and MEK1/2 pathways, as well as the mPTP [31].

Visfatin/NAMPT is associated with Sirt1. As the rate-limiting enzyme in the synthesis of nicotinamide adenine dinucleotide (NAD+), Visfatin/NAMPT plays a crucial role, while Sirt1, an NAD+-dependent histone deacetylase, helps protect the heart from ischemia/reperfusion (I/R) injury [31]. Recent studies have shown that circular RNAs (circRNAs) play a significant role in myocardial cell death following ischemia-reperfusion (I/R) injury. The ferroptosis-related circular RNA, FEACR, interacts with visfatin/NAMPT to regulate myocardial cell ferroptosis through the Sirt1-FOXO1-FTH1 signaling axis. This suggests that FEACR and its downstream factors could potentially serve as new targets for alleviating iron overload-related myocardial damage in ischemic heart disease [32]. The product of visfatin/NAMPT in the NAD+ salvage pathway, nicotinamide mononucleotide, can protect the heart from myocardial ischemia-reperfusion injury (MIRI) by mimicking ischemic preconditioning and activating Sirt1 [33]. Research indicates that inhibiting visfatin/NAMPT can reduce myocardial infarction damage by decreasing early neutrophil inflammation and oxidative stress-mediated tissue injury following reperfusion [34]. Visfatin/NAMPT can reduce inflammation and apoptosis in myocardial cells of MIRI rats through the PI3K-Akt-HSP70 signaling pathway, thereby decreasing myocardial injury markers and improving cardiac function. In vitro experiments show that visfatin/NAMPT also reduces inflammation and apoptosis factors in H9c2 cells [35]. Visfatin/NAMPT also has a protective effect on diabetic hearts. Studies indicate that the activation of visfatin/NAMPT can reduce infarct size by lowering the NADH/NAD+ ratio, improving biochemical signaling, and decreasing the release of troponin I and lactate dehydrogenase (LDH) [36].

4. C1q/TNF-related Protein 9

C1q/TNF-related proteins (CTRPs) are a family of adipokines similar to adiponectin, both possessing a C-terminal globular domain with sequence homology. They exhibit various biological activities, including anti-atherosclerosis, insulin sensitivity, anti-inflammatory effects, and vascular function [37]. All CTRPs (CTRP1-15) have remained highly conserved throughout vertebrate evolution [38]. CTRP9 is the only known molecule capable of forming a heteromer with APN, and the APN/CTRP9 complex can be detected in the serum of APN and CTRP9 transgenic mice [39].

CTRP9 improves cardiac dysfunction and inflammation following acute myocardial infarction. Research indicates that in the early stages of myocardial infarction, CTRP9 alleviates atrial inflammation and fibrosis by inhibiting the Toll-like receptor 4/nuclear factor-κB and Smad2/3 signaling pathways [40]; The regulation of macrophage polarization through the TLR4/MD2/MyD88 and AMPK/NF-κB pathways can improve early cardiac dysfunction and myocardial inflammation following myocardial infarction [41]. CTRP9

enhances the proliferation and survival of adipose-derived mesenchymal stem cells (ADSCs), stimulates their migration, and binds with N-cadherin. It activates the ERK-matrix metalloproteinase 9 and ERK-NF-E2-related factor 2 signaling pathways, leading to the upregulation of antioxidant protein secretion. This process aids in the colonization of stem cells in infarcted myocardial tissue, thereby improving the therapeutic efficacy of stem cells in treating ischemic cardiomyopathy [42].

The therapeutic effects of CTRP9 are related to cardiomyocyte apoptosis. CTRP9 prevents acute myocardial ischemic injury through an AMPK-dependent mechanism. Administering overexpressed circulating CTRP9 before ischemia can activate AMPK expression, reducing myocardial infarct size in wild-type mice after ischemia/ reperfusion. Additionally, a single dose of recombinant CTRP9 protein given during reperfusion can further decrease the myocardial infarct size and eliminate the inhibition of cardiomyocyte apoptosis. In an in vitro model of myocardial hypoxia/reoxygenation injury, the expression of CTRP9 in cardiomyocytes decreases. When cardiac-derived CTRP9 is administered, it interacts with the endoplasmic reticulum chaperone calreticulin located on the surface and in the cytoplasm of cardiomyocytes. This interaction activates the PKA-CREB signaling pathway, inhibits apoptosis, and provides protective effects against myocardial injury [43]. In summary, CTRP9 improves cardiac function and inhibits cardiomyocyte apoptosis in acute myocardial infarction and ischemia-reperfusion injury, although its specific protective mechanisms remain unclear.

5. Fibroblast Growth Factor 21

Fibroblast growth factors (FGFs) are polypeptide growth factors composed of highly homologous amino acid sequences, functioning in paracrine, autocrine, or endocrine manners [44]. FGF21, a key member of the fibroblast growth factor family, is an endocrine FGF composed of 209 amino acids. It can inhibit apoptosis in pancreatic β-cells, hepatocytes, cardiac vascular endothelial cells, and cardiomyocytes [45]. Fibroblast growth factor 21 (FGF21) is a novel peptide ligand shown to be involved in various physiological and pathological processes, including the regulation of glucose and lipids, as well as the reduction of atherosclerotic plaque formation in major blood vessels.

Previous studies have shown that FGF21 enhances the expression of antioxidant genes and enzymes through the Akt-GSK-3β-caspase-3 dependent pathway. This process inhibits oxidative stress and apoptosis, improves energy supply, and protects the heart from IR damage [46]. FGF21 enhances autophagy and exerts a protective effect in myocardial ischemia-reperfusion injury by increasing miR-145 levels and autophagy while inhibiting Angpt2 expression, which subsequently reduces serum levels of LDH, TNF-α, and IL-6 [47]. n the hypoxia/reoxygenation model of the H9C2 cell line, increasing the expression levels of Beclin-1 and Vps34 proteins enhances autophagic flux, thereby protecting the myocardium from damage [48]. During myocardial ischemia-reperfusion injury, FGF21 protects the heart by inhibiting Angpt2, inducing the expression of glucose transporter 1 (GLUT1), enhancing myocardial energy metabolism, suppressing apoptosis, and increasing cell migration capacity [49]. Under hypoxic conditions, FGF21 can inhibit cell apoptosis, reduce the expression of ColIaI, fibronectin, and α-SMA, and decrease galectin-3 levels, thereby preventing pathological cardiac remodeling after ischemia [50]. FGF21, secreted at high levels in the culture medium of high thermogenic beige adipocytes (HBACs) derived from rat adipose stem cells, enhances the expression of antioxidant and anti-apoptotic factors in H9c2 cardiomyocytes and activates NRF2 expression. This significantly alleviates ischemic myocardial damage in rats, suggesting its beneficial role in myocardial ischemia/ reperfusion injury and its potential as a therapeutic agent for myocardial infarction [51]. Myocardial ischemia not only causes damage to myocardial cells but also activates innate protective processes that enhance the heart's tolerance to ischemia. In response to myocardial ischemia/reperfusion injury in mice, FGF21 is upregulated and released into circulation from hepatocytes and adipocytes. This release improves post-injury cardiac function and reduces cell apoptosis through the FGFR1/b-Klotho-PI3K-Akt1-BAD signaling pathway [52].

6. Conclusion

In conclusion, adipokines are closely associated with myocardial ischemia-reperfusion injury (MIRI), yet the underlying mechanisms remain incompletely understood. Various adipokines are involved in the development and progression of MIRI, contributing to its complex pathophysiology. Given the current limitations in research, further in-depth studies are necessary to potentially identify new therapeutic targets for MIRI. Beyond the adipokines already mentioned, other factors are also being investigated for their roles in MIRI treatment. Notably, leptin has been clearly studied for its therapeutic effects on MIRI. Nesfatin-1, a novel cardiac peptide, has been shown to protect against MIRI by reducing infarct size, lactate dehydrogenase release, and post-ischemic contracture. Asprosin, a newly discovered fasting-induced glucose-generating adipokine, has been identified as a reliable biomarker for predicting the severity of coronary artery lesions in patients with unstable angina and as a prognostic biomarker for patients with dilated cardiomyopathy. However, its role in MIRI remains unclear and warrants further investigation. MIRI is a complex process involving multi-level and multi-factor interactions among genes, molecules, cells, and tissues. A comprehensive understanding of the pathogenesis and pathophysiological development of MIRI is essential. Due to the incomplete elucidation of MIRI's pathological mechanisms and existing discrepancies in some conclusions, further research is crucial to provide opportunities for potential future treatments.

References

[1] Task Force Members, Thygesen K, Alpert J S, et al. Universal definition of myocardial infarction: Kristian Thygesen, Joseph S. Alpert and Harvey D. White on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction [J]. European Heart Journal, 2007, 28(20): 2525-2538.

[2] Yellon D M, Hausenloy D J. Myocardial Reperfusion Injury [J]. The New England Journal of Medicine, 2007, 357(11):1121-1135.
[3] Verma S, Fedak P W M, Weisel R D, et al. Fundamentals of Reperfusion Injury for the Clinical Cardiologist [J]. Circulation, 2002, 105(20): 2332-2336.
[4] Yellon D M. Protecting the ischaemic and reperfused myocardium in acute myocardial infarction: distant dream or near reality? [J]. Heart, 2000, 83(4): 381-387.
[5] Kalogeris T, Baines C P, Krenz M, et al. Cell Biology of Ischemia/Reperfusion Injury [M/OL]//International Review of Cell and Molecular Biology. Elsevier, 2012, 229-317 [2023-01-06].
[6] Kershaw E E, Flier J S. Adipose Tissue as an Endocrine Organ [J]. The Journal of Clinical Endocrinology & Metabolism, 2004, 89(6): 2548-2556.
[7] Zorena K, Jachimowicz-Duda O, Ślęzak D, et al. Adipokines and Obesity. Potential Link to Metabolic Disorders and Chronic Complications [J]. International Journal of Molecular Sciences, 2020, 21(10): 3570.
[8] Fasshauer M, Blüher M. Adipokines in health and disease [J]. Trends in Pharmacological Sciences, 2015, 36(7): 461-470.
[9] Nakamura K, Fuster J J, Walsh K. Adipokines: A link between obesity and cardiovascular disease [J]. Journal of Cardiology, 2014, 63(4): 250-259.
[10] Ouwens D M, Sell H, Greulich S, et al. The role of epicardial and perivascular adipose tissue in the pathophysiology of cardiovascular disease [J]. Journal of Cellular and Molecular Medicine, 2010, 14(9): 2223-2234.
[11] Jun Y, Xiao T, Guoyong Y, et al. Recombinant globular adiponectin inhibits lipid deposition by p38 MAPK/ATF-2 and TOR/p70 S6 kinase pathways in chicken adipocytes [J]. Biochemistry and Cell Biology, 2014, 92(1): 53-60.
[12] Tian X-Q, Yang Y-J, Li Q, et al. Globular Adiponectin Inhibits the Apoptosis of Mesenchymal Stem Cells Induced by Hypoxia and Serum Deprivation via the AdipoR1-Mediated Pathway [J]. Cellular Physiology and Biochemistry, 2016, 38(3): 909-925.
[13] Kim Y, Cho J Y, Oh S W, et al. Globular adiponectin acts as a melanogenic signal in human epidermal melanocytes [J]. British Journal of Dermatology, 2018, 179(3): 689-701.
[14] Onay-Besikci A, Altarejos J Y, Lopaschuk G D. gAd-globular Head Domain of Adiponectin Increases Fatty Acid Oxidation in Newborn Rabbit Hearts [J]. Journal of Biological Chemistry, 2004, 279(43): 44320-44326.
[15] Han X, Wu Y, Liu X, et al. Adiponectin improves coronary no-reflow injury by protecting the endothelium in rats with type 2 diabetes mellitus [J]. Bioscience Reports, 2017, 37(4): BSR20170282.
[16] Chandran M, Phillips S A, Ciaraldi T, et al. Adiponectin: More Than Just Another Fat Cell Hormone? [J]. Diabetes Care, 2003, 26(8): 2442-2450.
[17] Han W, Yang S, Xiao H, et al. Role of Adiponectin in Cardiovascular Diseases Related to Glucose and Lipid Metabolism Disorders [J]. International Journal of Molecular Sciences, 2022, 23(24): 15627.
[18] Cao C, Liu H, Li W, et al. Role of adiponectin in diabetes myocardial ischemia-reperfusion injury and ischemic postconditioning [J]. Acta Cirúrgica Brasileira, 2020, 35(1): e202000107.
[19] Zhu D, Zhang Z, Zhao J, et al. Targeting Adiponectin Receptor 1 Phosphorylation Against Ischemic Heart Failure [J/OL]. Circulation Research, 2022, 131(2) [2023-07-11].
[20] Huang L, Ding L, Yu S, et al. Propofol postconditioning alleviates diabetic myocardial ischemia-reperfusion injury via the miR-200c-3p/AdipoR2/STAT3 signaling pathway [J]. Molecular Medicine Reports, 2022, 25(4): 137.
[21] Potenza M A, Sgarra L, Nacci C, et al. Activation of AMPK/SIRT1 axis is required for adiponectin-mediated preconditioning on myocardial ischemia-reperfusion (I/R) injury in rats [J]. PLOS ONE, 2019, 14(1): e0210654.
[22] Ren C, Yi W, Jiang B, et al. Diminished AdipoR1/ APPL1 Interaction Mediates Reduced Cardioprotective Actions of Adiponectin against Myocardial Ischemia/Reperfusion Injury in Type-2 Diabetic Mice [J]. Stem Cells International, 2023, 2023: 1-8.
[23] Zhu Q, Li H, Xie X, et al. Adiponectin Facilitates Postconditioning Cardioprotection through Both AMPK-Dependent Nuclear and AMPK-Independent Mitochondrial STAT3 Activation [J]. Oxidative Medicine and Cellular Longevity, 2020, 2020: 1-17.
[24] Zhu K, Guo J, Yu X, et al. Polypeptide Globular Adiponectin Ameliorates Hypoxia/Reoxygenation-Induced Cardiomyocyte Injury by Inhibiting Both Apoptosis and Necroptosis [J]. Journal of Immunology Research, 2021, 2021: 1-14.
[25] Guo J, Zhu K, Li Z, et al. Adiponectin Protects Hypoxia/Reoxygenation-Induced Cardiomyocyte Injury by Suppressing Autophagy [J]. Journal of Immunology Research, 2022, 2022: 1-11.
[26] Dakroub A, A. Nasser S, Younis N, et al. Visfatin: A Possible Role in Cardiovasculo-Metabolic Disorders [J]. Cells, 2020, 9(11): 2444.
[27] Samal B, Sun Y, Stearns G, et al. Cloning and Characterization of the cDNA Encoding a Novel Human Pre-B-Cell Colony-Enhancing Factor [J]. 1994, 14.
[28] Dakroub A, Nasser S A, Kobeissy F, et al. Visfatin: An emerging adipocytokine bridging the gap in the evolution of cardiovascular diseases [J]. Journal of Cellular Physiology, 2021, 236(9): 6282-6296.
[29] Avesta L, Doustkami H, Zamani B, et al. Association of plasma visfatin with epicardial fat thickness and severity of coronary artery diseases in patients with acute myocardial infarction and stable angina pectoris [J/OL]. ARYA Atherosclerosis Journal, 2022, 18(July) [2024-02-28].
[30] Zhang H, Lei D, Zhang M, et al. Correlations of visfatin with severity of acute myocardial infarction, cardiovascular risk factors and atrial fibrillation after percutaneous coronary intervention [J]. Journal of Medical Biochemistry, 2023, 42(4): 650-657.
[31] Lim S Y, Davidson S M, Paramanathan A J, et al. The novel adipocytokine visfatin exerts direct cardioprotective effects [J]. Journal of Cellular and Molecular Medicine, 2008, 12(4): 1395-1403.
[32] Ju J, Li X-M, Zhao X-M, et al. Circular RNA FEACR inhibits ferroptosis and alleviates myocardial ischemia/

reperfusion injury by interacting with NAMPT [J]. Journal of Biomedical Science, 2023, 30(1): 45.
[33] Yamamoto T, Byun J, Zhai P, et al. Nicotinamide Mononucleotide, an Intermediate of NAD+ Synthesis, Protects the Heart from Ischemia and Reperfusion [J]. PLoS ONE, 2014, 9(6): e98972.
[34] Montecucco F, Bauer I, Braunersreuther V, et al. Inhibition of Nicotinamide Phosphoribosyltransferase Reduces Neutrophil-Mediated Injury in Myocardial Infarction [J]. Antioxidants & Redox Signaling, 2013, 18(6): 630-641.
[35] Xin BR, Li P, Liu XL, Zhang XF. Visfatin relieves myocardial ischemia-reperfusion injury through activation of PI3K/Akt/HSP70 signaling axis [J]. European review for medical and pharmacological sciences, 2020, 24(20):10779-10789.
[36] Tur J, Badole S L, Manickam R, et al. Cardioprotective Effects of 1-(3, 6-Dibromo-carbazol-9-yl)-3-Phenylamino-Propan-2-Ol in Diabetic Hearts via Nicotinamide Phosphoribosyltransferase Activation [J]. Journal of Pharmacology and Experimental Therapeutics, 2022, 382(2): 233-245.
[37] Kawano J, Arora R. The Role of Adiponectin in Obesity, Diabetes, and Cardiovascular Disease [J]. Journal of the CardioMetabolic Syndrome, 2009, 4(1): 44-49.
[38] Seldin M M, Tan S Y, Wong G W. Metabolic function of the CTRP family of hormones [J]. Reviews in Endocrine and Metabolic Disorders, 2014, 15(2): 111-123.
[39] Su H, Yuan Y, Wang X-M, et al. Inhibition of CTRP9, a novel and cardiac-abundantly expressed cell survival molecule, by TNFα-initiated oxidative signaling contributes to exacerbated cardiac injury in diabetic mice [J]. Basic Research in Cardiology, 2013, 108(1): 315.
[40] Liu M, Li W, Wang H, et al. CTRP9 Ameliorates Atrial Inflammation, Fibrosis, and Vulnerability to Atrial Fibrillation in Post-Myocardial Infarction Rats [J]. Journal of the American Heart Association, 2019, 8(21): e013133.
[41] Liu M, Yin L, Li W, et al. C1q/TNF-related protein-9 promotes macrophage polarization and improves cardiac dysfunction after myocardial infarction [J]. Journal of Cellular Physiology, 2019, 234(10): 18731-18747.
[42] Yan W, Guo Y, Tao L, et al. C1q/Tumor Necrosis Factor–Related Protein-9 Regulates the Fate of Implanted Mesenchymal Stem Cells and Mobilizes Their Protective Effects Against Ischemic Heart Injury via Multiple Novel Signaling Pathways [J]. Circulation, 2017, 136(22): 2162-2177.
[43] Zhao D, Feng P, Sun Y, et al. Cardiac-derived CTRP9 protects against myocardial ischemia/reperfusion injury via calreticulin-dependent inhibition of apoptosis [J]. Cell Death & Disease, 2018, 9(7): 723.
[44] Klagsbrun M. The fibroblast growth factor family: Structural and biological properties [J]. Progress in Growth Factor Research, 1989, 1(4): 207-235.
[45] Bookout A L, De Groot M H M, Owen B M, et al. FGF21 regulates metabolism and circadian behavior by acting on the nervous system [J]. Nature Medicine, 2013, 19(9): 1147-1152.
[46] Cong W-T, Ling J, Tian H-S, et al. Proteomic study on the protective mechanism of fibroblast growth factor 21 to ischemia–reperfusion injury [J]. Canadian Journal of Physiology and Pharmacology, 2013, 91(11): 973-984.
[47] Hu S, Cao S, Tong Z, et al. FGF21 protects myocardial ischemia-reperfusion injury through reduction of miR-145-mediated autophagy [J]. American journal of translational research, 10(11), 3677–3688.
[48] Ren Z, Xiao W, Zeng Y, et al. Fibroblast growth factor-21 alleviates hypoxia/reoxygenation injury in H9c2 cardiomyocytes by promoting autophagic flux [J/OL]. International Journal of Molecular Medicine, 2019 [2023-01-02].
[49] Hu S, Cao S, Liu J. Role of angiopoietin-2 in the cardioprotective effect of fibroblast growth factor 21 on ischemia/reperfusion-induced injury in H9c2 cardiomyocytes [J]. Experimental and Therapeutic Medicine, 2017, 14(1): 771-779.
[50] Sun M, Jin L, Bai Y, et al. Fibroblast growth factor 21 protects against pathological cardiac remodeling by modulating galectin-3 expression [J]. Journal of Cellular Biochemistry, 2019, 120(12): 19529-19540.
[51] Moon H, Choi J-W, Song B-W, et al. Brite Adipocyte FGF21 Attenuates Cardiac Ischemia/Reperfusion Injury in Rat Hearts by Modulating NRF2 [J]. Cells, 2022, 11(3): 567.
[52] Liu S Q, Roberts D, Kharitonenkov A, et al. Endocrine Protection of Ischemic Myocardium by FGF21 from the Liver and Adipose Tissue [J]. Scientific Reports, 2013, 3(1): 2767.