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Short Communication

Hub Genes and Therapeutic Pathways of CTRP9 in Cardiac Ischemia/Reperfusion Injury: A Bioinformatics Perspective

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Abstract

Background: Ischemia/reperfusion injury (IRI) is a significant contributor to cardiac morbidity, while therapeutic options remain limited. According to previous evidence, C1q/TNF-related protein 9 (CTRP9), an adipokine with cardiometabolic regulatory properties, may serve as a potential modulator of myocardial injury. In this study, comprehensive bioinformatics analyses were primarily employed to identify hub genes and elucidate key therapeutic pathways associated with CTRP9 in the context of IRI.

Methods: An interrelation analysis of hub genes was conducted to identify direct and indirect interactions. The resulting network and enrichment data were extracted from Cytoscape-GeneMANIA3.6.*0*, based on a genome-wide human interaction map, for further analysis and visualization.

Results: Protein-protein interaction networks and functional enrichment analyses revealed that CTRP9 exerts cardioprotective effects primarily through the activation of adenosine monophosphate-activated protein kinase (AMPK) signaling, which leads to reduced cardiomyocyte apoptosis and enhanced angiogenesis. Notably, bioinformatics data suggested several downstream effectors, such as ucp1, gsk3b, and rps6kb1, as well as collagen-related genes (i.e., *col4a2*, *col14a1*, and *col18a1*), linked to the beneficial effects of CTRP9, considering it a promising therapeutic option related to IRI.

Conclusion: These findings recommend several hub genes and pathways that may serve as novel therapeutic targets, highlighting the potential of CTRP9-based interventions for managing IRI-induced cardiac damage and improving clinical outcomes, particularly in cases of myocardial damage caused by IRI. Uncovering all possible underlying mechanisms could enhance our ability to better address the pathological sequelae following IRI.

Keywords: AMPK signaling, Angiogenesis, C1q/TNF-related protein 9 (CTRP9), Ischemia/Reperfusion injury, Bioinformatics analyses

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Introduction

Restoring blood flow, also known as reperfusion, to ischemic tissue results in adverse events, such as endothelial cell injury, local and systemic inflammation, tissue edema, and increased vascular permeability.[1,2] This phenomenon, characterized as ischemic/reperfusion injury (IRI), can diminish the efficacy of reperfusion therapy, which is the mainstay of managing ischemic conditions.[3,4] Notably, our recent review dominantly elucidated the potential role of C1q tumor necrosis factor-related protein-9 (CTRP9) in favor of IRI prevention and treatment.[5]

The CTRP9 is one of the members of the adiponectin paralog family, drawing attention for its potential roles, especially in cardiovascular physiopathology. Initially identified as a cardiokine, CTRP9 is abundantly expressed in cardiac tisssue, where it functions with significant autocrine and paracrine effects. Emerging evidence highlights CTRP9's protective role against myocardial IRI, a major contributor to cardiac dysfunction following acute myocardial infarction.[6] During IRI, the sudden restoration of blood flow leads to oxidative stress, inflammation, and cardiomyocyte apoptosis, exacerbating myocardial damage. CTRP9 has been shown to mitigate these deleterious effects by activating intracellular signaling pathways that promote cell survival and inhibit apoptosis. In this regard, experimental studies also demonstrated that CTRP9 deficiency exacerbates cardiac injury and dysfunction post-IRI, whereas CTRP9 overexpression or supplementation confers significant protection, highlighting its therapeutic potential.

One critical and well-established pathway implicated in CTRP9-mediated cardioprotection is the adenosine monophosphate-activated protein kinase (AMPK) signaling cascade.[7] AMPK serves as a cellular energy sensor and regulator, orchestrating metabolic homeostasis and stress responses.[8,9] Furthermore, CTRP9-induced AMPK activation inhibits apoptosis and endoplasmic reticulum stress in cardiomyocytes subjected to ischemic insult, thereby preserving myocardial function.

To the best of our knowledge, CTRP9 activates AMPK signaling directly through binding to the adiponectin receptor 1 (AdipoR1), but not AdipoR2, on target cells such as endothelial cells and cardiomyocytes, leading to the phosphorylation and activation of AMPK, and subsequent downstream protective cellular responses, e.g., nitric oxide production through the AMPK-endothelial nitric oxide synthase pathway.[9] During the AdipoR1-AMPK axis, CTRP9 stimulates the phosphorylation of AMPK at the Thr172 site on the α subunit.[10,11]

Beyond the AMPK signaling pathway, CTRP9 also engages other pro-survival signaling pathways, including protein kinase A-cAMP response element-binding protein axis, which further contributes to its anti-apoptotic effects in cardiomyocytes.[12] The interaction between CTRP9 and molecular chaperones, such as calreticulin, facilitates the activation of these protective pathways, highlighting a complex regulatory network. Additionally, CTRP9 influences vascular remodeling and angiogenesis, which are essential processes for myocardial repair and recovery after ischemic injury.

Considering the indispensable role of CTRP9 in alleviating IRI, the identification of involved effectors and relevant signaling pathways must be addressed. Accordingly, this study aims to provide insights into potential strategies for enhancing cardiac repair potential against ischemic stress. It particularly explores the potency of candidate factors using the bioinformatics analysis regarding the interplay of c1qtnf9 with possible signaling pathways.

Methods

An interrelation analysis of the identified hub genes to determine their interactions was performed, essentially among the genes that interacted with one another directly or indirectly. Using Cytoscape-GeneMANIA (version 3.6.0),[13] it was attempted to predict gene function and construct gene interaction networks, integrating numerous biological data types, such as protein-protein interactions, genetic interactions, co-expression, co-localization, and shared protein domains, to identify genes related to a given query gene set, c1qtnf9. The final network and enrichment results were exported from Cytoscape-GeneMANIA for downstream analysis, to interpret and visualize the significant gene sets identified, and figure preparation according to the results obtained from a genome-wide map of human genome interaction. This is a comprehensive, global representation of how various regions of the genome physically associate and communicate within the three-dimensional space of the cell nucleus, offering an essential understanding of gene regulation mechanisms that extend beyond the simple linear DNA sequence.

Results and Discussion

Notably, our results revealed that the CTRP-9-related encoded gene (*c1qtnf9*) has the potential to interact with three genes, including *rps6kb1*, *gsk3b*, and *ucp1* (Figure 1). The *rps6kb1* gene encodes ribosomal protein S6 kinase beta-1 (RPS6KB1), **a** serine/threonine kinase in humans, which has a crucial role in protein synthesis[14] and belongs to the PI3K-dependent signaling pathway. Mechanistically, the rps6kb1 is mainly activated by the phosphoinositide 3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathway, regulating protein synthesis via ribosomal protein S6 phosphorylation.[15] Previous results elegantly demonstrated the close interaction of the rps6kb1 factor with the mTOR/autophagy pathway (as AMPK downstream), in which the binding of rps6kb1 to mTOR-related effectors promotes the autophagic response.[16] In ischemic cardiac microvascular endothelial cells, it has also been shown that the inhibition of rps6kb1 promotes the down-regulation of vascular endothelial growth factor via the hypoxia-inducible factor 1-α-related pathway and aberrant angiogenesis by suppressing MAPK/PI3K/Akt signaling, further highlighting its importance in vascular repair during ischemia.[17]

Gsk3b, the second identified factor by bioinformatics analysis, is an isoform of the GSK-3 enzyme, known as an energy regulatory sensor, mainly acting through Wnt/β-catenin and PI3K/AKT pathways. The GSK3b has been a promising therapeutic target for some ischemic diseases.[18,19] However, a dual function of GSK3β has been identified in myocardial injury caused by IRI. During extended ischemia, the activation of GSK3β stimulates autophagy by inhibiting mTOR, which promotes the survival of cardiomyocytes. Conversely, in the reperfusion phase, inhibiting GSK3β helps protect the heart by reducing excessive autophagy, thereby mitigating myocardial damage.[20] Hence, it is evident that the opposite regulation of GSK3β throughout IRI plays a crucial role in balancing cell survival and death in ischemic heart disease. Collectively, both gsk3b and rps6kb1 have a cross-link in mTOR signaling,[21] influencing both angiogenesis and autophagy during ischemia and modulating signaling cascades affecting vascular function.

The latter factor, *Ucp1* gene, encoding a transmembrane protein, UCP1, also named thermogenin, is crucial in energy-induced hemostasis in epicardial adipose tissue and can be altered during cardiometabolic syndromes.[22-24]

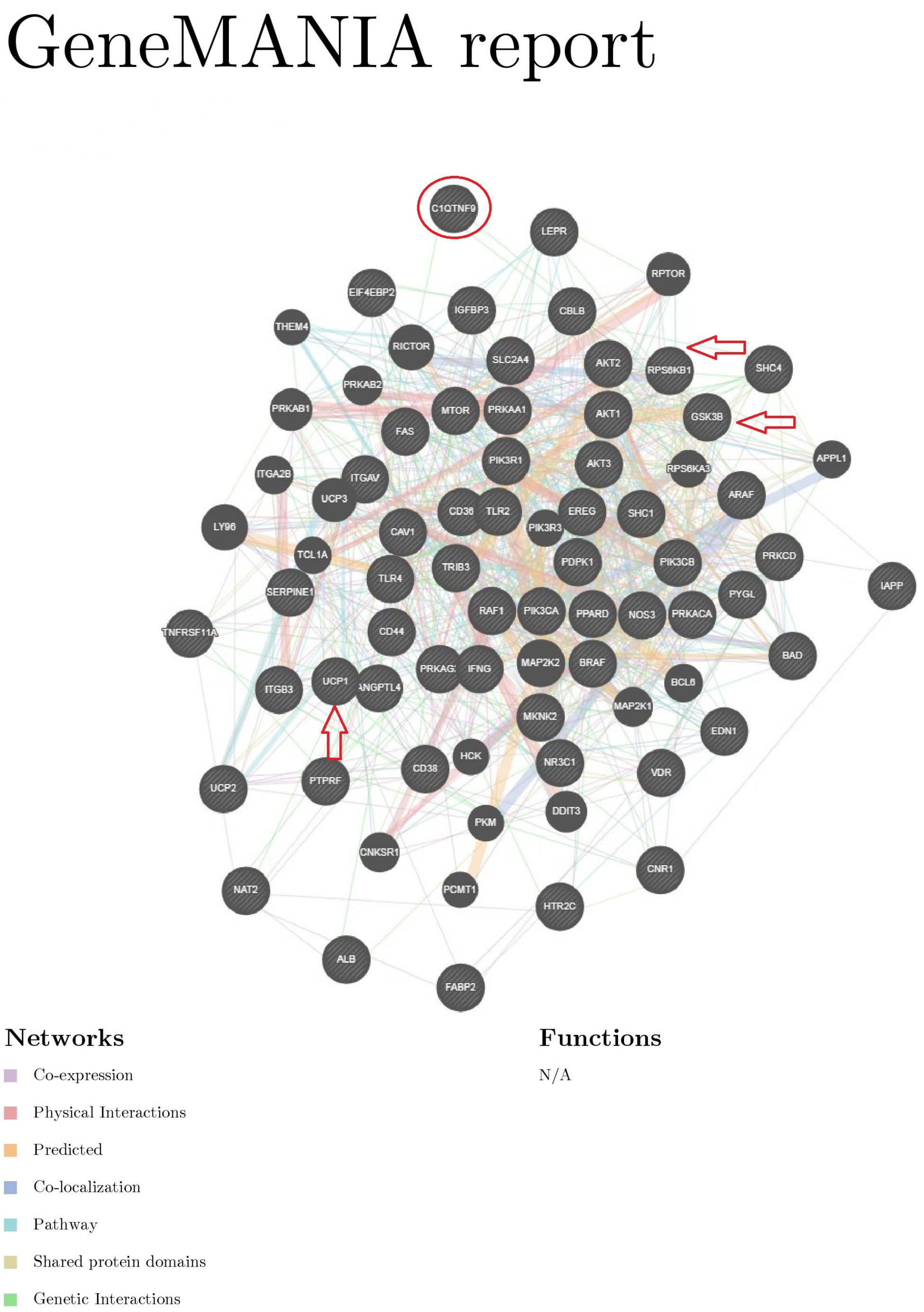

Figure 1. Application of an Integrated Pathway Gene-Related Database to Identify Common Pathways Involved in CTRP9 Effects: Possible Genetic Interplay Between c1qtnf9 and the AMPK Signaling Pathway by GeneMANIA Software
Note. CTRP9: C1q tumor necrosis factor-related protein-9; AMPK: Adenosine monophosphate-activated protein kinase.

Recently, it has been postulated that single-nucleotide polymorphisms of *Ucp1* were associated with the risk of cardiometabolic syndromes.[25]

Further genome-wide association analysis was also performed using GeneMANIA Cytoscape software. The results interestingly confirmed that *c1qtnf9* has the potential to directly interact with *COL4A2*, *COL14A1*, and *COL18A1*, which are related to collagen activity (Figure 2).

Collagen-related pathways in cardiomyocytes play a protective role by maintaining cardiac structure and function, as well as influencing the remodeling processes in the heart. In detail, collagen fibers provide a supporting framework for myocytes and endothelial cells, maintaining tissue architecture and coordinating force delivery generated by myocytes.[26] Given the pivotal role of type IV collagen in cardiovascular diseases (CVD), the recent genomic study on patients with various CVD indicated that genetic variants associated with coronary heart disease are at the locus of *COL4A1/COL4A2*. Additionally, Col4A1/Col4A2 are also known as structural components of basement membranes critical for vascular

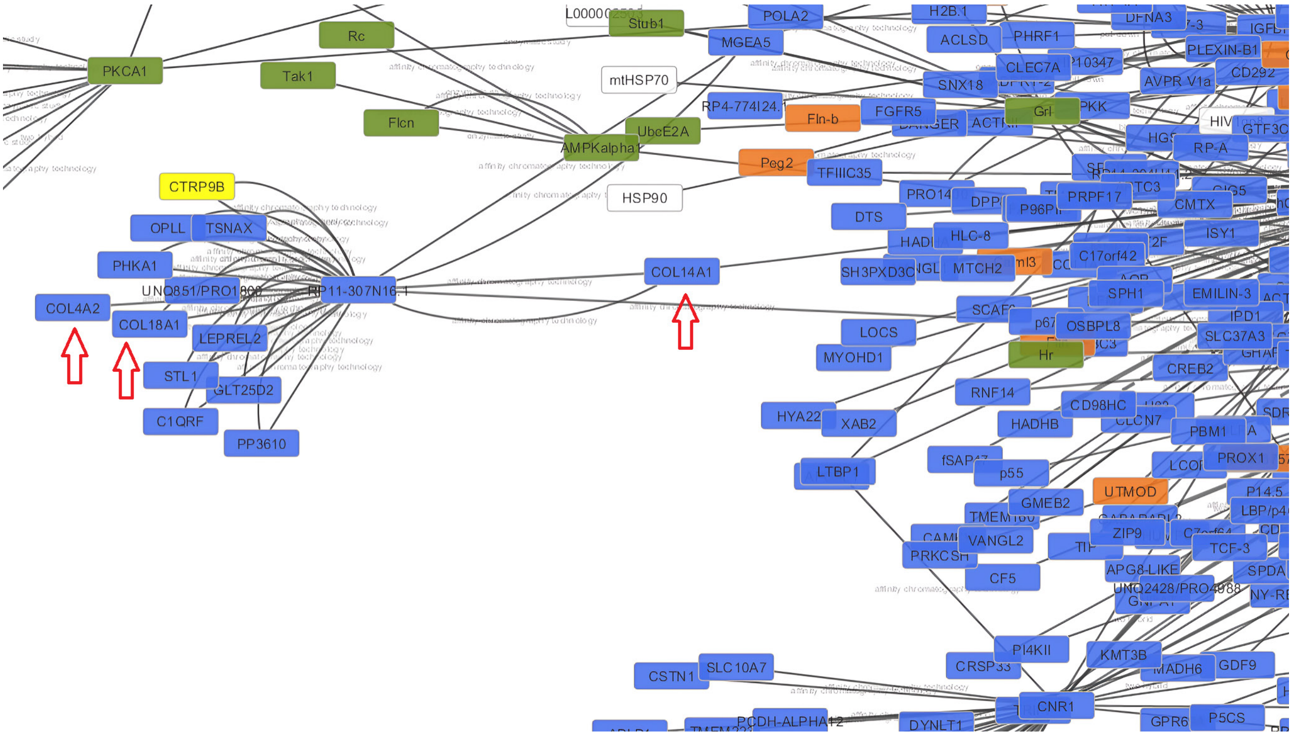

Figure 2. Utilizing a Comprehensive Gene-Pathway Database to Uncover Shared Pathways Influenced by CTRP9: Evaluation of Direct Interactions Between the *CTRP9* gene (*c1qtnf2*) and Related Genes by Cytoscape
Note. CTRP9: C1q tumor necrosis factor-related protein-9

integrity and angiogenesis, which are a part of multi-locus genetic risk scores for coronary artery diseases, increasing hemorrhagic stroke risk. These traits can affect atherosclerotic plaque stability, preventing macrovascular pathologies and the risk of MI.[27] A preprint study also revealed that dysregulation in collagen-related pathways has a crucial role in the abolished hearts and identified molecular defects using single-cell mRNA sequencing data in the subset of newborns. Noteworthy, some pre-collagen pathways, including MAS and connective tissue growth factor (MAS-CTGF-collagen pathway), may also act to modulate pro-collagen expression, such as *Col1A1*, *Col1A2*, *Col3A1*, and *Col4A2*.[28] Moreover, it has been well-documented that the mutations in *col4a1/a2* genes potentially disrupt basement membranes, enhancing the risk for small vessel disease, including deep intracerebral hemorrhage,[29] hypertension, aortic dilation, and coronary artery dissections.[30, 31]

Furthermore, compelling evidence demonstrated the key role of collagen XIV, especially Col14a1, in the regulation of early stages of fibrillogenesis, cardiomyocyte proliferation, cell survival, and heart maturity, which was further confirmed by hub-gene assessment.[32, 33]

Regarding the Col18a1, it has also been proven that by engaging a structural role in the basement membrane alongside its angiostatic fragment endostatin, Col18a1 is considered a critical regulator of vascular homeostasis in CVD.[34] In this line, preclinical data declared that *Col18a1* deficiency contributes to atherosclerosis progression, microvascular damage,[35] and cardiac remodeling.[36] These findings further indicate that Col18a1 is a potential biomarker and therapeutic target in various cardiovascular conditions.

Conclusion

These results highlight key hub genes and pathways that could serve as potential therapeutic targets, proposing the promise of CTRP9-based treatments more likely mediated by ucp1, gsk3b, and rps6kb1, as well as collagen-related genes, for addressing myocardial injury due to IRI and improving patient outcomes. Uncovering the full spectrum of underlying mechanisms may further enhance our ability to effectively manage the pathological consequences following IRI.

Ethical statement

Not applicable.

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This study received no financial support.

Conflict of interests declaration

The authors declare no conflict of interests.

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Data availability statement

The corresponding author will provide the datasets used and/or analyzed during the current work upon reasonable request.

Author contributions

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Consent for publication

Not applicable.

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