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REVIEW

Advances in the Study of MG53 in Cardiovascular Disease

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Abstract: Cardiovascular diseases represent a global health crisis, and understanding the intricate molecular mechanisms underlying cardiac pathology is crucial for developing effective diagnostic and therapeutic strategies. Mitsugumin-53 (MG53) plays a pivotal role in cell membrane repair, has emerged as a multifaceted player in cardiovascular health. MG53, also known as TRIM72, is primarily expressed in cardiac and skeletal muscle and actively participates in membrane repair processes essential for maintaining cardiomyocyte viability. It promotes k-ion currents, ensuring action potential integrity, and actively engages in repairing myocardial and mitochondrial membranes, preserving cardiac function in the face of oxidative stress. This study discusses the dual impact of MG53 on cardiac health, highlighting its cardioprotective role during ischemia/reperfusion injury, its modulation of cardiac arrhythmias, and its influence on cardiomyopathy. MG53's regulation of metabolic pathways, such as lipid metabolism, underlines its role in diabetic cardiomyopathy, while its potential to mitigate the effects of various cardiac disorders, including those induced by antipsychotic medications and alcohol consumption, warrants further exploration. Furthermore, we examine MG53's diagnostic potential as a biomarker for cardiac injury. Research has shown that MG53 levels correlate with cardiomyocyte damage and may predict major adverse cardiovascular events, highlighting its value as a biomarker. Additionally, exogenous recombinant human MG53 (rhMG53) emerges as a promising therapeutic option, demonstrating its ability to reduce infarct size, inhibit apoptosis, and attenuate fibrotic responses. In summary, MG53's diagnostic and therapeutic potential in cardiovascular diseases presents an exciting avenue for improved patient care and outcomes.

Keywords: Mitsugumin-53, MG53, cardiovascular disease, cell membrane repair, ischemia/reperfusion

Introduction

Cardiovascular disease, a broad term encompassing conditions affecting the heart and blood vessels, is closely linked to both metabolic and lifestyle risk factors. These conditions result in various pathological changes, such as lesions that can lead to reduced blood supply, hypoxia, and, in severe cases, tissue necrosis in the circulatory system and myocardial tissues. Heart disease significantly impairs the normal physiological functioning of the human body and stands as the leading cause of mortality worldwide across diverse populations.[1] Key contributors to cardiovascular disease include coronary artery disease (CAD), heart failure, hypertension, myocardial infarction, cardiomyopathy, abnormal heart rhythms, congenital heart disease, valvular heart disease, heart inflammation and peripheral arterial disease. The confluence of an aging global population and the prevalence of unhealthy dietary habits has added to the metabolic burden on the human cardiovascular system, thereby presenting a substantial challenge in terms of prevention and control of these diseases.

Notably, cardiomyocytes, which are specialized cells in the heart responsible for its contractile function, are terminally differentiated with limited self-renewal capacity. Rupture of cardiomyocyte cell membranes is a primary cause of cell death following injury, and the process of membrane repair is essential for preserving cardiomyocyte

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viability.[2] Consequently, investigating the pathophysiological role of cell membranes in the development of cardiovascular diseases is crucial for identifying potential therapeutic targets and underlying mechanisms.

Under natural conditions, physiologically damaged cells can be rapidly repaired by inherent biological processes.[3] However, in individuals with cardiovascular and other diseases, the natural repair process of cell membrane repair can be hindered and disrupted. The ability of cells to autonomously repair membrane damage stands as a vital component of overall organismal physiology. Mitsugumin-53 (MG53), alternatively known as TRIM72, belongs to the tripartite motif family of proteins and is prominently expressed in skeletal and cardiac muscle.[4] There is a study elucidated its initial biological role,[5] claiming that it plays a key role in repairing cell membrane damage and promoting tissue regeneration. Ongoing investigations into the association between MG53 and cardiovascular disease have given rise to two principal hypotheses. First, some research postulates that MG53 is localized and involved in protecting cardiomyocyte membranes from damage such as ischaemia-reperfusion, Second, an alternative line of inquiry suggests that sustained increase and overexpression of MG53 brings about a range of metabolic disorders (including lipid accumulation) and oxidative damage in the cardiovascular system. Given the divergent findings in current research, it becomes imperative to comprehensively expound upon various facets of MG53's biology and its involvement in the pathology of cardiovascular disease. This paper aims to establish a theoretical foundation and delineate research directions for drug development and mechanistic investigations. It achieves this by providing a concise overview of the biological functions of MG53 protein, delineating its potential mechanisms within cardiac tissues, and exploring the therapeutic potential of MG53 in myocardial protection. Furthermore, it assesses the viability of MG53 as a therapeutic target for addressing cardiovascular diseases.

Molecular Structure and Physiological Significance of MG53 Protein

MG53, also referred to as TRIM72, is a multifaceted molecule with a molecular weight of 53 kDa and is comprised of 477 amino acids. Similar to other proteins in the TRIM family, MG53 contains a typical tripartite motif consisting of a RING finger ring, a B-box and a coiled-coil portion (also known as the RBCC domain), as well as an amino-terminal TRIM structural domain and a carboxy-terminal SPRY structural domain.[6] The RING finger-loop structural domain forms the catalytic centre of MG53, which contains the Cys3 HisCys4 amino acid motif and binds two zinc cations. It is a characteristic marker of the E3 ubiquitin ligase subfamily and is involved in mediating the process of ubiquitination.[7] The B-box domain is another portion of the protein, featuring zinc-binding amino acid sequences that aid in the catalytic functions of the RING domain or independently participate in substrate ubiquitination.[8] Curly helical structural domains mediate homo- and heterogeneous interactions between TRIM proteins, and some of these specific domains such as leucine zip motifs provide active sulfhydryl groups that can even promote the oligomerisation of MG53 proteins during the assembly of cell membrane repair mechanisms.[6,7] Previous studies[9] have proposed that the B-box structural domain, together with the RBCC structural domain, facilitates the mediation of protein-protein interactions by providing a binding site for ubiquitinated substrates through the ring structural domain. The carboxy-terminal SPRY domain is responsible for binding of the target protein and exhibits potential for membrane modifying properties. Whereas the TRIM domain mediates interactions with intracellular vesicles in the context of the MG53 molecule, the coordinated interaction between TRIM and SPRY is essential to facilitate MG53 targeting to the cell membrane.

MG53 exhibits a distinctive localization, primarily observed in transverse myocytes. This protein is secreted from human embryonic stem cell-derived cardiomyocytes, akin to its presence in rodent cardiomyocytes. Notably, MG53 is found in relatively minute quantities within the human system when compared to other members of the TRIM family.[6] Zhong et al[10] quantify that MG53 protein levels in the human heart are 1 to 3% of those in the mouse heart. Despite its relatively limited presence, both endogenous and exogenous MG53 are found in intracellular vesicles and myofibrils actively participating in a range of physiological processes within the myocardium. Firstly, the MG53-mediated response specifically promotes k-channel activity. MG53 maintains stable k-ion currents on the surface of cardiac myocytes by controlling the translocation of acidic vesicles containing k ions (KV2.1), which is critical in ensuring normal action potential integrity.[11,12] Secondly MG53 is closely involved in membrane repair in cardiac myocytes. The need for acute membrane repair is particularly pronounced in cardiomyocytes due to the substantial membrane stress generated during myocardial contraction. This emergency cellular response process is intricately linked to membrane transport

mechanisms, where cellular components involved in regular cellular function are repurposed for resealing damaged cell membranes.[3,13] This myocardium-specific repair mechanism is notably initiated in a redox-dependent manner. When cellular damage occurs, the localized environment shifts from a reducing to an oxidizing state, leading to the exposure of phosphatidylserine (PS) on the inner leaflet of the plasma membrane. This exposure triggers the binding of MG53 to PS, forming oligomeric complexes, while extracellular calcium ions (Ca2+) enter the cell. With Ca2+ accumulation, the local concentration of these complexes increases, signaling the translocation of vesicles, along with cholesterol exposed due to cell membrane rupture. This cascade of events ultimately results in the fusion of vesicles with the plasma membrane at the site of injury, forming a repair patch.[13,14] However, it's worth noting that there is some controversy regarding this process. While it has been suggested that dysferlin may serve as a fusion factor facilitating membrane repair,[15] more scholarly studies have shown that the ability to translocate vesicles to sites of myocardial injury is retained even in the absence of dysferlin, indicating that it may not be a prerequisite for cardiomyocyte repair.[16,17] In addition to its direct involvement in repairing damaged cell membranes, MG53 may enhance cardiomyocyte survival and tissue function by safeguarding mitochondrial health following ischemic injury. During ischemia/reperfusion injury, mitochondria in cardiomyocytes experience severe damage due to elevated oxidative stress, resulting in excessive mitochondrial reactive oxygen species (ROS) production and mitochondrial autophagy. MG53 may mitigate these effects by utilizing lipid rafts to repair mitochondrial membranes through binding to cardiolipin (CL), thereby reducing mitochondrial ROS accumulation and mitochondrial autophagy. This mechanism helps preserve mitochondrial integrity in the face of oxidative stress and prevents myocardial dysfunction.[12,18,19] This approach to membrane repair in mitochondria mirrors that of the myocardial plasma membrane due to the lack of phosphatidylserine in the mitochondrial membrane.

The Dual Impact of MG53 on Cardiac Health: Positive and Negative Aspects

Signal pathways that are associated with the regulatory role of MG53 in heart in the Figure 1.

Cardioprotective Benefits Following Ischaemia/Reperfusion Injury

The abrupt reinstatement of coronary blood flow following a period of ischemia can effectively salvage the ischemic myocardial tissue, leading to a reduction in infarct size, mitigation of cardiac remodeling, and an enhancement in systolic

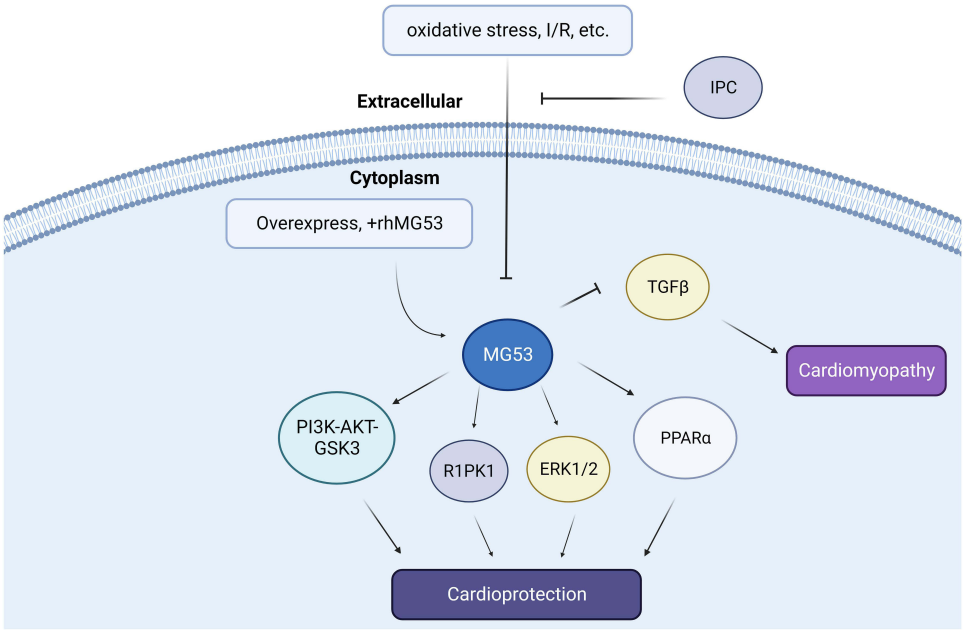

Figure 1 Signal pathways that are associated with the regulatory role of MG53 in heart.

function. However, this reperfusion process may also trigger supplementary myocardial cell damage and myocardial fibrosis due to the initiation of oxidative stress induced by reactive oxygen species, calcium overload, or calpain activation. is typically inevitable and is clinically designated as myocardial ischemia/reperfusion injury (MIRI/IR).[20] To investigate the association between ischemia/reperfusion-induced myocardial injury and MG53, Cao et al[21] initially subjected cultured mouse cardiomyocytes to ischemic or hypoxic conditions. As cardiomyocyte viability declined progressively over time, there was a concomitant reduction in MG53 expression.Notably, the decrease in MG53 protein levels exhibited a positive correlation with declining cardiomyocyte viability. The ischemic myocardium of the mouse model was reperfusion while MG53 changes were monitored. As the severity of myocardial ischemia improved, the downregulation of MG53 induced by IR slowed down, which proved effective in safeguarding myocardial cells against hypoxia- and oxidative stress-induced cell death. The cardioprotective effect of MG53 after IR injury is underpinned by the concept of ischaemic preconditioning (IPC), a strategy of reducing organ damage by briefly blocking blood flow and then restoring perfusion before the causative factor takes effect.[22] IPC is recognized for its capability to avert severe IR injury and substantially mitigate IR-induced damage, including reducing myocardial infarct size. It has been observed that IPC prevents the decline in MG53 expression induced by IR, and the maintenance or enhancement of MG53 expression may constitute one of the mechanisms contributing to IPC-mediated cardioprotection.[21]

Previous research[23,24] has demonstrated that MG53 is a critical factor in the biphasic activation of the PI3K-Akt-GSK3 and ERK1/2 cell survival signalling pathways, which are indispensable for IPC-induced cardioprotection. Inhibition of either pathway completely reverses IPC-induced MG53-dependent cardioprotection. Furthermore, Dan et al[25] found that IPC and oxidative stress could trigger MG53 secretion in perfused mouse hearts via an H2O2-protein kinase-C-δ-dependent mechanism. Although basal expression of MG53 in the heart is relatively low, oxidative stress from H2 O2 enhances MG53 secretion. In turn, secreted MG53 is involved in IPC-induced cardioprotective signaling, which modulates cardiac function and cardiomyocyte viability, and significantly ameliorates IR injury.

In addition, extracellular MG53 could be delivered systemically to mimic elevated circulating MG53, which not only restored IPC function in MG53-deficient mice, but also protected mouse hearts from ischemia/reperfusion injury even in the absence of IPC. Conversely, artificially induced MG53 deficiency in mice completely abolishes IPC-mediated cardioprotection, as evidenced by IPC's failure to reduce the size of IR-induced myocardial infarcts. Wang et al[26] subsequently showed that MG53 can act as an E3 ligase for protein kinase 1 (RIPK1) and ubiquitinate and degrade RIPK1 to reduce cardiomyocyte necroptosis during IR injury, thereby protecting the heart. These in vitro and in vivo studies not only advance our fundamental comprehension of MG53's cardioprotective mechanisms but also emphasize the promising potential of using circulating MG53 as a novel therapeutic target for treating various human heart diseases.

Impacts of Diverse Cardiac Disorders

Cardiac Arrhythmias

With increasing interest in arrhythmia research, there are compelling evidence indicating that MG53 plays a critical role in cardiac arrhythmogenesis.[27,28] Masumiya et al[28] revealed that MG53-mediated membrane transport maintains cell surface K current density to ensure the integrity of the cardiomyocyte action potential profile. Fast transient outward K currents (Ito,f) are contributors to the early repolarization phase of the ventricular action potential (AP), and a decrease in Ito,f is a prominent electrophysiological remodelling problem in cardiac hypertrophy. KChIP2 (myocardial K-channel interacting protein 2) is an essential regulatory subunit for Ito,f activity, and Liu et al[29], through a ChIP assay, demonstrated that MG53 controls KChIP2 expression by regulating the NF-κ b signalling pathway. Reduced MG53 expression or deficiency is associated with decreased myocardial Ito,f, which increases susceptibility to ventricular arrhythmias in the heart. The common pathogenesis of atrial fibrillation is atrial structural remodeling, with fibrosis being one of the most direct forms of this remodeling process.[30] The activation of the transforming growth factor TGF-β1/Smad pathway is closely linked to the extent of atrial fibrosis and structural remodeling, contributing to a pro-fibrotic effect and playing a pivotal role in atrial fibrillation.[31] Clinical studies conducted by GUO et al[32] suggest that MG53 may function upstream of the TGF-β1/Smad pathway. MG53 regulates myofibroblast differentiation, promotes cell migration, proliferation and extracellular matrix synthesis, ultimately leading to atrial fibrosis. In contrast, MG53 is expressed in the human atria and its levels increase with the degree of atrial fibrosis, potentially causing atrial fibrillation. Patients with

atrial fibrillation have higher levels of atrial MG53 expression compared to those with normal sinus rhythm or congenital heart disease. These findings underscore the significance of restoring normal MG53 expression to maintain cardiac rhythm stability and offer new avenues for future arrhythmia treatment.

Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease characterised by pathological hypertrophy of the myocardium.[33,34] Previous studies have shown that AKT and ERK signalling pathways are involved in cardiomyocyte hypertrophy and proliferation.[35] Ham et al[36] also found that factors leading to cardiomyocyte hypertrophy can increase MG53 expression. When MG53 is consistently expressed at high levels, IGF1 triggers the ubiquitination and degradation of IRS-1. This results in reduced mTOR phosphorylation and downregulation of AKT signaling, ultimately reducing cardiomyocyte hypertrophy and improving myocardial health. However, due to interference with compensatory mechanisms, ERK expression increases, and pathological hypertrophy re-emerges in the heart muscle. The NF-κ b signaling pathway known to be important in cardiac development and has been implicated in the development of cardiac hypertrophy.[37] Previous studies[29] have shown that NF-κ b activation patterns are similar to those observed when MG53 is knocked down. MG53 overexpression inhibited NF-κ b activity by direct interaction with TAK1 through phosphorylation of ikk β and i κ b α, which increases the transcriptional activity of KChIP2 and attenuates myocardial hypertrophy. When MG53 expression is reduced, NF-κB activity increases, leading to myocardial hypertrophy. Dysregulation of the cardiac transverse (T)-tubule membrane system is a characteristic of end-stage dilated or ischaemic cardiomyopathy, and maintaining normal cardiac T-tubule development as well as integrity is essential to improve ventricular hypertrophy.[38] According to data from Zhang et al.[39] MG53 is not required for the development and maintenance of T-tubules in normal physiological states.[40] As a muscle-specific membrane repair protein, when chronic pathological MG53 levels are significantly upregulated in the presence of chronic pathological left ventricular pressure overload. It also plays a surveillance role in the heart by increasing membrane vesicle transport that antagonises T-tubule damage to prevent structural remodeling leading to myocardial hypertrophy. Furthermore, MG53 deficiency exacerbates cardiac hypertrophy and dysfunction, further worsening myocardial disease.[40] Restoring MG53 expression therefore has potential medical applications in the treatment of cardiomyopathy.

Diabetic cardiomyopathy (DCM) refers to the altered myocardial structure, function, and metabolism observed in individuals with long-standing diabetes mellitus. It manifests as a distinct cardiac condition independent of other heart diseases, such as coronary artery disease and hypertension.[41] The precise evolution of pathological changes associated with DCM remains incompletely understood. One well-established aspect is the reduced utilization of glucose and increased oxidation of free fatty acids (FFA) in the hearts of diabetic patients.[42] This metabolic shift leads to the accumulation of FFA in cardiomyocytes, culminating in lipotoxicity, cardiomyocyte death,[43] and subsequent fibrosis.[44] Alterations in substrate utilization appear to play a pivotal role in the development of DCM. A study conducted by Liu et al[45] identified a significant role for MG53 in regulating cardiac substrate utilization. Through RNA-seq analysis in a mouse model, they demonstrated that cardiac-specific overexpression of MG53 directly activated the promoter of peroxisome proliferator-activated receptor-α (PPAR-α), a central regulator of lipid metabolism in cardiac myocytes. This activation, in turn, influenced PPAR-α expression at the transcriptional level, resulting in a cardiac phenotype resembling DCM in mice. This phenotype included features such as insulin resistance, lipid accumulation, ventricular dilatation, and myocardial fibrosis. Conversely, inhibiting PPAR-α expression through gene silencing mitigated MG53-induced FFA uptake and oxidation, while also inhibiting glucose utilization in cardiac myocytes.[46] This suggests that MG53 contributes to a shift in myocardial energy substrate preference towards lipids, hindering insulin signaling and promoting lipid-dependent energy substrate use, thereby fostering lipid accumulation and its associated toxicity.

Interestingly, some laboratory studies have suggested that MG53 may not be intricately associated with DCM. For example, sustained elevations in plasma and myocardial MG53 levels resulting from a high-fat diet did not impair insulin signaling and glucose handling in mice. Additionally, sustained elevation of MG53 had no discernible effect on the diabetic phenotype in db/db mice. Another study by Philouze et al[47] indicated that MG53 is not a central regulator of the insulin signaling pathway in skeletal muscle. MG53 expression levels in skeletal muscle were not consistently altered in various clinical models of insulin resistance, and decreasing MG53 gene expression in muscle cells did not compromise

insulin responses, including Akt phosphorylation and glucose uptake. Furthermore, the administration of recombinant human MG53 did not significantly inhibit insulin-mediated AKT phosphorylation.

In addition, the prolonged usage of antipsychotic medications[48,49] or over-alcohol consumption is frequently associated with myocardial injury, cardiomyopathy, and, in severe cases, sudden cardiac deaths. The precise relationship between this phenomenon and MG53 remains unclear, necessitating further comprehensive investigation to elucidate the potential connections and underlying mechanisms.

Heart Failure

The structural integrity of the myocardial membrane of cardiomyocytes is critical for cardiac contraction, and remodelling of myocardial structure is also a key feature in the development and progression of the primary etiology of heart failure (HF).[50,51] A recent study[52] examined the impact of erythromycin, a chemotherapeutic agent, in the context of heart failure and its effects on myocardial membrane integrity. The study observed that increased expression of MG53, a protein known for promoting the repair of plasma membranes by facilitating the fusion of intracellular vesicles at the site of injury, led to damage to the myocardial membrane. This discovery has generated interest in the potential therapeutic use of interventions aimed at restoring the integrity of damaged myocardial cell membranes as a strategy for treating HF. Another study conducted by He et al[53] utilized animal models lacking δ-glycan (δ-SG), a protein important for membrane stability. In these models, the overexpression of the MG53 gene, facilitated by adeno-associated virus (AAV) vectors, provided protection to cardiomyocytes. This protection was achieved through the activation of cell survival kinases such as Akt, extracellular signal-regulated kinase (ERK1/2), and glycogen synthase kinase-3β (GSK-3β), along with the inhibition of the pro-apoptotic protein. In mouse models, this intervention resulted in a significant improvement in myocardial contractile function, contributing to the mitigation of congestive heart failure conditions. Previous studies[37] have established a link between HF and the upregulation of NF-κ b signaling, a pathway associated with inflammation. Inhibition of NF-κ b signaling in mice has shown positive effects on heart failure. Wang et al[54] observed in human and mouse hearts that MG53, a negative regulator of NF-κ b, exhibited decreased expression during the onset of heart failure, concomitant with elevated NF-κ b activation. HF significantly increased NF-κ b mediated inflammatory responses and reduced the expression of antioxidant proteins in cardiac tissue. In contrast, long-term treatment with rhMG53 reduced NF-κ b activity, resulting in decreased cardiac inflammation and improved contractile function in the mouse heart. These findings present a novel therapeutic approach to reduce mortality in heart failure and enhance the quality of life for affected patients.

Cardiac Fibrosis

The myocardium is composed of cardiac fibroblasts, cardiomyocytes, smooth muscle cells and endothelial cells. In response to physiological or pathological stimuli, fibroblasts are activated and proliferate, migrating and excreting extracellular matrix (ECM) to maintain the structural and functional integrity of the myocardium.[55] However, if the repair phase is not properly terminated, excessive deposition of ECM will lead to chronic fibrosis and eventual progression to heart failure, cardiac hypertrophy adverse prognostic outcomes.[56] Therefore, a primary focus in combatting cardiac fibrosis is to restore cardiac myofibroblasts to their quiescent fibroblast state. Zhao et al[57] demonstrated that MG53 is implicated in the migration and proliferation of cardiac fibroblasts through the transforming growth factor-β (TGF-β) signaling pathway. Silencing MG53 using small interfering RNA (siRNA) reduced expression levels of TGF-β1 and TGF β receptor I, thereby inhibiting fibrotic transformation during myocardial remodeling.

Furthermore, studies on the pathophysiological role of MG53 in myocardial fibrosis have shown that MG53 is involved in regulating STAT3/notch-1 signaling changes.[58] Activation of STAT3 phosphorylation, induced by MG53 upregulation in a myocardial fibrosis model using the transverse aortic constriction (TAC) approach, resulted in the inhibition of Notch ligand jagged-1 and its downstream gene expression. This overexpression of MG53 enhanced the proliferation and migration of cardiac fibroblasts, both of which are significant features of myocardial fibrosis.[59] Additionally, inhibiting MG53 through tail vein delivery of TRIM72-shRNA significantly reduced the deposition of collagen, including type I collagen and α-smooth muscle actin, in angiotensin II-stimulated cardiac fibroblasts. This intervention improved left ventricular systolic pressure and reduced left ventricular end-diastolic pressure in a mouse

model, indicating the reversal of TAC-induced cardiac fibrosis.[58] Li et al[60] found the same mechanism in mice with MG53 deficiency, suggesting that MG53 may intervene in the treatment of pathological myocardial fibrosis. In different myocardial tissues, disruption of cell membrane repair can lead to many diseases. Valve interstitial cells (VICs) are the main cells in the valve and maintaining their integrity is essential for valve function.[61] MG53, as a cell membrane repair protein, has been found to promote the repair of VIC damage and regulate the fibrous calcification process that contributes to valvular heart disease (VHD) development.[62] Following endothelial layer damage in the valve, VICs are affected by hemodynamics, leading to over-activation of the TGF-β signaling pathway. This results in a transition of quiescent VICs to a myofibroblast-like phenotype, leading to valvular fibrous calcification and VHD development. MG53 can regulate this process, inhibiting the expression of fibronectin genes downstream of TGF-β signaling while maintaining valve cell homeostasis.

Atrial fibroblasts are more prone to fibrosis compared to ventral fibroblasts, making the inhibition of the fibrotic phenotype of atrial fibroblasts crucial in treating atrial fibrillation.[63] Recent studies[64] have linked the niche protein Caveolin-1(CAV1) to myocardial fibrosis, with CAV1 knockout mice exhibiting structural changes in the ventricle and interstitial fibrosis. Zhang et al[65] demonstrated that MG53 can regulate TGF-β1/SMAD2 signalling pathway-induced atrial fibrosis through a molecular target of CAV1. MG53 expression was negatively correlated with CAV1 and positively correlated with tissue collagen content. Knockdown of MG53 in CAV1-upregulated atrial fibroblasts resulted in reduced expression of TGF-β1, P-SMAD2, α-smooth muscle actin, and collagen I. Conversely, MG53 overexpression via adenovirus led to more extensive collagen deposition in atrial myocytes. Given the long-term, slow-developing nature of atrial fibrosis, MG53 may exhibit different biological functions in acute and chronic lesions.

Biomarkers and MG53

The potential of MG53 as a biomarker of cardiac injury is a subject of study, as it exhibits characteristics that align with biomarker criteria. Research by Marshall et al[66] aimed to identify molecular components associated with cardiomyocyte necrosis, and MG53 was found to show time-dependent elevation following necrotic induction via oxidative stress. Another study conducted by Lemckert et al[67] utilized a mouse model of cardiac Langendorff ischemia-reperfusion injury, and their findings established a strong correlation between MG53 levels in coronary effluent and cardiac dysfunction following ischemic injury. This study highlighted MG53's potential as a novel biomarker for accurate assessment of cardiac ischemia-reperfusion injury across a range of ischemic scenarios. Additionally, Xie et al[68] investigated 300 patients with ST-segment elevation myocardial infarction (STEMI) and found a significant positive correlation between serum MG53 levels and well-established infarction biomarkers. The combination of MG53 levels with other biomarkers improved predictive power for major adverse cardiovascular events (MACEs), suggesting that MG53 may reflect the presence and severity of cardiac injury to some extent. The Kaplan-Meier survival curve indicated that patients with MG53 levels above a certain threshold were at a higher risk of MACEs and cardiovascular mortality, supporting the potential of MG53 as a biomarker for myocardial injury.

Exogenous RhMG53 and Therapeutic Potential

Compared to rodents, humans have lower levels of endogenous MG53 protein in skeletal muscle. Nonetheless, experiments have emphasized the importance of MG53 for cardioprotection, making exogenous recombinant human MG53 (rhMG53) a valuable therapeutic option in cardiovascular disease. Pu et al[67] examined the pharmacokinetics and safety of intravenous rhMG53 administration in a large animal model. Meanwhile, Noah et al[68] demonstrated the feasibility of producing rhMG53 using E. coli and its long-term storage potential. These developments have paved the way for safe biological interventions involving systemic administration of rhMG53 protein in heart disease treatment. Liu et al[69] investigated the therapeutic value of rhMG53 in myocardial infarction (MI) treatment. They utilized mouse and porcine models to show that rhMG53 administration reduced infarct size, decreased creatine kinase (CK) levels, and inhibited apoptosis. The long-term benefits suggested that rhMG53 treatment could mitigate myofibrillar damage following I/R-induced myocardial injury. Furthermore, Adesanya et al (referenced as study 81) demonstrated that rhMG53 attenuated the fibrotic response induced by TGF-β in valve interstitial cells (VICs). The development of an oral or injectable rhMG53-based formulation could potentially mitigate and

prevent valvular heart disease (VHD), improving its surgical outcomes. As highlighted, exogenous rhMG53 holds significant therapeutic promise in the management of cardiovascular disease.

Conclusion and Prospective

Furthermore, beyond its well-established role in skeletal muscle, MG53 exhibits significant implications within cardiac muscle. This multifaceted protein primarily functions as a critical membrane repair component, ensuring the integrity of cardiomyocytes. It actively participates in cardioprotective mechanisms, notably contributing to the effectiveness of ischemic preconditioning and post-conditioning strategies during ischemia/reperfusion injuries. Nevertheless, MG53's involvement in the development of atrial fibrosis raises questions about its impact on promoting atrial fibrillation, an area of ongoing research and debate. Controversies persist regarding MG53's potential involvement in mediating and even exacerbating conditions such as diabetes, diet-induced metabolic disorders, and diabetic cardiomyopathies, with studies presenting divergent findings. Network Medicine approaches may provide a new insight to MG53 in cardiovascular disease. In summary, the promising potential of MG53 as a diagnostic biomarker for various cardiac conditions and its application as recombinant human MG53 (rhMG53) in clinical therapeutics demand further exploration and comprehensive investigation.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

All authors report no conflicts of interest in this work.

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