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REVIEW

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Biological function of RNA-binding proteins in myocardial infarction: a potential emerging therapeutic limelight

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Abstract

Myocardial infarction (MI) is currently one of the most fatal cardiovascular diseases worldwide. The screening, treatment, and prognosis of MI are top priorities for cardiovascular centers globally due to its characteristic occult onset, high lethality, and poor prognosis. MI is caused by coronary artery occlusion induced by coronary atherosclerotic plaque blockage or other factors, leading to ischemic necrosis and apoptosis of cardiomyocytes. Although significant advancements have been made in the study of cardiomyocytes at the cellular and molecular levels, RNA-binding proteins (RBPs) have not been extensively explored in the context of MI. RBPs, as key regulators coordinating cell differentiation and tissue homeostasis, exhibit specific functions in gene transcription, RNA modification and processing, and post-transcriptional gene expression. By binding to their target RNA, RBPs coordinate various RNA dynamics, including cellular metabolism, subcellular localization, and translation efficiency, thereby controlling the expression of encoded proteins. Classical RBPs, including HuR, hnRNPs, and RBM family molecules, have been identified as critical regulators in myocardial hypoxia, oxidative stress, pro-inflammatory responses, and fibrotic repair. These RBPs exert their effects by modulating key pathophysiological pathways in MI, thereby influencing specific cardiac outcomes. Additionally, specific RBPs, such as QKI and fused in sarcoma (FUS), are implicated in the apoptotic pathways activated during MI. This apoptotic pathway represents a significant molecular phenotype in MI, offering novel perspectives and insights for mitigating cardiomyocyte apoptosis and attenuating the progression of MI. Therefore, this review systematically summarizes the role of RBPs in the main pathophysiological stages of MI and explores their potential therapeutic prospects.

Keywords Myocardial infarction, RNA-binding proteins, Post-transcriptional modification, Alternative splicing

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Introduction

Globally, myocardial infarction (MI) remains a significant and serious public health issue, significantly impacting the quality of life and life expectancy of the population. According to the latest report from the American Heart Association, acute myocardial infarction (AMI) remains the leading cause of death worldwide. In the United States, an individual experiences an AMI approximately every 40 seconds, with an annual fatality rate of 13.5%. The annual incidence of MI is estimated at 605,000 new cases and 200,000 recurrent cases [1]. Given these statistics, it is imperative to prioritize the prevention and treatment of MI. MI can be roughly divided into AMI and convalescent MI, also known as chronic MI. AMI is mainly characterized by significant decline in left heart function, manifested as acute heart failure or sudden cardiac death. In contrast, chronic MI (recovery stage) is characterized by left ventricular dilation, scar formation, ventricular muscle fibrosis, and reduced ejection fraction [2]. At present, it is generally believed that MI is caused by a sharp decline in myocardial oxygen supply due to coronary artery occlusion or epicardial vessel stenosis, resulting in hypoxic necrosis and apoptosis of myocardial cells in the infarction area, inducing heart failure and significantly aggravating cardiac function damage [3]. A meta-analysis revealed that individuals over 60 years of age have a significantly increased risk of MI, with prevalence rates of 9.5% and 3.8% in those over and under 60, respectively [4]. However, MI is also not negligible in younger individuals, despite their fewer cardiovascular risk factors. Specific syndromes such as coronary microvascular dysfunction, plaque erosion, and drug-related coronary spasms can also contribute to MI in this age group [5]. Consequently, strategies to suppress myocardial cell damage, prevent heart failure (HF), and enhance cardiac function have become focal points in MI prevention. Although there are currently many effective clinical methods for diagnosing and treating MI, further research on new biomarkers and molecular therapeutic targets is still needed. Recent studies have highlighted the role of alternative polyadenylation in regulating myocardial injury and HF post-MI. For instance, the 3' untranslated region of the apoptotic repressor gene, AVEN, exhibits a lengthening pattern mediated by alternative polyadenylation, offering a potential therapeutic target for post-MI [6, 7]. Additionally, RNA-binding proteins (RBPs) have been shown to engage in the metabolic reprogramming of cardiomyocytes by regulating lncRNA-H19, providing new avenues for improving cardiomyocyte structure and function post-injury [8]. The potential application of RBPs in cardiomyopathy and developing hearts has garnered significant attention, with LIN28a regulating new cardiomyocyte formation via the lncRNA-H19 pathway, potentially reactivating cardiac developmental signals post-myocardial injury [8]. Furthermore, RBPs with multi-splicing are essential for cardiac function and cardiomyocyte contractility, acting as critical regulators of gene splicing in myocardial sarcomeric [9]. These RBPs may directly regulate the splicing of target gene exons by recognizing intron CAC motifs, offering new hope for dilated cardiomyopathy [9]. Another study indicated that RNA-binding motif protein 24, a tissue-specific RBP highly expressed in human and mouse hearts, plays a potent role in RNA splicing during myocardial remodeling postnatal development [10]. Cardia-specific knockout mice of RNA-binding motif protein 24 exhibited dilated cardiomyopathy and heart failure, likely due to the loss of RNA-binding motif protein 24 on alternative splicing. Collectively, RBPs are crucial in post-transcriptional regulation and protein-specific expression in cardiomyocytes [11].

With the comprehensive exploration and deeper understanding of the human genome, the transcription processes of both protein-coding and non-protein-coding RNAs have demonstrated significant importance. RBPs, which play a central role in coordinating and influencing processes such as inter-molecular interactions, RNA splicing, and RNA stability, have emerged as promising targets for further research and development. RBPs, as the name suggests, exert a profound effect on target genes at the post-transcriptional level by binding to their target RNA. It is well established that RBPs participate in and regulate numerous biological metabolic processes involving RNA molecules including transcription, translation, stability of RNA, intracellular localization, degradation, and modification [12]. RBPs coordinate a range of RNA dynamics, including cellular metabolism, subcellular localization, and translation efficiency, by binding to target messenger RNA (mRNA) or other non-coding RNA (ncRNA), thereby regulating multiple gene expression in cells [13]. Currently, the molecular mechanisms of RBPs in oncology, such as gene mutation and gene modification of tumor cells have been extensively explored [14]. However, in cardiovascular diseases (CVDs), particularly MI, the role of RBPs has not been fully elucidated. Considering that RBPs have a general and extensive role in the modification and regulation of genes in cells at the post-transcriptional level, RBPs have received much attention from researchers, and their application in the field of CVDs has been increasingly studied. In particular, RBPs may offer critical emerging therapeutic directions and clinical strategies for targeting the pathological and pathophysiological processes underlying MI. By modulating gene expression at the post-transcriptional level, as well as subsequent protein synthesis and functional execution, RBPs represent promising molecular targets for the comprehensive management of MI. In this review, we examined the literature on RBPs and MI, with a focus on

their roles in hypoxia, ischemia-reperfusion injury, apoptosis, inflammation, and fibrosis. Additionally, we analyzed the mechanisms of action and limitations of RBPs in CVDs as reported in current literature, particularly their potential applications and challenges in the context of MI. This review aims to provide new insights into the molecular mechanisms of post-transcriptional regulation by RBPs for the treatment of MI.

The role of RBPs in regulating RNA metabolism and physiological function of RBPs in the heart

It is now well-appreciated that the interaction of RBPs with RNA is mediated by multiprotein-RNA complex assembly [15]. RBPs typically utilize multiple RNA binding domains to recognize specific RNA structures or sequences, or both, facilitating promiscuous or specific interactions with RNA [16]. Currently, it is thought that RBPs can bind to various types of RNA molecules, including pre-messenger RNA (pre-mRNA), mRNA, and non-coding RNAs such as small nuclear RNAs (snRNAs), long non-coding RNA (lncRNA), circular RNA (circRNA) and microRNA (miRNA) [16]. Also, RBPs have been found to bind to DNA or proteins [17, 18]. RBPs bind to RNA in a sequence/domain-dependent manner, utilizing multiple types of RNA binding regions: RNA recognition motifs, zinc finger domains, cold shock domains, etc [12, 19]. These interactions regulate various aspects of RNA metabolism, including splicing, stability, transcription localization, translation efficiency, and nuclear output. The possible mechanisms of alternative splicing include exon inclusion/skipping, mutually exclusive exons, intron retention, alternative 5' splice sites, alternative 3' splice sites, and alternative polyadenylation [15, 20, 21]. In the case of mRNA (Fig. 1), RBPs participate in all stages of its life cycle, from pre-mRNA production to mRNA degradation. The pre-mRNA is capped at the 5' end, cleaved, spliced and polyadenylated at the 3' end to produce mRNA. Subsequently, mRNAs are transported into the cytoplasm, localized to different cellular subcellular compartments depending on their function, where they serve as templates for protein synthesis. In addition to binding to RNA, RBPs can interact with intracellular auxiliary factors to modify post-transcriptional regulation, and in some cases, RBPs can form other types of RBP complexes [22]. RBPs constitute a complex and refined RNA regulatory network. Each RBP can regulate thousands of genes in a cell [23], and a gene can also be jointly regulated by multiple RBPs [24], making it challenging to identify a specific target that causes a disease phenotype in a cell or tissue.

RBPs are fundamental to genetic processing across life forms, from prokaryotes to humans. RBPs have demonstrated pivotal cardio-biological effects in embryonic heart tissues of zebrafish, mouse, frog, and other animals, playing a significant role in maintaining normal cardiac development [25]. Similarly, a variety of RBPs exist in humans, with recent authoritative reports suggesting that the number of RBPs in the human genome may be as high as 42,745 [26]. However, only a limited number of studies have documented the association of RBPs with CVDs. RBPs and RNA splicing have been shown to play vital roles in heart development and the maintenance of normal cardiac physiological functions [27–32]. Cardiac RBPs ensure the normalization of cytoplasmic division of cardiomyocytes during cardiac embryonic development [29]. RBPs with multi-splicing prevent premature cardiomyocyte binucleation in cardiac development, thereby avoiding noncompaction cardiomyopathy to a certain extent [29]. RBPs play a coordinated and balanced role in various stages of cardiac development, including cardiac tube formation, trabecular formation, endocardial cushion development and cardiomyocyte differentiation and maturation [28]. A recent study also found that zinc fingers and homeoboxes 1 protein activated multiple transcription factors by interacting with heterogeneous nuclear ribonucleoprotein (hnRNP) A1, promoting the specialization of cardiac progenitors [33]. Additionally, several RBPs, such as RBM20 and RBFOX2, are strongly associated with human cardiomyopathies [34, 35]. RBM24, a tissue-specific RBP, is required for myocyte sarcomere assembly and cardiac contraction, and the loss of RBM24 function could lead to Z-disc abnormalities, reduced sarcomeric proteins, and diminished heart contractility in zebrafish embryos [36]. Collectively, RBPs exert an irreplaceable role in cardiac development and functional expression, coordinating the expression during cardiomyocyte development and normal physiological function through post-transcriptional modification. Furthermore, the transition from fetal to adult heart function is precisely regulated by RBPs at the levels of mRNA stability, alternative splicing, and target RNA translation regulation [27]. Post-transcriptional modifications of RNA, including alternative splicing and metabolic reprogramming, are of paramount significance throughout the heart's developmental cycle. However, most studies of RBPs in the heart have focused on embryonic heart development. Recent studies have found that some RBPs are significantly expressed after cardiac ischemia-reperfusion, showing an elevated trend, suggesting that RBPs are generally activated during myocardial injury [37].

In Fig. 2, we illustrate the subcellular changes in the heart during the dynamic progression from MI to cardiac recovery. These changes are integral to several critical pathophysiological processes in MI, offering multiple perspectives for analyzing the functional roles of RBPs. In the following sections, we will focus on the mechanisms by which RBPs mediate RNA metabolic reprogramming

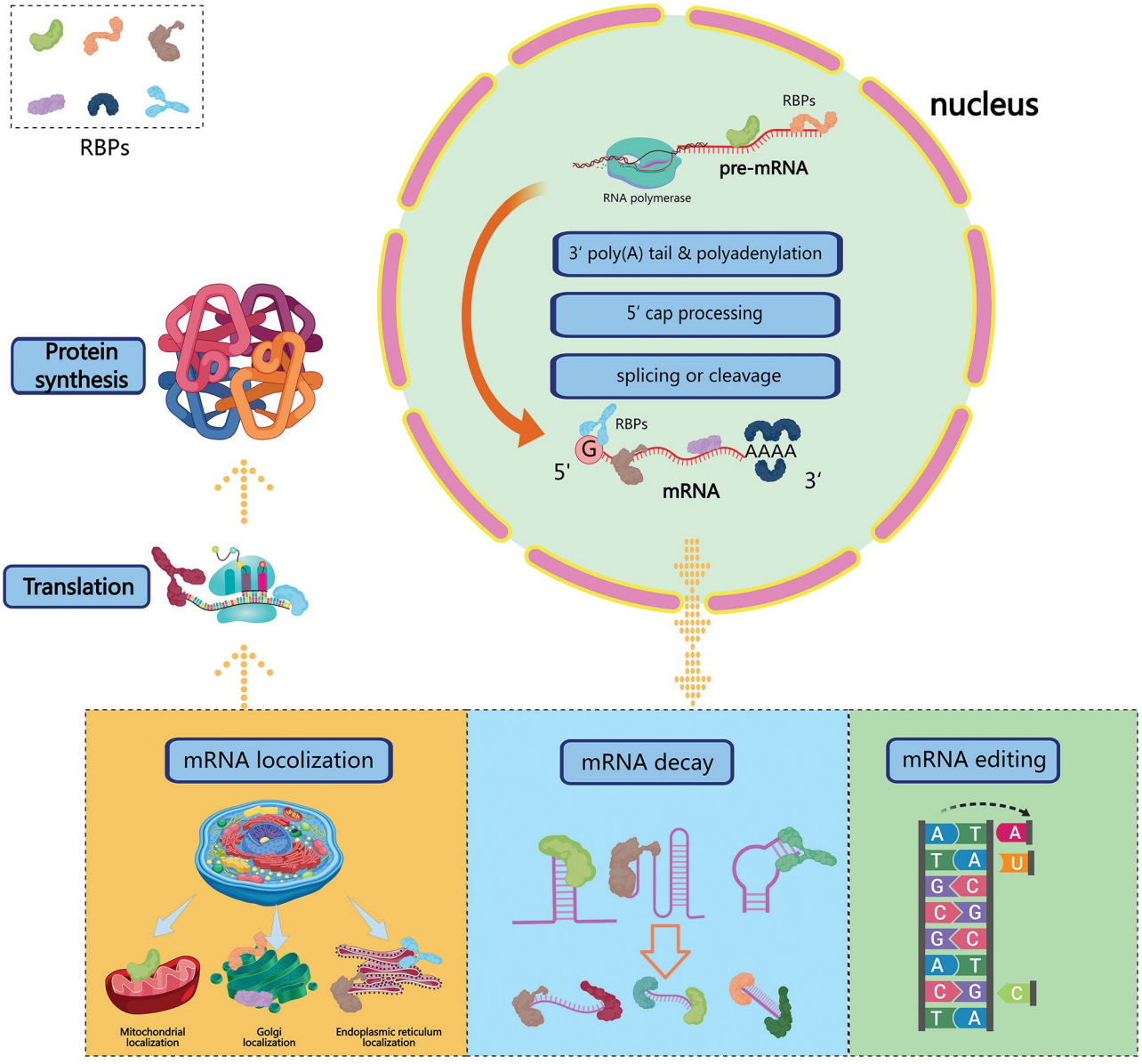

Fig. 1 RBPs participate in the whole process of mRNA metabolic cycle. RBPs play a critical role in coordinating various mRNA processes, including polyadenylation, alternative splicing, editing, organelle localization, translation, and decay. Specifically, it encompasses: pre-regulatory mRNA processing; 5′ capping; 3′ polyadenylation; alternative splicing to retain novel codons or introns; facilitation of mRNA nucleocytoplasmic transport; regulation of mRNA subcellular localization, and targeted mRNA degradation

of cardiomyocytes in the adult heart and the role of RBPs in cardiomyocytes post-injury.

Effects of RBPs on cardiomyocytes under hypoxia and ischaemia

The primary pathophysiological characteristics of MI involve the interruption of coronary blood flow, leading to myocardial ischemia and hypoxia caused by atherosclerotic plaque blockage, coronary artery spasm, or other factors, which ultimately result in MI [38]. A genome-wide analysis identified 493 RBPs that were differentially expressed in myocardial ischemic injury, particularly after reperfusion, with most of these RBPs being associated with alternative splicing [39]. Notably, RBPs exhibit various adaptive responses to hypoxic signals, coordinating gene post-transcriptional modification, alternative splicing, and protein expression [11, 40]. This cluster of RBPs, including hnRNP-E1 [41], hnRNP-A2/B1 [40], human antigen R (HuR) [42] and αCP-1 [43], enhances the translation efficiency of mRNAs encoding glucose transporters and glycolytic proteins. Hypoxia-sensitive RBPs, such as HuR, hnRNP-A2/B1, PCBP1, and PCBP2, constitute a hypoxia-induced translational remodeling network by improving the translation

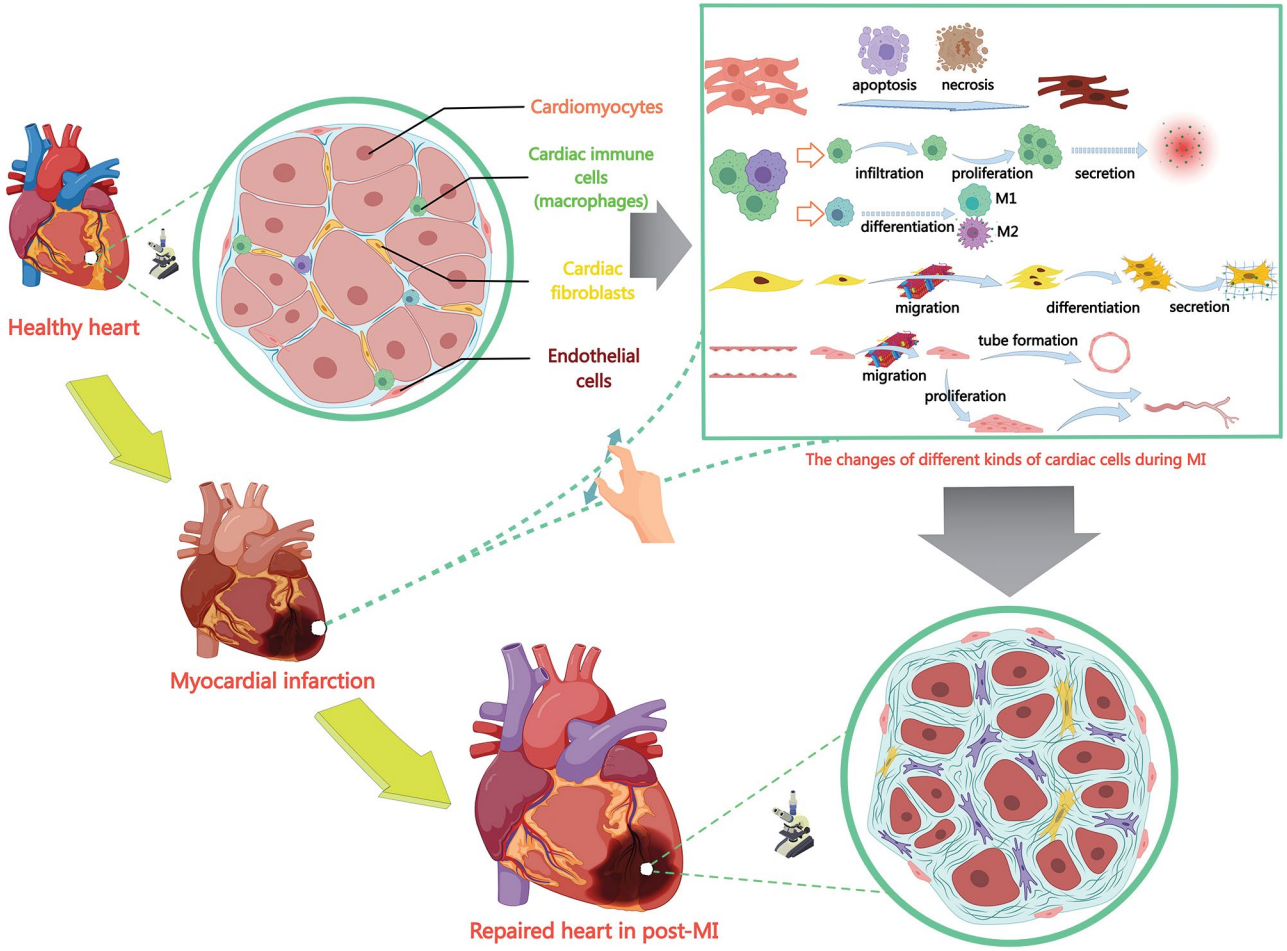

Fig. 2 Dynamic characteristics and pathophysiological processes of subcomponents from healthy heart to post-myocardial infarction heart. The main components of myocardial tissue include cardiomyocytes, cardiac immune cells, cardiac fibroblasts, and endothelial cells. When the heart is subjected to hypoxic stress, these diverse cell types exhibit distinct outcomes or undergo a series of adaptive changes in response to the stimulus, ultimately stabilizing. Among these cell types, cardiomyocytes undergo ischemic hypoxia-induced apoptosis and necrosis; macrophages mediate inflammatory damage and polarization; and cardiac fibroblasts and endothelial cells undergo dynamic changes, including migration, proliferation, and differentiation, which significantly influence the recovery of cardiac morphology and function

efficiency of target mRNAs involved in hypoxic adaptation pathways [11, 44] (Fig. 3a).

The CUGBP- and ETR-3-like factor (CELF) protein family constitutes a group of RBPs. Studies have shown that CUG triplet repeat RNA-binding protein 1 (CUGBP1) is downregulated in mice with MI [42]. CUGBP1 binds to the mRNA of vascular endothelial growth factor A (VEGF-A), promoting vascular regeneration at the infarct border by activating VEGF-A gene expression [42]. Further research has revealed that in AMI mice, HuR translocates from the nucleus to the cytoplasm, where it inhibits CUGBP1 expression by binding to AU-rich elements in the CUGBP1 mRNA, thereby exacerbating MI [42]. These findings suggest that HuR and CUGBP1 play opposing roles in MI, and that knocking down HuR or re-expressing CUGBP1 may confer therapeutic benefits. Although HuR and CUGBP1 share similar overall protein domains and belong to monophyletic clades, they exhibit distinct mRNA-binding preferences. HuR primarily binds to AU-rich elements, whereas CUGBP1, although capable of binding AU-rich elements (ARE) [45], shows a stronger preference for GU-rich elements (GREs) [46]. Consequently, HuR and CUGBP1 may target overlapping regions on the same transcript. What's more, a cytological experiment also proved that HuR, also known as ELAVL1, stabilized SMAD7 expression, which further suppressed MI by binding to circ-RNA_0000848 [47]. The activity of HuR is related to its nucleocytoplasmic dynamic shuttle [48]. As Fig. 3b, in hypoxia, HuR is transferred from the nucleus to the cytoplasm in response to cellular stimulation. As a key hypoxia-induced RBP, HuR produces significantly different outcomes on hypoxic cardiomyocytes by stabilizing diverse downstream target mRNAs. Additionally, signal transducer and activator of transcription 3 (STAT3) is activated in ischemic-oxidative stress and

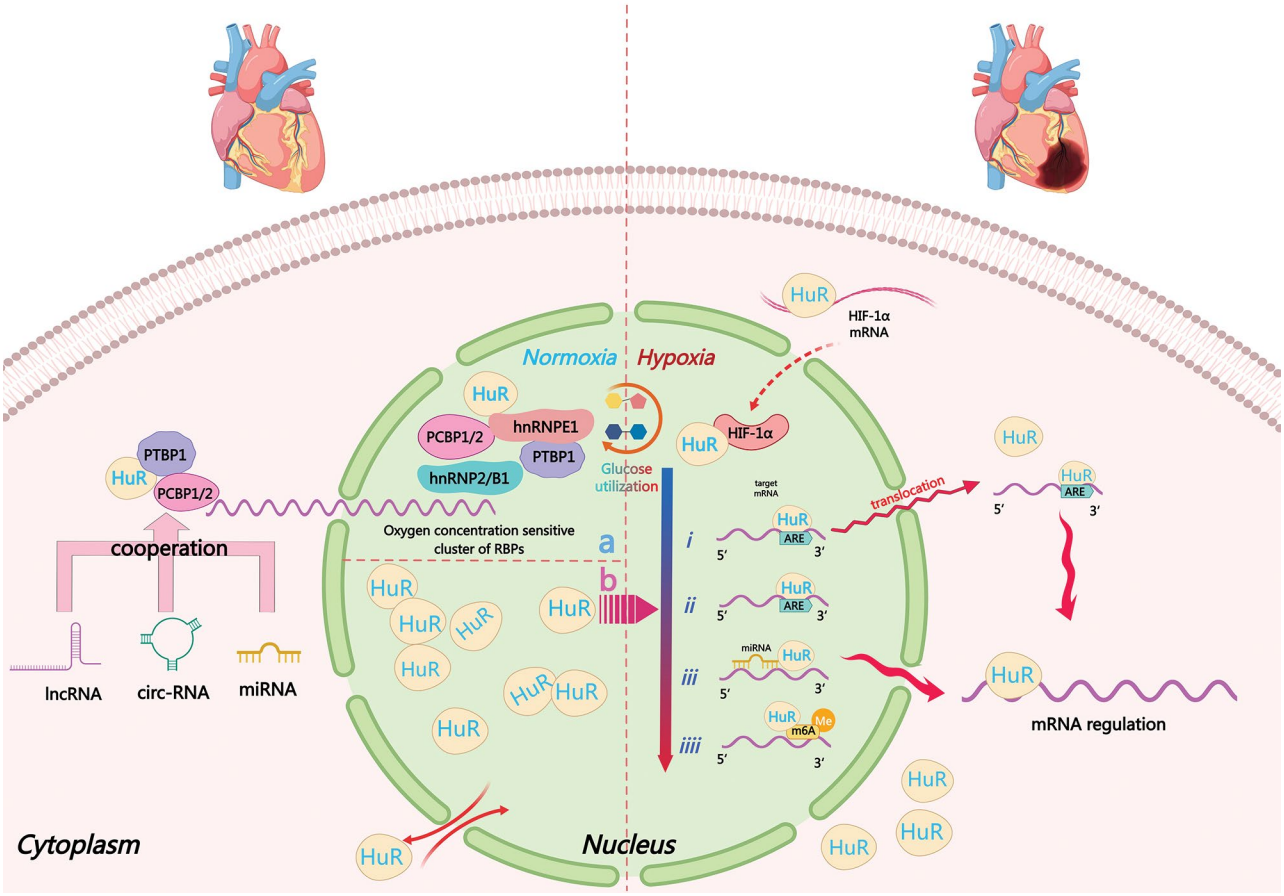

Fig. 3 A cluster of RBPs in cardiomyocytes regulates target mRNA. **a**: Under hypoxic conditions, a cluster of RBPs enhances glucose utilization by improving the transcription and translation efficiency of glucose transporters and glycolytic-related proteins. **b**: As a common and representative molecule within this cluster of RBPs, HuR regulates target mRNA through various mechanisms under hypoxic conditions. HuR can be regulated through four primary mechanisms: (1) binding to the AU-rich elements (ARE) on target mRNA and inducing nuclear-cytoplasmic shuttling; (2) binding to ARE elements on target mRNA to modulate its stability; (3) co-regulating target mRNA with non-coding RNAs; and (4) regulating the methylation modification of target mRNA

exerts cardio-protection. STAT3 is necessary to protect the heart from ischemic hypoxic damage, control the deposition of interstitial matrix, and promote the growth of myocardial capillaries [49]. One report observed that a type of RBPs called QKI (Quaking) was elevated in pulmonary artery vascular smooth muscle tissue in rodents and humans with pulmonary hypertension. By binding to its target mRNA, STAT3, QKI enhanced its stability, thereby promoting the transcription of miR-146b and exacerbating pulmonary vascular remodeling [50]. This demonstrates the effect of RBPs on alleviating or exacerbating hypoxic diseases by affecting tissue-specific reprogramming of target organs.

As a common hypoxia "switch," hypoxia inducible factor 1 (HIF-1) mediates the transformation of the physiological function of RNA in cells [51]. HIF-1 consists of an oxygen concentration-sensitive α subunit (HIF-1α) and a constitutively expressed β subunit (HIF-1β), both of which belong to the bHLH-PAS protein family [52]. HIF-1 has various mechanisms of action in myocardial energy metabolism, fibrosis, ventricular remodeling, angiogenesis, oxidative stress, and inflammatory response, providing multiple potential therapeutic targets for the clinical treatment of MI. It promotes the adaptive response of ischemic and hypoxic cardiomyocytes through these various mechanisms. The mechanism by which HIF-1 regulates cardiomyocyte apoptosis depends on the degree of myocardial ischemia-hypoxia. Under mild hypoxia, HIF-1 can protect cardiomyocytes from impairment. It can inhibit apoptosis by promoting anti-apoptotic signaling pathways, regulating the cardiotrophin-1 gene promoter, and enhancing the expression of miR-24 and miR-145 [53–55]. It was reported that cardiac fibroblasts and mesenchymal progenitors were more hypoxic than other myocardial interstitial components, expressed more HIF-1α, and showed increased anaerobic glycolysis [56]. In the context of ischemia, reactive oxygen species (ROS) in cardiac fibroblasts increased significantly due to the impairment of the adaptive metabolic pathways of HIF dependence in mitochondria. After MI,

HIF-1α-knockout mice exhibited increased fibrosis in the infarct area and enlarged scar size, resulting in the deterioration of systolic and diastolic heart function [56]. On the other hand, under severe and persistent hypoxia of cardiomyocytes, HIF-1α increases dramatically to reduce oxygen consumption and save the surrounding tissue of the infarct area by fostering p53-dependent apoptosis or pyroptosis [52, 57]. Bioinformatics analysis showed that there was a HIF-1α binding site in the promoter region of lncRNA taurine-upregulated 1 (TUG1) [58]. HIF-1α expression was increased in myocardial hypoxia/reoxygenation models, and it also increased TUG1 expression in cardiomyocytes by binding to the TUG1 promoter region. The results showed that HIF-1α promoted pyroptosis and mitochondrial dysfunction of cardiomyocytes through direct binding to the TUG1 promoter [58]. Fused in sarcoma (FUS), a DNA/RNA binding protein, has been previously reported to be involved in regulating gene differential expression and RNA alternative splicing in MI [59]. In this MI model, FUS was shown to bind to TUG1, and their expression in mitochondria was increased, mediating the accumulation of ROS and impairment of mitochondria [58]. Therefore, we speculate that HIF-1α may have a double-edged sword effect in MI. In conclusion, FUS, as an RBP, has a negative regulatory effect on MI under the condition of HIF-mediated hypoxia.

HIF can not only mediate the information exchange between RNA and RNA interactions but also affect translation efficiency and protein expression through the binding of the 5' and 3' UTRs subunits and RBPs [60]. Iron is an essential element for human life activities and participates in various metabolic processes. Current literature has elucidated that iron metabolism is closely related to MI [61], ischemia reperfusion [62], atrial fibrillation [63], and other CVDs [64]. Iron regulatory proteins can regulate iron homeostasis in hypoxic cells by binding to the 5' UTRs of HIF-2α mRNA [65]. The reduction of iron concentration enhances the binding of iron regulatory protein to the 5' UTR of HIF-2α mRNA [65, 66], thereby inhibiting the translation efficiency of HIF-2α, affecting iron absorption, and exacerbating cellular oxygen deprivation. A recent study demonstrated that spontaneous progression of myocardial iron deficiency may be a novel mechanism for worsening heart failure and left ventricular remodeling after MI, and prophylactic iron supplementation may be a therapeutic target after MI [61]. Similarly, a standard randomized controlled trial study found that dapagliflozin improved outcomes in patients with heart failure, possibly by increasing iron use, irrespective of iron status at baseline [67]. Another study found that HIF-1 can affect the complex Ca^{2+} signal transduction in cardiomyocytes under hypoxia by altering the alternative splicing of calcium/calmodulin-dependent protein kinase II gamma (CaMK2γ) [68]. Previous studies have demonstrated that the basal activity of Cav1.2 ion channels is regulated by CaMKII-mediated calmodulin binding to the channels and subsequent phosphorylation [69, 70]. Though the role of HIF as a transcription factor has been recognized for some time, it can also act on the mRNA level of other genes, including gene splicing and translation [71–73]. Chromatin immunoprecipitation analysis suggested that HIF1 directly binds to CaMK2γ in post-MI [68]. Meanwhile, in post-MI, abundance of Rbfox1 RNA and expression of Rbfox1 protein were found to decrease substantially, following the same trend as CaMK2γ variant 1. The members of the Rbfox protein family are highly conserved and have an RNA recognition motif near the central sequence of their proteins, which is widely involved in multiple gene modification or splicing [74, 75]. These results suggest that HIF influences the homeostasis of CaMK2γ under myocardial hypoxia by regulating the expression of Rbfox1 [68]. Rbfox1 expression has also been observed to be significantly reduced in heart tissue from both humans and mice with stress overload-induced heart failure [76]. Collectively, it is concluded that some of specific RBPs such as Rbfox1 protein could affect the physiological activity and prognosis of cardiomyocytes through various signaling pathways under hypoxic conditions mediated by HIF. Additionally, we systematically summarized the roles of various RBPs in myocardial injury, their target RNAs, and related molecular pathways in Table 1.

Regulation of oxidative stress by RBPs in MI

In AMI, ischemic myocardial tissue produces a large number of ROS, especially after ischemia-reperfusion [77, 78]. Oxidative stress is a vital precursor inducer of tissue damage. As a key core molecule inducing cell death, ROS induced by oxidative stress is directly involved in cell and tissue damage. After ischemia-reperfusion, ROS generation mainly comes from nicotinamide adenine dinucleotide phosphate oxidase in inflammatory cells, the mitochondrial electron transport chain in cardiomyocytes, xanthine oxidase in endothelial cells, etc [79, 80]. Notably, ROS-mediated inflammatory reactivity molecules disrupt cardiac Ca^{2+} homeostasis, depressing heart function. Generally, Ca^{2+} overload is the most common cause of mitochondrial damage. ROS can cause intracellular Ca^{2+} overload by peroxidation of membrane lipids and opening of voltage-sensitive Ca^{2+} channels or Na^{+}/Ca^{2+} exchangers [81]. We have previously discussed the adverse effects of iron deficiency on myocardial remodeling following MI under hypoxic conditions in the hypoxia chapter. However, an mRNA-binding protein, tristetraprolin (TTP), can be activated under iron-deficient conditions to mitigate mitochondrial dysfunction, reduce ROS production and alleviate subsequent cardiac dysfunction [82]. The quantitative or functional changes

Table 1 Summarizes recent studies that have identified novel and canonical RBPs implicated in MI, their molecular targets, collaborators, and observed effects on cardiac tissue

RBPs	Coordinating or interventional factors	Mechanisms and signaling pathways associated with RBPs in MI	Targeting RNAs	Signaling cascades involving RBPs in different pathophysiological contexts	Potential effects on heart of RBPs	References
HuR	/	Intracellular relocalization of HuR induced changes in CUGBP1 expression in MI. CUGBP1 affects the transcription and expression of VEGF-A by binding to its mRNA, and promotes vascular regeneration and tissue repair in infarction area.	CUGBP1	HuR---CUGBP1---VEGF-A (angiogenesis)	HuR-negative; CUGBP1-positive	[42]
	circ-RNA_0000848	HuR can coordinate with Has circ-RNA_0000848 to bind and stabilize SMAD7 mRNA to counteract hypoxia-induced apoptosis of cardiomyocytes.	SMAD7	circ-RNA_0000848---HuR---SMAD7 (apoptosis)	positive	[47]
	IL-10	HuR may promote inflammatory infiltration and myocardial fibrosis after myocardial infarction by promoting the stability of MMP9 and TGF-β mRNAs, aggravating ventricular pathological remodeling and heart failure.	TGF-β/MMP9	HuR---TGF-β (fibrosis) HuR---MMP9 (inflammation)	negative	[114, 115]
	/	HuR may increase the stability of iNOS mRNAs, and further aggravate the inflammatory infiltration and pathological remodeling of myocartis after ischemia reperfusion.	iNOS	HuR---iNOS (inflammation)	negative	[119–121]
FUS	HIF-1α	FUS aggravates mitochondrial function and myocardial injury in cardiomyocytes under hypoxia by participating in the HIF-FUS-TUG1 axis.	TUG1	HIF-1α---FUS---TUG1 (pyroptosis)	negative	[58]
	circ-Fndc3b	Overexpression of circ-Fndc3b can enhance the degree of binding to FUS, inhibiting the repression of VEGF-A and anti-angiogenesis mediated by FUS.	VEGF-A	circ-Fndc3b---FUS---VEGF-A (angiogenesis)	negative	[137]
	miR-200a	Up-regulation of miR-200a, a sponge of FUS, can inhibit the activity of FUS, vitalise mir-200a-dependent apoptotic signaling pathway, and aggravate myocardial injury.	/	miR-200a---FUS (apoptosis)	positive	[138]
Rbfox1/fox2	HIF-1α	Rbfox1/fox2 reduces the expression of CaMK2γ through alternative splicing under the stimulation of HIF-1α.	CaMK2γ	HIF-1α---Rbfox1/fox2---CaMK2γ	/	[68]
TTP	/	TTP can degrade mRNAs of mitochondrial Fe/S-cluster containing proteins in the case of iron deficiency, avoiding oxidative damage caused by mitochondrial electron leakage.	Ndufs1/Uqcrfs1	TTP---Ndufs1/Uqcrfs1 (oxidative stress)	positive	[82]
PTBP1	lncRNA-SNHG8	LncRNA-SNHG8 cooperates with PTBP1 to enhance the mRNA stability and protein expression of ALAS2, which aggravates the oxidative stress of cardiomyocytes.	ALAS2	lncRNA-SNHG8---PTBP1---ALAS2 (oxidative stress)	negative	[86]
	TGF-β	By binding Nur77 mRNA and reducing its stability, PTBP1 aggravates TGF-induced collagen accumulation and excessive proliferation of cardiac fibroblasts, which worsened cardiac function.	Nur77	PTBP1---Nur77 (fibrosis)	negative	[167]
PCBP2	lncRNA-TTN-AS1	TTN-AS1 transcriptionally regulated by ELF5 can alleviate myocardial injury, recruiting PCBP2 to enhance the stability of CDK6 mRNAs.	CDK6	ELF5---lncRNA-TTN-AS1---PCBP2---CDK6 (mitochondrial damage)	positive	[88]
YTHDF2	METTL14	YTHDF2 reduces the stability of BNIP3 mRNAs and down-regulates BNIP3 through m6A methylation modification, improving myocardial cell injury and mitochondrial autophagy.	BNIP3	METTL14---YTHDF2---BNIP3 (autophagy)	positive	[106]

Table 1 (continued)

RBPs	Coordinating or interventional factors	Mechanisms and signaling pathways associated with RBPs in MI	Targeting RNAs	Signaling cascades involving RBPs in different pathophysiological contexts	Potential effects on heart of RBPs	References
CIRBP	/	Down-regulation of CIRP can reduce LPS-induced myocardial inflammation, apoptosis and oxidative stress.	/	CIRBP (apoptosis and inflammation)	negative	[124]
EZH2	lncRNA-Malat1	EZH2 can form a complex with lncRNA-Malat1 in macrophage, reducing the production of PPAR-γ and inhiting inflammation after MI.	PPAR-γ	lncRNA-Malat1---EZH2---H3K27me3---PPAR-γ (inflammation)	positive	[128]
EGR1/E2F1	circ-JA760602	circ-JA760602 can influence the affinity of EGR1 and E2F1 to the Bcl-2 promoter.	Bcl-2	circ-JA760602---EGR1/E2F1---Bcl-2 (apoptosis)	positive	[134]
QKI	miR-155	miR-155 may be involved in the regulation of QKI, promoting the apoptosis of cardiomyocytes and increasing the area of myocardial infarction by down-regulating QKI expression.	/	miR-155---QKI (oxidative stress and apoptosis)	positive	[139]
ILF3	miR-215-5p	ILF3 can enhance mRNA stability and protein expression of LRRFIP1, while miR-215-5p mimics (overexpression) can target ILF3/LRRFIP1 and counteract the proapoptotic effect on them.	LRRFIP1	miR-215-5p---ILF3---LRRFIP1 (apoptosis)	negative	[140]
RBM25	/	RBM25 is involved in splicing and post-transcriptional modification of apoptosis genes related to CHOP pathway, which enhances apoptosis of myocardial cells in MI.	CHOP-related pathways	RBM25---CHOP/BBC3-related pathways (apoptosis)	negative	[142, 143]
RBM15	/	RBM15 is involved in methylation modification and stabilizes NAE1 mRNAs, attenuates cardiomyocyte apoptosis and improves cardiac function in MI.	NAE1	RBM15---NAE1 (apoptosis)	positive	[144]
MBNL1	TGF-β	MBNL1 can bind the target mRNAs of CnAb and serum response factor under the stimulation of TGF-β, thereby augmenting the differentiation of myoblasts and promoting the repair after MI.	CnAb/serum response factor	TGF-β---MBNL1---CnAb/serum response factor	positive	[158]
Csde1/hnRNP-H1	TGF-β	TGF-β stimulation reduces the binding of Csde1 to mRNA and promoted the endothelial cells to mesenchymal activation. The increase in HNRNP-binding mRNAs induced by TGF stimulation counteracted mesenchymal progression to some extent and prevented complete loss of endothelial cell function.	Endothelial cell related genes	TGF-β---Csde1 TGF-β---hnRNP-H1	dynamic balance	[157]
EWSR1	VGLL3	The reduction of VGLL3 or EWSR1 can release collagen-targeting miR-29b and increase its expression, thereby alleviating post-infarction fibrosis and contributing to the recovery of cardiac function.	miR-29b	VGLL3---EWSR1---miR-29b (fibrosis and collagen)	positive	[166]

in RBPs in response to stress conditions warrant further investigation. The adaptive regulatory mechanisms elicited by the body under such stress conditions may hold significant therapeutic potential for targeting RBPs. Additionally, a comprehensive review has concluded that the axis of oxidative stress-ROS-inflammation-alternative splicing plays a significant role in ischemia-reperfusion [15]. The relationship between oxidative stress and gene selective splicing is complex and subtle, and both are involved in disease progression, so we have reason to better understand the underlying mechanisms of the two. Next, we will discuss in detail how RBPs mediates ROS to affect the survivability of cardiomyocytes.

Researchers demonstrated for the first time that an RBP, PTBP1 (Polyrimidine tract binding protein 1), interacts with lncRNA-SNHG8 through RNA binding protein immunoprecipitation and RNA pull-down assays. Simultaneously, PTBP1 also binds to the ALAS2 (aminolevulinic acid synthase 2) mRNA, thereby affecting ROS production. ALAS2 is a rate-limiting enzyme for heme synthesis [83]. Stress factors such as hypoxia can increase the transcription efficiency of ALAS2, leading to a surge in heme content, which is also an important source of oxidative stress [84, 85]. On one hand, PTBP1, was found to interact with lncRNA-SNHG8 mediated by N6-methyladenosine (m6A) methylation. On the other hand, PTBP1, as an RBP, binds to ALAS2 mRNA and regulates its expression, thereby increasing oxidative stress and exacerbating MI [86]. The possible theoretical basis is that the combination of lncRNA and RBP-PTBP1 enhances the biological function of PTBP1, increasing the stability of ALAS2 mRNA and affects a series of subsequent mRNA processing [86, 87]. Additionally, Titin-antisense RNA1, a lncRNA mapping to chromosome 2q31.2, was also found to enhance CDK6 stability and reduce mitochondrial damage and ROS production by recruiting poly-rC-binding protein-2 [88]. Another RBP, FUS, was also thought to alleviate mitochondrial damage and pyroptosis in cardiomyocytes by interacting with the HIF-1α/lncRNA-TUG1 axis and reducing ROS production [58]. Moreover, in diabetic cardiomyopathy, druggable ncRNA-RBP axes regulate mitochondrial quality control and redox homeostasis, presenting novel targets for intervention in this cardiometabolic disorder [89]. These results suggest that lncRNA is involved in the regulation of mRNA by RBPs and influences the subsequent processing of genes.

Lipid peroxidation is one of the significant signatures of ferroptosis, generating much ROS and exacerbating cardiomyocyte injury [63]. A recent study found that methyltransferase-like 3 (METTL3) exacerbated ferroptosis after MI and accelerated the progression of heart failure by mediating m6A methylation of SLC7A11 mRNA and repressing its expression [90]. As Fig. 4, several key molecules involved in the methylation modification process play a critical role in regulating myocardial ROS production and mitochondrial function. Methyltransferases are a broad class of highly conserved protein molecules that modify various substrates. m6A methylation modification of RNA is one of the most abundant mRNA methylation systems and is considered an important layer of epigenetics [91, 92]. And METTL3 is one of the representative "writers" of m6A modification. It specifically binds to RNA containing a 5'-GGACU-3' consensus sequence via the Cys-Cys-Cys-His zinc-finger domain, promoting methylation modification of target genes and affecting mRNA regulation [91, 93]. Generally, METTL3 and methyltransferase-like 14 (METTL14) show weak in vitro methyltransferase activity individually and need to cooperate to exert full catalytic activity [94, 95]. The C-terminal arginine-rich region of METTL14 carries positive charge, contributing to RNA binding. The interface of the complex protein comprised of METTL3 and METTL14 forms positively charged grooves, critical for stimulating methyltransferase activity and binding RNA substrates [95]. What's more, evidence revealed that the role of methyltransferase-like 16 (METTL16) as an RBPs may be more important than currently recognized methylation [96]. METTL16 is thought to have RNA-binding effects independent of m6A methylation. It has also been identified as having multiple RNA-binding domains with different functions. One study found that RBM25 and METTL16 may be involved in m6A methylation mediated by METTL16 in LPS-induced myocardial injury and inflammation [97]. Current research suggestes that the N-terminal RNA binding domain of METTL16 may form a hairpin structure that can accommodate double-stranded RNA [98], and the C-terminal RNA binding domain may also bind double-stranded RNA through a clamp-like structure [99]. Interestingly, despite previously mentioning the role of METTL3 and METTL14 in binding RNA, METTL16 is widely accepted and identified as an RBP in most current omics studies on RBP, while METTL3 and METTL14 are not [100–102]. Alternatively, METTL3 and METTL14 should be classified as RNA-modifying enzymes or "unconventional RBPs". Regardless, they also modify or directly affect RNA transcription and translation by binding to target RNA substrates. Meanwhile, YTHDF2, as a "reader" of m6A methylation, has been found to promote the degradation of SLC7A11, affect the intracellular glutamate cycle, reduce GPX4 synthesis, and promote cardiomyocyte ferroptosis [103]. Bcl-2 19-kDa interacting protein 3 (BNIP3) mediates mitochondrial autophagy, which benefits reducing mitochondrial damage and avoiding ROS accumulation [104, 105]. The RNA methylation reading protein YTHDF2 reduced BNIP3 mRNA stability and downregulated BNIP3 through m6A methylation

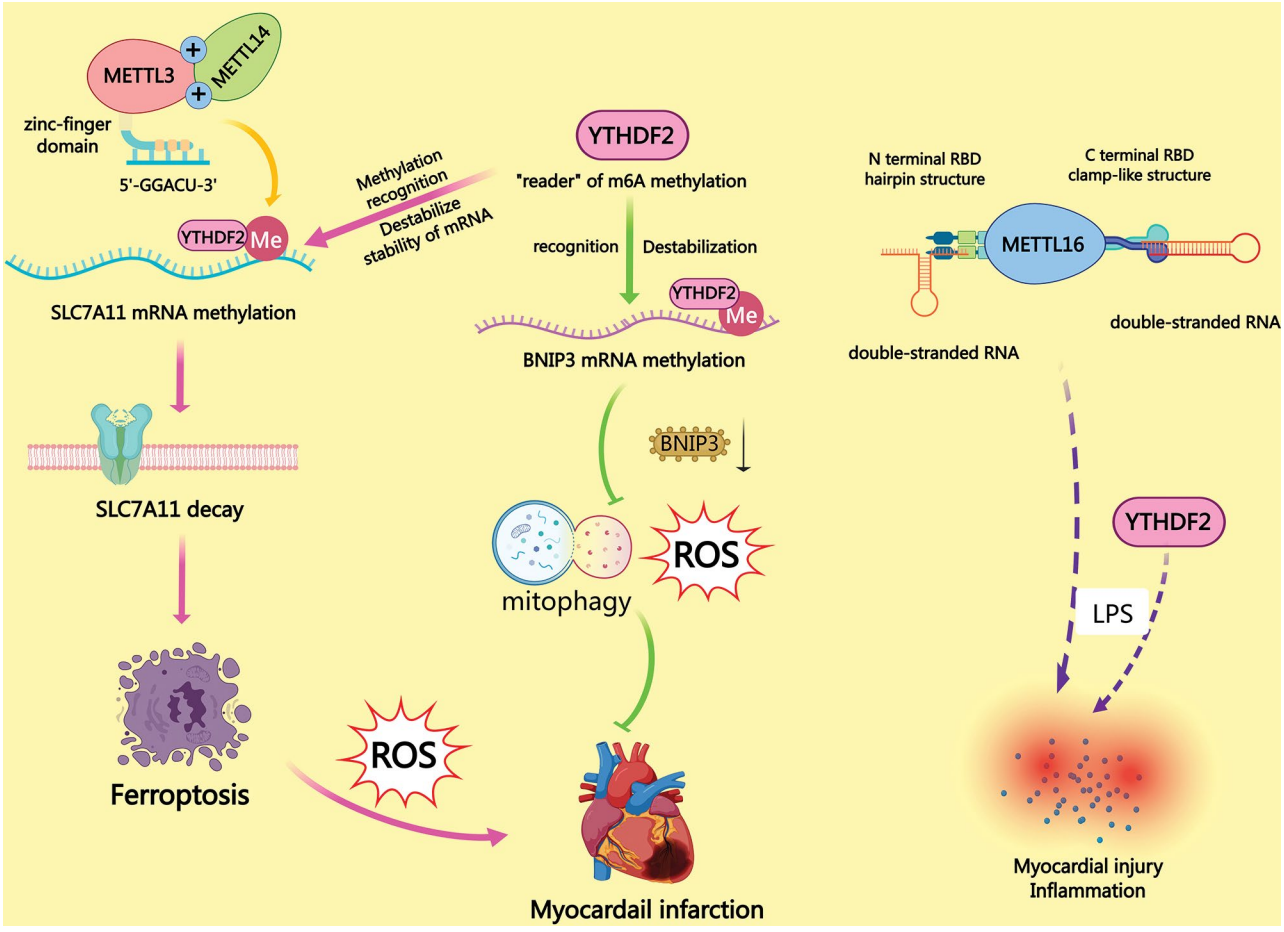

Fig. 4 RBPs participate in methylation modification and regulate oxidative stress in cardiomyocytes. Methylation is commonly mediated by the writer complex METTL3/METTL14 and the reader protein YTHDF2, which promote methylation modifications and regulate the stability of target mRNAs (e.g., SLC7A11 and BNIP3). This process modulates mitochondrial stress and ROS production

modification, thereby alleviating ROS and mitochondrial damage induced by ischemia-reperfusion [106]. Insulin-Like Growth Factor 2 mRNA-Binding (IGF2BP2) expression was significantly elevated in both mice and patients with MI. Its overexpression is associated with post-myocardial stress, including mitochondrial dysfunction [107]. Additionally, as a reader of m6A methylation, IGF2BP2 may enhance its binding to target mRNA on account of the upregulation of m6A methylation, thereby promoting ventricular wall hypertrophy and dilation, and contributing to the progression of mitochondrial stress and dilated cardiomyopathy [107–109]. These findings expose that the relationship between RBPs and m6A methylation plays a complex and subtle role in ferroptosis, oxidative stress, and RNA modification.

The regulatory role of RBP in inflammatory cytokine signaling network under MI

The activation of chronic inflammatory response in post-MI is one of the vital factors inducing left ventricular dysfunction and adverse remodeling. Due to long-term ischemia, or sudden blood flow recovery, reoxidation, and massive production of ROS, cardiomyocytes can initiate programmed necrosis, apoptosis, and autophagy. Damaged cardiomyocytes and extracellular matrix release danger-associated molecular patterns (DAMPs) [110], and surviving cells in the infarct margin area may also secrete a series of cytokines in response to the activation of pro-inflammatory cytokines such as IL-1 or ROS, triggering an inflammatory response [111]. In addition to damaged cardiomyocytes and extracellular matrix, some activated inflammatory factors and leukocytes may also upregulate and secrete specific DAMPs [112]. RBPs and post-transcriptional regulation are widely involved in the regulation of various inflammatory genes and play an important role in the regulation of immune response and inflammatory diseases [113, 114]. It is well known that oxidative stress and inflammatory response are closely related, and the function of RBPs in regulating inflammatory cytokine networks will be discussed in detail in this chapter.

It has been previously reported that knockdown of HuR, an mRNA stabilizing protein, may attenuate the inflammatory response in post-MI caused by the loss of the anti-inflammatory cytokine IL-10 [115, 116], which may be related to the attenuation of the accompanying inflammatory response via suppression of HuR and the promotion of angiogenesis activated by STAT3. HuR is also involved in the expression of tumor necrosis factor-α (TNF-α) secreted by macrophages and the stabilization of the cyclooxygenase-2 gene [117, 118]. In cardiomyocytes, inflammatory cytokines such as TNF-α, interferon γ, and IL-β can induce the expression of inducible nitric oxide synthase (iNOS) [119]. At the same time, iNOS can contribute to the inflammatory damage of cardiomyocytes and inhibit the heart after ischemia-reperfusion [119, 120]. HuR can bind to the 3'-UTR of iNOS containing AU-rich sequence, mediating the stability of iNOS mRNA [121]. Also, the initiating process of TNF-α translation also requires HuR [122]. HuR can stabilize the mRNA of pro-inflammatory factors and inflammatory mediators, potentially exacerbating MI and adverse ventricular remodeling post-MI. TTP, an RBP of the zinc finger family member, has been found to promote the degradation of pro-inflammatory factors such as IL-3, IL-6, and TNF-α mRNA [122]. TTP inhibits the stability of the mRNA and the release of pro-inflammatory factors such as TNF and IL-6, while HuR promotes the mRNA stability and expression of pro-inflammatory factors [123]. Currently, the stabilizing factor of the HuR family and the destabilizing factor of the AUF1 family have been well characterized [114]. HuR, hnRNP-A1, and the trans-acting factor AUF1 have also been shown to mediate the stability of β adrenergic receptor mRNA [114], affecting myocardial contraction after MI and congestive heart failure. Interestingly, as the opposite regulatory effects of HuR, hnRNP-A1, and AUF1 on mRNA stability, the changes of cardiac β adrenergic receptor mRNA may be controlled in both positive and negative ways [121]. Moreover, cold-inducible RNA-binding protein (CIRBP) can specifically bind to the 3'UTR of HIF-1α transcripts to enhance their stability and induce increased HIF-1α protein synthesis in response to hypoxia [124]. Downregulation of CIRBP was also thought to protect cardiomyocytes and ameliorate cardiac function by attenuating oxidative stress, inflammation, and apoptosis in cardiomyocytes [125]. M1 macrophages play a crucial role in inducing and maintaining the inflammatory microenvironment in post-MI by secreting a variety of chemokines and inflammatory cytokines [110]. Enhancer of zeste homolog 2 (EZH2), as a catalytic subunit of methyltransferase, has been found to be widely involved in the occurrence and deterioration of hepatocellular carcinoma and cholangiocarcinoma [126, 127]. Whereas, EZH2 is also an RBP that has the ability to bind RNA and regulate its functions [127]. A recent study demonstrated that EZH2 binds to lncRNA-Malat1 in cardiac macrophages, forming a complex that suppresses peroxisome proliferator-activated receptor gamma (PPAR-γ) production and attenuates inflammation following MI [128]. Specifically, EZH2 interacts with lncRNA-Malat1 to enhance the stability of trimethylated histone H3 lysine 27 (H3K27me3), thereby downregulating PPAR-γ expression and mitigating myocardial inflammation. In addition, cardiomyocyte-specific ribosome profiling showed that ischemia-reperfusion enhanced inflammatory responses in infarct and marginal areas and translation of mRNA networks associated with inflammatory cell infiltration [129]. For a majority of transcripts, mRNA translation initiation is activated by eukaryotic initiation factor (eIF) 4 F, consisting of eIF4E, eIF4G, and eIF4A, which is a heterotrimeric protein complex [130]. mTOR is considered the core mediator of the translation initiation process, integrating biological information regarding energy, oxygen, stress, and nutrition, and coordinating eIF4E binding protein 1 (4EBP1) translation through its kinase activity. Using a combination of pharmacological and genetic approaches, researchers found that changes in the activity of the mTOR-4EBP1-eIF4F pathway stimulate the regulation of cardiomyocyte translation in response to inflammatory stress during ischemia-reperfusion [129]. Cardiomyocyte-specific overexpression of 4EBP1 inhibited eIF4F formation and translation activation in the marginal zone after reperfusion. More importantly, temporary inhibition of eIF4F-dependent translation during reperfusion may reduce inflammation and improve cardiac function [129]. Therefore, 4EBP1, as a key regulator of the translation initiation network, controls inflammatory monocyte infiltration via the mTORC1-4EBP1-eIF4F axis, reducing cardiac inflammation and improved cardiac function. Currently, in view of the dynamic process of cardiac oxidative stress and inflammation, the function of RBPs in the association between cardiac oxidative stress and inflammation remains to be further explored in the future.

Application of RBPs in cardiomyocyte apoptosis

Apoptosis is a common cellular outcome in MI and is a proactive change in response to ischemia and hypoxia stress. RBPs play a prominent role in the occurrence and progression of apoptosis. Inflammatory cytokines stimulate apoptosis through the caspase pathway/TNF-α receptor, whereas the massive production of ROS can induce Ca^{2+} overload, enhancing mitochondrial membrane permeability and leading to apoptosis. Currently, research on RBPs and apoptosis has achieved remarkable results in the occurrence, progression, and treatment of oncology [131]. The mechanism of immune escape from apoptosis is the basis of the proliferation, invasion, and

metastasis of malignant tumors. Apoptosis is currently considered a natural barrier against tumor progression. Many studies have focused on the processing of anti-apoptotic family molecules by RBPs and their interactions with non-coding RNA such as microRNA, lncRNA, and circ-RNA, hoping to find new mechanisms to inhibit the anti-apoptotic escape of tumors [132]. However, the role between RBPs and apoptosis in MI needs to be further explored.

Recent studies have revealed that circ-RNAs or miRNAs may function upstream of RBPs and regulate RBPs by promoting, stabilizing, or sequestering them, thereby influencing the binding of RBPs to downstream target mRNAs. Circ-RNA participates in the regulation of apoptosis in MI, and the relationship between RBPs and it has also been extensively discussed in MI [133]. Figure 5 illustrates the interaction of several key RBPs with circ-RNAs and miRNAs to regulate cardiomyocyte apoptosis. It is well known that Bcl-2 is a common anti-apoptotic protein. Recently, two protein molecules, early growth response protein 1 (EGR1) and E2F transcription factor 1 (E2F1), were identified to bind to circ-JA760602, and circ-JA760602 was elevated in MI mice [134]. Further experiments demonstrated that circ-JA760602 binds with EGR1 and E2F1, inhibiting their nuclear translocation, thereby inhibiting Bcl-2 transcription and aggravating cardiomyocyte apoptosis [134]. Specifically, rescue assays revealed that downregulation of circ-JA760602 contributed to the accumulation of EGR1 and E2F1 in the nucleus, strengthening the affinity of EGR1 and E2F1 to the BCL2 promoter. In conclusion, by downregulating circ-JA760602 binding to EGR1 and E2F1, EGR1 and E2F1 can be indirectly released, thereby enhancing the transcription and expression of Bcl-2, which inhibits apoptosis. It is evident that RBPs, such as EGR1 and E2F1, not only interact with the promoters of downstream target genes but also bind to circ-RNAs and are regulated by them to play a pivotal role in transcriptional regulation. In addition, a review has also elaborated on the interaction mode between circ-RNA and RBPs, as well

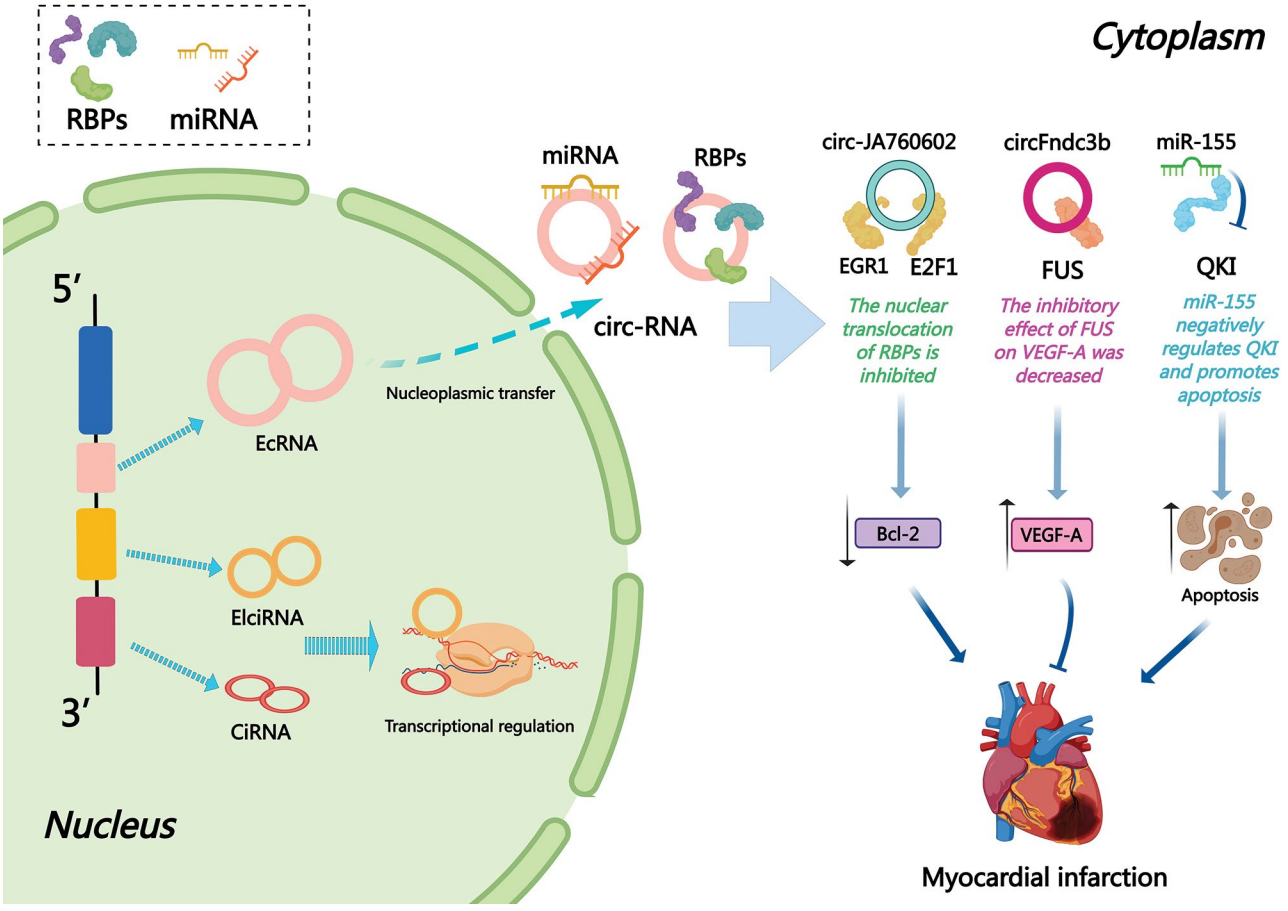

Fig. 5 RBPs cooperated with non-coding RNA to regulate apoptosis of cardiomyocytes. In the nucleus, pre-miRNA is processed to generate three types of circ-RNAs. Among these, exon-intron circRNA (ElciRNA) and circular intronic RNA (CiRNA) function exclusively in transcriptional regulation within the nucleus. As the predominant form of circRNA, exonic circRNA (ecRNA) undergoes processing and is subsequently transported to the cytoplasm where it forms mature circular RNA. Similar to miRNA, ecRNA can function as a protein sponge, binding to RBPs such as EGR1, E2F1, FUS, and QKI. This interaction modulates RBP activity and consequently influences the apoptotic processes in MI

as the role and outcome of them in MI [135]. EcRNA is a precursor type of circ-RNA. After maturation, EcRNA is transported outside the nucleus to become the majority of circ-RNA in the cytoplasm. Meanwhile, EcRNA can act as a sponge for miRNA or RBPs, affecting the biological activity of downstream targets and the efficiency of protein translation [135, 136]. Similarly, another circular RNA, circFndc3b, may also bind to FUS, functioning as a sequestration agent for FUS. This interaction inhibits the repression of VEGF-A and the anti-angiogenic effects mediated by FUS. Significantly reduced circFndc3b levels were found in heart tissue from human ischemic cardiomyopathy as well as in post-MI mice hearts [137]. Researchers found that the overexpression of circFndc3b enhanced the binding effect of FUS to it. Precisely, combination of circFndc3b and FUS weakens the repression of expression and signal transduction of VEGF-A by FUS, and consequently, promoting angiogenesis, inhibiting apoptosis, alleviating left ventricular dysfunction in post-MI [137]. However, another study found that FUS was also negatively regulated by miR-200a. The oxidative stress and apoptosis induced by miR-200a could be reversed by FUS overexpression in cardiomyocytes [138]. The potential for opposing effects of RBPs, such as FUS, in MI raises critical questions regarding how to accurately assess their functional and downstream impacts and develop targeted therapeutic strategies. Although RBPs play a crucial role in the post-transcriptional regulation of genes, such as gene splicing and stabilization, the mRNA of RBPs is also regulated by miRNAs. Another RBP called QKI was found to be a target gene for miR-155 in cardiomyocytes. As shown in their findings, the miR-155 binding site exists on the 3' UTR of QKI in humans, rats, and mice. Furthermore, QKI may be directly regulated by miR-155 to promote apoptosis in cardiomyocytes and aggravate MI [139]. Interleukin enhancer binding factor 3 (ILF3) is a protein that binds to double-stranded RNA. ILF3 was shown to have a facilitating effect on cardiomyocyte apoptosis by targeting LRR binding FLII interacting protein 1 (LRRFIP1) [140]. Whereas, the researchers found that miR-215-5p mimics were also involved in regulating the apoptotic signaling pathway of H9C2 by targeting ILF3 and inhibiting apoptosis [140]. By targeting ILF3, miR-215-5p may inhibit its ability to stabilize LRRFIP1 mRNA, thereby attenuating their pro-apoptotic effects. In the present, the circ-RNA/miRNA-RBP-mRNA axis, like the one mentioned above has shown prominent role in regulating apoptosis. These regulatory mechanisms of RBPs may offer novel therapeutic strategies for modulating structural remodeling and functional recovery following MI.

Members of the RBM protein family typically contain primary structural sequences of RNA recognition motifs, also known as RNA binding domains [141]. The biological function of the RNA recognition motif is undoubtedly foremost since it is widely present in the organelles of any cell found to contain RNA, and is conserved in animals, plants, bacteria, and viruses [141]. It is important to note that a large number of RBPs containing RNA-binding motifs have been found so far and have not been named RBM. More and more RBPs discovered in the future will be named based on their gene, function, location, and other information. Several of the RBMs discussed next belong to members of the protein family initially named "RBM". In mice mimicking ischemic heart failure, RBM25 was found to exacerbate cardiomyocyte apoptosis by modulating endoplasmic reticulum stress response and activating C/EBP homologous protein (CHOP)-related pathways [142]. At the cytological level, bioinformatics tools were used to analyze the involvement of RBM25 in alternative splicing of apoptotic genes in H9c2 cells [143]. RBM25 can upregulate the expression of genes associated with inflammation and apoptosis in H9c2 cells, thereby promoting the endoplasmic reticulum stress pathway through the CHOP/BCL2-binding component 3 (BBC3) branch [143]. RBM15, a prominent regulative RBP of RNA methylation in CVDs, was recently elucidated to enhance m^6A methylation, resulting in increased expression stability of the E1 subunit of NEDD8 activating enzyme (NAE1), which could repress apoptosis [92, 144]. Overexpression of RBM15 and enhanced m^6A methylation of the E1 subunit of NEDD8 may be a protective mechanism to reduce apoptosis in MI [144]. RBM15 participates in the regulation of m6A methylation, conferring myocardial protection by stabilizing NAE1 mRNA. Lin-28 homolog A (LIN28A) is an evolutionarily conserved RBP that promotes cell growth and self-regulation [145]. Previous progress suggests that LIN28A enhances autophagy and reduces apoptosis by activating the Sirt1 signaling pathway, thereby mitigating inflammation and apoptosis-induced cardiac remodeling in post-MI [109, 146]. Additionally, the RNA-binding motif protein RBM3 was significantly upregulated in cardiomyocytes models simulating AMI or ischemia-reperfusion-induced injury [147]. RBM3 was found to interact with Raptor to regulate autophagy by inhibiting the Raptor-mTOR axis, thereby protecting cardiomyocytes from apoptosis. Moreover, RBM3 may also inhibit apoptosis in cardiomyocytes by regulating the Bcl-2/BAX balance [147]. These data provided a theoretical basis for the potential therapeutic role of RBM3 in AMI. Furthermore, CUGBP1, as a multifunctional RBP, is involved in post-transcriptional regulation of CVDs [148, 149]. Researchers have found that CUGBP1 binds to the 3' UTR of phosphatidylethanolamine-binding protein 1 (PEBP1) mRNA, inhibits the expression of PEBP1, and weakens the activation of MAPK signaling, a typical signaling pathway facilitating myocardial remodeling [150].

In global CUGBP1 knockout mice, they also found that CUGBP1 deficiency mitigated apoptosis and oxidative stress in cardiomyocytes [150]. Although CUGBP1 has been shown to promote the post-transcriptional modification of VEGF-A and reduce cardiomyocyte apoptosis [42], this work has also demonstrated that CUGBP1 may exacerbate myocardial oxidative stress, apoptosis, and pathological hypertrophic cardiomyopathy [150]. Therefore, CUGBP1 may have distinct cardiac effects by participating in post-transcriptional modifications of different genes. Beyond that, Wilms' tumor 1-associating protein was also found to regulate the m6A modification of activating transcription factor 4 (ATF4) and increase its mRNA stability by binding to ATF4 mRNA, thus promoting ATF4-mediated CHOP-related apoptosis pathway [151]. To sum up, RBPs regulate multiple processing forms of mRNA of target genes and are also regulated by a variety of non-coding RNAs rigorously.

Effect of RBPs on cardiomyocytes fibrosis in post MI

Fibrosis is a common pathology in many cardiac disorders, including AF, dilated cardiomyopathy, and repair of infarct areas in post-MI. Myocardial fibrosis is one of the significant factors affecting the complications and mortality of MI and is a major public health problem of CVDs worldwide. Cardiac fibrosis contributes to pathological scarring, myocardial sclerosis, and cardiac contractile and diastolic dysfunction. Cardiac fibrosis is a complex process involving a variety of cellular and inflammatory factors, and fibrosis is mainly driven by the activation of resident fibroblasts triggered by humoral factors like transforming growth factor (TGF)-β, which could activate Smad signaling [111, 152–154]. Fibrosis is not only a consequence of inflammation during acute ischemia-reperfusion, but also a compensatory recovery after MI [155]. However, the larger area of fibrosis for recovery will seriously affect the systolic and diastolic function of the myocardium. Thus, a comprehensive study has discussed the importance of RBPs in regulating translation networks in myocardial fibrosis [156]. TGF has widespread translational regulatory roles in the transformation of cardiac fibroblasts to myofibroblasts. TGF-β profoundly influences the function of RBPs at the post-transcriptional level, entailing feedforward and feedback mechanisms [157]. Some specific RBP targets were found to be significantly enriched in translational rather than transcriptional regulatory genes, which may reveal the post-transcriptional regulatory footprint of RBPs in fibroblast activation stimulated by TGF-β1 [156].

Healing and fibrotic remodeling of injured tissues are mediated by the differentiation of fibroblasts into myofibroblasts. One study investigated the expression of the RNA-binding protein muscleblind-like1 (MBNL1) in cardiac fibroblasts and found that only a small amount of MBNL1 was expressed at rest, while the content of MBNL1 was significantly increased under TGF-β stimulation [158]. In the model of MI-mouse, MBNL1 was found to be elevated, promoting the transformation of fibroblasts into myofibroblasts [158]. As a direct mechanism, the study revealed that MBNL1 amplifies myofibroblast differentiation, fully exerting calcineurin activity by binding calcineurin Aβ (CnAβ) and serum response factor (SRF) target mRNAs. For this reason, MBNL1 could be used to promote damaged myocardial tissue repair and healing by enhancing myofibroblast differentiation. Nevertheless, perennial, excessive cardiac fibrosis is pathological and can deteriorate heart function, eventually leading to heart failure and other complications [159–162]. The inflammatory response and subsequent fibrosis are dynamically balanced in the process of tissue injury and healing. Excessive or debilitating effects on either side may negatively affect tissue recovery. Activation of IL-1β induced-MMP-9 has previously been associated with cardiac fibrosis [163, 164]. In vitro experiments, knockdown of HuR in macrophages significantly reduced the mRNA stability of MMP9 and TGF-β [114, 115], which may provide valuable ideas for alleviating fibrosis secondary to cardiac inflammatory response. RBPs also play a key role in TGF-regulated endothelial fibrotic response at the post-transcriptional level. HnRNP and Cold shock domain containing E1 (Csde1) significantly contribute to the maintenance of endothelial cell function and the counteraction of interstitial fibrous activation [157]. In endothelial cells and fibroblasts, RBPs have a complex and elaborate network that regulates cellular response to TGF-β stimulation at the post-transcriptional level. It was found that TGF-β stimulation reduced the binding of Csde1 to target mRNA, which in turn promoted endothelial to mesenchymal cell activation in the feed-forward loop. Correspondingly, the increased binding capacity of hnRNP induced by TGF stimulation counteracts this and acts as a brake in a negative feedback mechanism to prevent pro-mesenchymal progression and loss of function for endothelial cells, conducting a transient mesenchymal cell phenotype [157]. It is evident that RBPs, under the synergistic influence of TGF, exert a profound impact on fibrosis-related molecules at the post-transcriptional level. This regulation involves both feedforward and feedback mechanisms, enabling fine-tuned control of endothelial-to-mesenchymal transition. Herein, making full use of the dynamic balance and RNA binding ability of RBPs in cardiac endothelial cells and fibroblasts may provide a valuable opportunity to prevent and treat myocardial fibrosis and improve cardiac function in the future. Figure 6 illustrates the predominant patterns of cardiac fibrosis along with their associated RBPs, highlighting key molecular regulators of fibrotic remodeling in cardiovascular pathology.

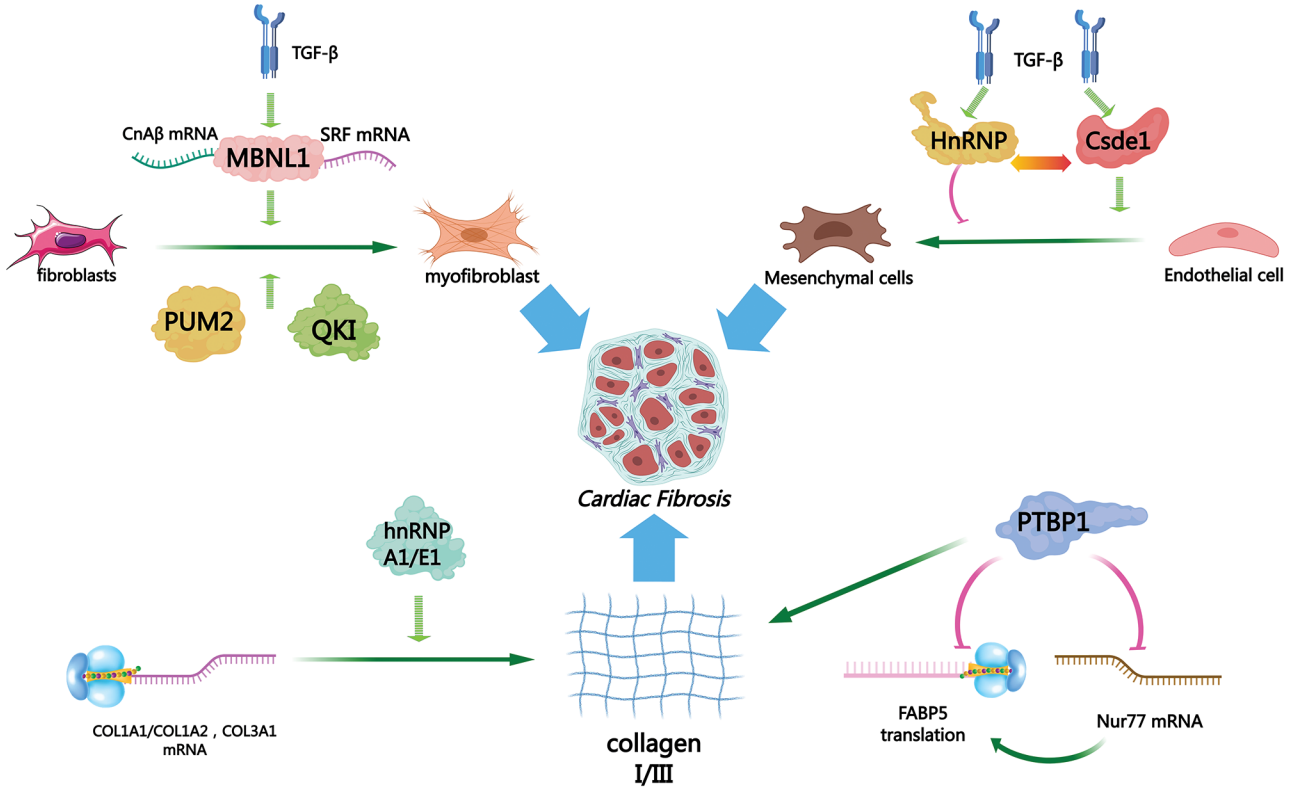

Fig. 6 RBPs primarily participate in three key processes: (1) the transformation of fibroblasts into myofibroblasts, (2) endothelial-to-mesenchymal transition, and (3) the regulation of collagen fiber formation. Under TGF-β stimulation, the RNA-binding proteins MBNL1, PUM2, and QKI coordinately regulate fibroblast-to-myofibroblast transdifferentiation through enhanced transcriptional and translational control, thereby promoting cardiac fibrosis progression. In addition, both Csede1 and HnRNP restrain each other and maintain balance, which is of vital significance for maintaining the dynamic balance of endothelial mesenchymal. PTBP1 and hnRNP A1/E1 have also been found to promote the stability of collagen target mRNA and aggravate cardiac fibrosis

Genome-wide changes in RNA transcription and translation during fibroblast activation were detected by ribosome profiling and RNA sequencing of human heart fibroblasts. Key RBPs that have been identified include Pumilio RNA binding family member 2 (PUM2) and QKI, which, when stimulated by TGF-β1, could coordinate transcription translation and enhance the transformation of fibroblasts into profibrotic myofibroblasts [156]. In other words, PUM2 or QKI knockdown can inhibit the activation of downstream fibroblasts caused by TGF stimulation. This suggests significant application for both QKI and PUM2 in cardiac fibrosis. Furthermore, clinical and molecular data suggest that hnRNP binds to collagen-associated mRNA and is involved in the mechanism of inducing collagen synthesis and cardiac fibrosis. Researchers have investigated that hnRNP A1, E1, and K participated in the synthesis of collagen I and III aggravating cardiac fibrosis [165], and these kind of RBPs may act as a stabilizer of collagen mRNA and effectively promote collagen synthesis. A recent study found that vestigial-like family member 3 (VGLL3) collaborated with EWS RNA-binding protein 1 (EWSR1) to bind and inhibit miR-29b targeting collagen mRNA [166]. This conclusion was further supported by animal experiments: in mice with VGLL3-KO, cardiac fibrosis was significantly attenuated following MI due to increased miR-29b levels, which suppress the expression of collagen and other fibrotic molecules [166]. Overall, EWSR1 controls fibroblast collagen production in a VGLL3-mediated pathway, which may serve as a novel therapeutic target for the treatment of organ fibrosis. Regarding PTBP1, we have discussed its function of stabilizing ALAS2 to regulate myocardial oxidative stress. Nevertheless, PTBP1 has also recently been reported to be involved in the synthesis and accumulation of collagen as well as the excessive proliferation of cardiac fibroblasts [167]. Specifically, PTBP1 reduces the stability of nuclear receptor NR4A1 (Nur77) mRNA by binding to it, thereby affecting the transcription and translation of downstream collagen-related transcripts and promoting cardiac fibrosis. PTBP1 enhances the proliferation of cardiac fibroblasts and subsequent collagen deposition by promoting Nur77 mRNA decay, which aggravates cardiac function [167]. All things considered, PTBP1 may negatively regulate MI, both in acute myocardial oxidative stress and fibrotic collagen deposition during convalescence. In cardiac repair after MI, extracellular matrix (ECM) is also an important component that

supports cellular connections, maintains protein transport, and provides a microenvironment for tissue repair after injury. As a non-structural ECM protein, periostin is extremely vital for the remodeling of ECM [168–170]. The RBP RBM24 is known to be a key splicing factor in heart development, and its deletion is fatal to embryonic mice [171]. Animal experiments showed that overexpression of RBM24 in adult mouse cardiomyocytes increased the expression of TGF-β and associated genes in the ECM [172]. High-resolution microarray analysis revealed that overexpression of RBM24 induced increased expression of TGF signaling genes, similar to the robust expression of cardiac periostin, which induced extensive cardiac fibrosis [172]. In fact, whether promoting infarct repair through myofibroblast differentiation, maintaining the dynamic stability of endothelial and mesenchymal cells, or regulating the excessive proliferation of fibroblasts and collagen induced by TGF-β, these fibrotic processes are extensively and precisely modulated by RBPs. While these processes significantly influence post-MI repair and myocardial fibrosis. Therefore, investigating the detailed molecular mechanisms of RBPs in myocardial fibrosis is highly warranted. These findings will open new avenues for exploring the roles of other RBPs in the regulatory mechanisms of cardiac fibrosis.

Potential therapeutic prospect of RBPs in MI

Through a detailed discussion of the diverse roles of RBPs in MI, it is evident that RBPs hold an indispensable position in the pathophysiology of MI. Enhancing our understanding of the physiological and pathophysiological mechanisms underlying MI will facilitate the identification of potential novel therapeutic targets. Figure 7 illustrates representative RBPs that play roles during distinct pathophysiological stages of MI.

It is noteworthy that RBPs mediate post-transcriptional regulation of multiple genes during MI. Numerous reports also highlight the promise and significant progress of RBPs in CVDs research, marking the dawn of a new era in the treatment of CVDs [173, 174]. Simultaneously, precise targeting of molecular mechanisms associated with RBPs, remains a top priority for the prevention and treatment of cardiovascular diseases in the future. Therefore, further exploration of the precise regulatory networks of RBPs is essential, as they play a crucial and decisive role in the prevention and treatment of MI, both at the cellular and organ levels. Currently, the biological dysfunction and behavioral changes of RBPs in MI are central to mediating the pathophysiological change of MI. Thus, restoring the normal physiological function of RBPs or specifically targeting their regulatory mechanisms may become a central focus for the prevention and treatment of MI.

Unsurprisingly, the RBPs discussed above play a pivotal role in MI and can be broadly categorized into two groups: protective and pathogenic. As we all know, each RBP molecule possesses a specific domain or binding conformation that facilitates sequence-dependent binding to target mRNAs. Based on this, mimetics of beneficial RBPs or inhibitors of pathological RBPs should be specifically designed and developed to prevent or treat diseases. To this end, several promising oligonucleotide-based therapeutic technologies, including antisense oligonucleotides, miRNAs, small interfering RNAs (siRNAs), aptamers, and CRISPR/Cas systems, have been extensively explored and developed [175–177]. The development of these technologies enables targeted intervention in RBP-RNA interactions or the specific modulation of disease-associated RBPs, thereby limiting disease onset and progression. As early as a few years ago, the FDA approved Spinraza™, a targeted RNA therapeutic oligonucleotide for the treatment of spinal muscular atrophy (SMA) [178]. This approval marked a significant breakthrough in the field of RBPs-RNA therapy. In this context of SMA, an RBP, hnRNP A1/A2, aberrantly bind to SMN2, leading to the alternative splicing defect that drives the onset and progression of the disease [179]. In terms of specific mechanisms, Spinraza™ (Nusinersen) can bind to the pre-mRNA of Survival Motor Neuron 2 (SMN2) and competitively hinder the attachment of hnRNP A1/A2 to the pre-mRNA of SMN2, thereby exposing the splice site of SMN2 exon 7 and promoting the generation of complete, full-length, functional mature SMN mRNA. Meanwhile, small-molecule splicing modifiers, such as risdiplam, and gene replacement therapies, including onasemnogene abeparvovec, have also been employed in the treatment of SMA [180]. However, these therapeutic approaches still face significant challenges in clinical translation, particularly due to their complex delivery systems and side effects, including systemic metabolic disorders. In addition, molecular biology techniques that modulate the function, quantity, or RNA-binding activity of RBPs may demonstrate potential therapeutic capabilities. Aptamers or small molecules can be engineered to target specific RBPs, thereby inducing their degradation or blocking their mutual binding to the target RNA. Blocking glycosylation or phosphorylation of RBPs to directly inactivate them may also inhibit the post-translational modification of target mRNAs [173].

Coronary atherosclerosis is the predominant cause of MI, and alternative splicing mediated by RBPs has also been identified to be associated with atherosclerosis [181]. Emerging evidence from comprehensive reviews indicates that HuR plays a significant role in atherosclerosis progression. Notably, elevated HuR expression has been linked to adverse coronary outcomes, suggesting its potential as a pathogenic mediator in CVDs [109, 173,

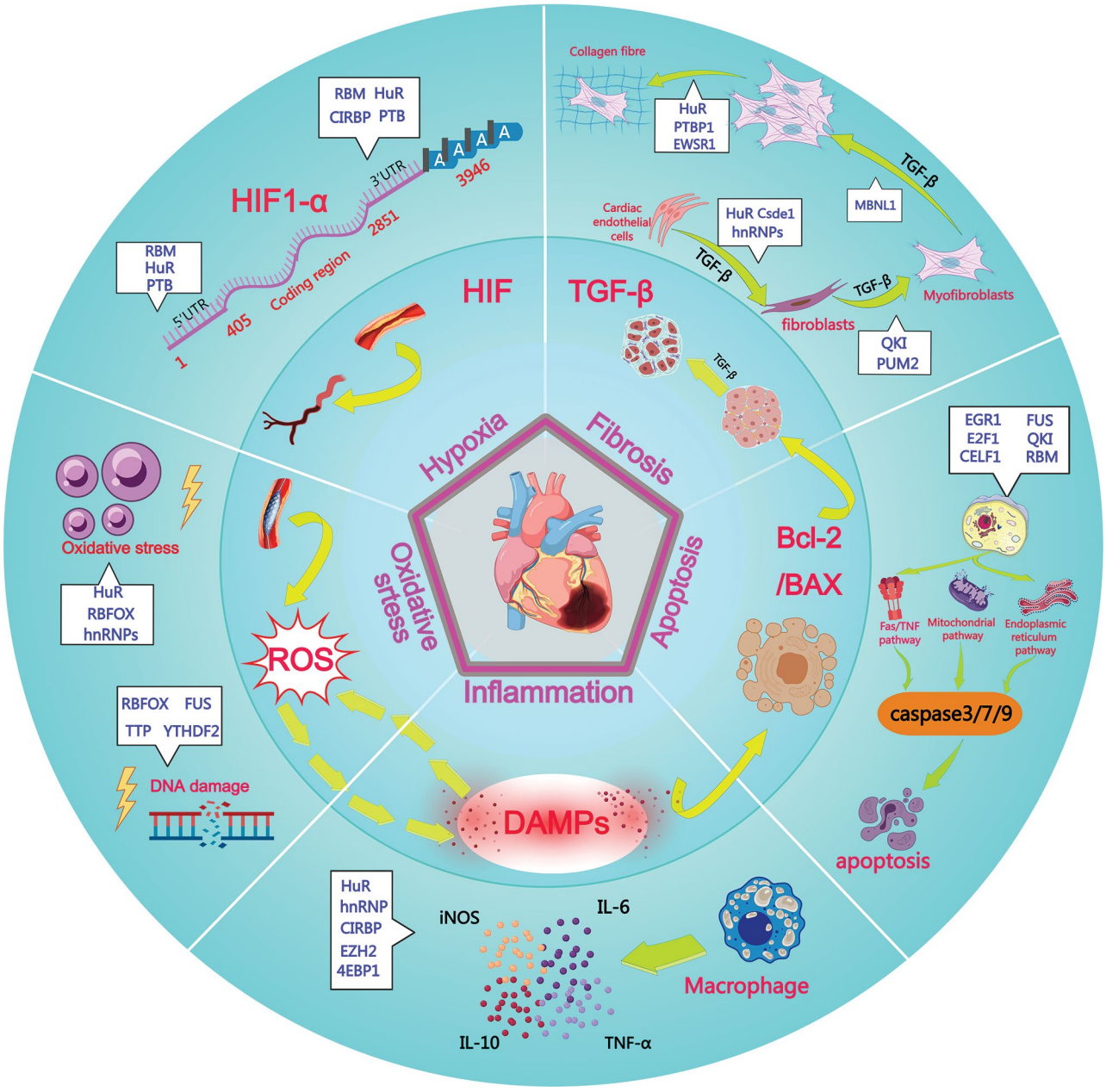

Fig. 7 Representative RBPs play a pivotal role in the five major pathophysiological stages of MI: hypoxia, oxidative stress, inflammation, apoptosis, and fibrosis

182]. However, our prior analysis has elucidated HuR's multifaceted role across distinct pathophysiological stages of MI. Mechanistic studies reveal that HuR exerts differential effects depending on its specific downstream RNA targets, demonstrating context-dependent regulatory functions in cardiovascular pathology. HuR plays a dual role in cardiovascular pathophysiology. First, it maintains vascular endothelial cell stability and modulates pro-inflammatory macrophage activity, suggesting therapeutic potential for atherosclerosis management [183–185]. Second, hypoxia induces dynamic alterations in HuR expression levels and subcellular localization [42]. Furthermore, HuR influences MI prognosis through regulation of pathological mediators, including targets involved in cardiac inflammatory responses and fibrotic remodeling. Given its dual regulatory functions in vascular homeostasis and pathological remodeling, HuR represents a promising candidate for both diagnostic biomarker development and therapeutic targeting in CVDs. Future research should explore its clinical translatability for atherosclerosis management and post-infarction prognosis.

Furthermore, emerging cytotherapy approaches have garnered significant research attention in cardiovascular medicine. Vascular endothelial cell dysfunction and aberrant vascular smooth muscle cell behavior represent pivotal pathological mechanisms underlying coronary artery disease [186, 187], particularly in ischemic myocardial conditions. These cellular perturbations present promising targets for novel regenerative therapies. Recent studies have identified QKI5/6 as crucial regulators of vascular endothelial cell integrity and homeostasis. Furthermore, QKI5/6 mediate vascular smooth muscle cell differentiation from induced pluripotent stem cells (iPSCs) through alternative splicing mechanisms, highlighting their dual role in vascular development and maintenance [187]. Based on these findings, we propose that precise modulation of RBPs could enable the engineering of iPSCs-derived vascular cells with enhanced functional properties. This RBP/ iPSCs-targeted approach may offer a novel strategy to reconstruct the compromised vascular microenvironment in atherosclerosis and post-infarction patients, potentially yielding more precise and effective therapies for ischemic cardiovascular diseases. Moreover, recent investigations by leading research groups have provided novel insights into RBPs-mediated regulation of perivascular cell function through extracellular vesicle signaling pathways. They have identified RPL36, a ribosomal protein subunit, as a novel RNA-binding protein that selectively packages miR-4432 into extracellular vesicles. This RPL36-mediated miRNA loading mechanism affects intercellular communication that exacerbates vascular damage and potentiates pathogenic signaling in both endothelial and perivascular cells [188]. Comprehensive reviews now also establish extracellular vesicles as critical mediators of pathological cross-talk in myocardial infarction (via miRNA transfer), oxidative stress responses (through protein cargo), and heart failure progression (modulating fibroblast activation) [189, 190].

Consequently, therapeutic strategies targeting RBPs demonstrate substantial clinical potential through multiple approaches: (1) development of small-molecule modulators (including ncRNA-based sequestrants and antisense oligonucleotides), (2) design of selective mimics/inhibitors based on RBP-RNA interaction profiles, and (3) application of emerging technologies in molecular biology and engineered tissues. These parallel avenues collectively represent a robust framework for advancing cardiovascular therapeutics. Finally, with the deepening and comprehensive understanding of RBPs at the post-transcriptional level, it is clear that various RBPs are considered to be important effectors mediating cardiac injury and recovery. And their interactions help maintain cardiac homeostasis and may even provide novel insights into cardiac regeneration or proliferation in adult mammals [191].

Discussion

As we all know, RBPs play a critical role throughout the entire life cycle of various RNAs. In particular, an increasing number of studies have focused on the relationship between RBPs and CVDs, including cardiac dysplasia [192], cardiomyopathies [193] and atherosclerosis [183]. Our present work provides novel mechanistic insights into the causal relationship between RBPs and MI. For example, HuR, as a common and critical RBP, plays an irreplaceable role in a variety of CVDs. However, we can see that HuR, because of its extensive RNA binding properties and its multiple functions, may have consistent or diametrically opposite effects in different pathophysiological stages of MI. This may bring some limitations to the wide application of RBPs. Current research suggests that targeted RBP modulation through either selective aptamer development or precise in vivo activity manipulation may address these therapeutic limitations [194]. While this approach shows promise for developing RBP-based treatments for MI, significant translational challenges remain. At the same time, the therapeutic targeting of RBPs presents significant challenges due to their inherent susceptibility to diverse molecular and environmental modulators. Both functional alterations (e.g., post-translational modifications) and quantitative fluctuations in RBP expression create dynamic regulatory networks that complicate the precise targeting of individual RBPs and their downstream pathways. What's more, currently, there remains a notable paucity of large-scale clinical evidence establishing direct associations between RBPs dysregulation and MI outcomes in human populations. While numerous preclinical studies have elucidated the roles of specific RBPs in MI pathogenesis, a systematic framework integrating these molecular players into cohesive pathophysiological networks remains lacking. This knowledge gap persists particularly in understanding: (1) RBP interplay during ischemic injury progression, (2) temporal regulation of their activities across MI phases, and (3) cell-type-specific functions within the cardiac microenvironment. Therefore, substantial challenges remain in elucidating the complex relationship between RBPs and MI. Future research must prioritize: (1) establishing comprehensive RBP regulatory networks, (2) deciphering their dynamic roles across MI pathogenesis, progression, and recovery phases, and (3) identifying critical interaction partners within these pathways. Ultimately, systematic investigation of RBP-centric therapeutic strategies may yield transformative clinical benefits for MI patients.

Conclusion

Collectively, in this work, we presented in detail the association between RBPs and MI from the major stages of the pathophysiological process of MI. We reviewed a wealth of reliable information on the role of RBPs in MI, including some classic RBPs, such as RBM family proteins, hnRNP family members, HuR, and Quaking. Meanwhile, we also elaborated on the mechanism of action and possible targets of RBPs from the aspects of hypoxia, oxidative stress, inflammatory response, apoptosis, and fibrosis, providing a comprehensive overview for exploring the possibility of RBPs as a means to treat and ameliorate MI. Regulation of post-transcriptional levels of RBPS-mediated gene expression is critical in cardiovascular disease. At present, RBPs have emerged as valid regulators of cell function in both physiological and pathological states, determining the fate of RNAs. Therefore, RBPs show potent promise for therapeutic interventions in cardiovascular dysfunction. Importantly, it is urgent to correct the pathogenic pathogenicity of RBPs for MI and to enhance the therapeutic potential of RBPs. Specific modulators, such as RBP mimics or inhibitors, should be further explored and developed. These modulators can be delivered through targeted delivery systems to alleviate cardiac dysfunction, potentially contributing to early treatment strategies for patients with MI. In light of the current in-depth understanding of RBPs, as well as their sweeping regulation of post-transcriptional levels in MI, the application prospect of RBPs in the cardiovascular field is increasingly bright. It is hoped that these novel treatments associated with RBPs may provide considerable insights and revolutionary potential for combating MI and other CVDs in the 21st century.

Abbreviations

MI	Myocardial infarction
AMI	Acute myocardial infarction
CVDs	Cardiovascular diseases
RBPs	RNA-binding proteins
HF	Heart failure
mRNA	Messenger RNA
ncRNA	Non-coding RNA
lncRNA	Long non-coding RNA
snRNAs	Small nuclear RNAs
circ-RNA	Circular RNA
miRNA	MicroRNA
hnRNP	Heterogeneous nuclear ribonucleoprotein
HuR	Human antigen R
CUGBP1	CUG triplet repeat RNA-binding protein 1
STAT3	Signal transducer and activator of transcription 3
Quaking	QKI
HIF-1	Hypoxia inducible factor 1
ROS	Reactive oxygen species
TUG1	Taurine-upregulated 1
FUS	Fused in sarcoma
CaMK2γ	Calcium/calmodulin-dependent protein kinase II gamma
TTP	Tristetraprolin
PTBP1	Polyrimidine tract binding protein 1
ALAS2	Aminolevulinic acid synthase 2
m6A	N6-methyladenosine
METTL3	Methyltransferase-like 3
METTL14	Methyltransferase-like 14
METTL16	Methyltransferase-like 16
BNIP3	Bcl-2 19-kDa interacting protein 3
IGF2BP2	Insulin-Like Growth Factor 2 mRNA-Binding
DAMPs	Danger-associated molecular patterns
TNF-α	Tumor necrosis factor-α
iNOS	Inducible nitric oxide synthase
CIRBP	Cold-inducible RNA-binding protein
EZH2	Enhancer of zeste homolog 2
PPAR-γ	Peroxisome proliferator-activated receptor gamma
eIF	Eukaryotic initiation factor
4EBP1	eIF4E binding protein 1
ILF3	Interleukin enhancer binding factor 3
LRRFIP1	LRR binding FLII interacting protein 1
CHOP	C/EBP homologous protein
NAE1	E1 subunit of NEDD8 activating enzyme
LIN28A	Lin-28 homolog A
PEBP1	Phosphatidylethanolamine-binding protein 1
ATF4	Activating transcription factor 4
TGF	Transforming growth factor
MBNL1	Muscleblind-like1
CnAβ	Calcineurin activity by binding calcineurin Aβ
SRF	Serum response factor
Csde1	Cold shock domain containing E1
PUM2	Pumilio RNA binding family member 2
VGLL3	Vestigial-like family member 3
Nur77	Nuclear receptor NR4A1
FABP5	Fatty acid-binding protein 5
ECM	Extracellular matrix
siRNAs	Small interfering RNAs
SMN2	Survival Motor Neuron 2
SMA	Spinal muscular atrophy
iPSCs	Induced pluripotent stem cells

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Author contributions
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