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Review Article

Non-coding RNAs as biomarkers for acute myocardial infarction

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Abstract

Acute myocardial infarction (AMI) is a main threat to human lives worldwide. Early and accurate diagnoses warrant immediate medical care, which would reduce mortality and improve prognoses. Circulating non-coding RNAs have been demonstrated to serve as competent biomarkers for various diseases. Following the identification of cardiac-specific microRNA miR-208a in circulation, more non-coding RNAs (miR-1, miR-499 and miR-133) have been identified as biomarkers not only for the diagnosis of AMI but also for prognosis post infarction. Here, we summarized recent findings on non-coding RNAs as biomarkers for early diagnosis of ST-segment elevation myocardial infarction and for disease monitoring of myocardial infarction. In addition, the prognostic potential of non-coding RNAs in patients treated with percutaneous coronary intervention was also described. We also include studies based on biobanks, and build a miRNA release spectrum after AMI, which provides quantitative and time-lapse monitoring of AMI progress. With this spectrum, we are able to customize personal medical care, which prevents further damage. By constructing a network of circulating non-coding RNAs with high specificity and sensitivity, detailed diagnostic information was provided for personalized medicine. Unveiling the roles and kinetics of circulating non-coding RNAs may lead to a revolution in clinical diagnosis.

Keywords: acute myocardial infarction; biomarkers; non-coding RNAs; circulating RNA; cardiovascular diseases; diagnosis; prognosis

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Introduction

Over 790 000 people are diagnosed with acute myocardial infarction (AMI, often referred to as heart attack) annually in America alone[1]. Diagnosis as early and accurate as possible warrants immediate medical care, which would reduce mortality and improve the prognosis of AMI[2, 3]. AMI is classified into ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI)[4]. For STEMI, reperfusion therapy should be administered as quickly as possible to reduce infarct size and mortality[5]. For NSTEMI and unstable angina (UA), another non-ST-segment elevation acute coronary syndrome, detailed revascularization strategies were recommended based on the clinical features of individual patients[3]. Thus, STEMI patients require early diagnosis, whereas NSTEMI and UA patients require detailed clinical features. Hence, it is critical to build a nexus of molecular biomarkers for physicians to organize an effective, personalized therapeutic schedule.

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Biomarker tests combined with electrocardiographic (ECG) analysis is the main tactic for AMI diagnosis. Although ECG provide strong evidence for ischemia or infarction, ECG alone is incapable of diagnosing NSTEMI, which comprises 60%–75% of all myocardial infarctions[6]. In addition, both STEMI and NSTEMI demand biomarkers for final diagnosis according to European and American guidelines[4, 6]. Biomarkers for AMI should first be quantitatively altered in AMI and thus be used to predict and monitor the pathogenic processes of AMI[7, 8]. Meanwhile, a good biomarker should also be stable and easily accessible[9]. The currently preferred diagnostic biomarkers for AMI are cardiac troponin I and T (cTnI and cTnT)[10]. Circulating cTnI and cTnT have been the 'gold standard' of AMI diagnosis for over 20 years since they can be released from necrotic cardiomyocytes within 2–4 h post AMI[10, 11]. Circulating cTnI and cTnT reach peak levels at 24-48 h post AMI and last for over a week[12]. High-sensitive cardiac troponin I and T were recently developed to improve the sensitivity and accuracy of AMI diagnosis[13, 14]. However, false positive results with elevated cTn occurs in patients with heart failure, chronic kidney diseases and sepsis, especially in elderly

patients[15-18]. In addition, since cTn remains in the circulation for over 7 d[12], small repeat infarctions post major infarction are unlikely detectable. Thus, it is critical to identify sensitive biomarkers for extremely early diagnosis of STEMI as well as specific biomarkers that monitor the entire pathogenic processes of AMI.

Starting with the exploration of microRNAs, numerous efforts have been made to excavate the treasures underlying non-coding RNAs (ncRNAs), which consist of over ninety percent of the human genome. MicroRNAs (miRNAs), small interference RNAs (siRNAs), long non-coding RNAs (lncRNAs) and recently identified circular RNAs (circRNAs) have all been shown to have regulatory functions or diagnostic potential in cardiovascular diseases[19]. MicroRNAs are endogenous short non-coding RNAs with a length of approximately 22 nt expressed in almost every cell[20]. Mature miRNAs bind to RNA binding proteins (RBPs) and regulate mRNA stability via recognition sites, such as AU-rich elements, in the untranslated regions of mRNA[21-23]. In 2008, scientists in the UK[24], USA[25] and China[26] independently found that circulating microRNAs are sensitive biomarkers for cancer and other kinds of disease. Pioneering works have demonstrated that microRNAs possess huge potential as biomarkers for AMI[27, 28]. Recently, other classes of non-coding RNAs, such as lncRNAs and circRNAs, have also been suggested as biomarkers of AMI. Despite accumulating reports on non-coding RNAs as biomarkers of AMI, we summarize recent findings and discuss future applications of non-coding RNAs as biomarkers of acute myocardial infarction with special attention to the diagnostic value and prognostic potential of these non-coding RNAs.

Non-coding RNAs as diagnostic biomarkers for AMI

MicroRNAs

The first group of miRNAs identified as biomarkers for AMI patients were miR-208a, miR-499, miR-133[27] and miR-1[27, 28]. In the plasma of STEMI patients, miR-208a, miR-1, miR-499 and miR-133 were significantly increased. Among these miRNAs, miR-208a was expressed specifically in cardiomyocytes and more importantly, miR-208a showed 90.9% sensitivity and 100% specificity for AMI diagnosis, representing a more advantageous biomarker than even cTnI[27]. As we mentioned earlier, it is critical to identify new biomarkers for extremely early STEMI diagnosis to remedy the delayed plasma peak of cTn. Importantly, both rat models and mice models were utilized to screen for extremely early diagnostic miRNAs[27, 29]. In rat AMI models, miR-208a increased by more than 50 fold within 1 h post coronary artery occlusion surgery and reached a peak level at 3 h after surgery, displaying kinetics that peaked just before a significant elevation in cTn[27]. In addition, miR-1 showed an over 200-fold increase in rat AMI models at 6 h post surgery[30]. A most recent study that outlines the release kinetics of circulating miR-208a in AMI patients further supported the suggestion that miR-208a is a promising diagnostic index for early diagnoses of AMI[31]. Even though the increase in miR-499 was not as dramatic as that of miR-208a, plasma miR-499 levels were significantly increased in rat AMI models 1 h post AMI[27]. A subsequent report further demonstrated that miR-208b and miR-499 were released into the circulation upon various types of myocardial damage, including AMI, and miR-208b showed an over 1600-fold increase in AMI patients[32]. In addition, a cohort with one thousand patients validated the increase in circulating miR-208b and miR-499 in patients with chest pain[33].

The functions of miR-208a, miR-1, miR-499 and miR-133 have been well characterized in the heart[34-38]. miR-208a was initially identified in heart tissues and regulates the proper expression of β-MHC[36, 39]. In addition, miR-208 regulates cardiomyocyte apoptosis via Bcl-2 and Bax signaling[40, 41]. Most recently, miR-208a-3p was found to aggravate autophagy through the PDCD4-ATG5 pathway[42]. Recently, the diagnostic values of miR-208a, miR-1, miR-499 and miR-133 in the circulation have been intensively studied. In addition to mouse and rat AMI models, pig AMI models were established, and miR-208a, miR-1, miR-499-5p and miR-133a were all found to be elevated in pig plasma within 2 h post AMI[43]. Interestingly, in a pig AMI model and a rat AMI model, miR-1 was significantly increased in urine, and further analysis showed that miR-1 was also detectable in the urine of patients with AMI[43, 44]. Recently, a study in a Chinese Han population with plasma samples drawn from patients less than 2 h after the onset of symptoms further suggested the potential of rapid diagnosis with these miRNAs[45]. All these reports validated that circulating miR-208a, miR-1, miR-499 and miR-133 are *bona fide* biomarkers for AMI. Moreover, researchers found that these cardiomyocyte-enriched miRNAs are capable of differentiating STEMI from NSTEMI. In a 444-patient cohort, miR-133a was found to distinguish STEMI, NSTEMI and UA, and miR-208a was able to distinguish STEMI from NSTEMI, whereas miR-499 and miR-208b were not able to distinguish between STEMI and NSTEMI[46]. However, in another cohort, miR-499 and miR-208b were found to be able to distinguish STEMI from NSTEMI[47]. In addition, miR-499-5p was specifically highly sensitive as a NSTEMI biomarker in elderly patients[48]. Additionally, miR-133a displayed distinguishable circulating levels in the serum samples of STEMI and NSTEMI patients, and serum miR-133a also showed diagnostic value for UA and takotsubo cardiomyopathy (TTC)[49]. More importantly, since neither ECG nor cTn is able to differentiate TTC from STEMI, it is exciting that both serum and plasma miR-133a were able to differentiate TTC from STEMI[49, 50]. In addition, miR-499 was identified as a signature for perioperative myocardial infarction in patients undergoing coronary artery bypass graft surgery[51, 52]. All these data indicated that the first group miRNAs identified as biomarkers for AMI possess huge potential in clinical applications, and precise interpretations of these results are promising for Precision Medicine (Figure 1).

The number of novel miRNAs used as diagnostic biomarkers for AMI has increased rapidly. Although the sensitivity and accuracy of these circulating miRNAs vary, several novel circulating miRNAs with special release kinetics are promising candidates. Two circulating miRNAs, miR-30a and miR-

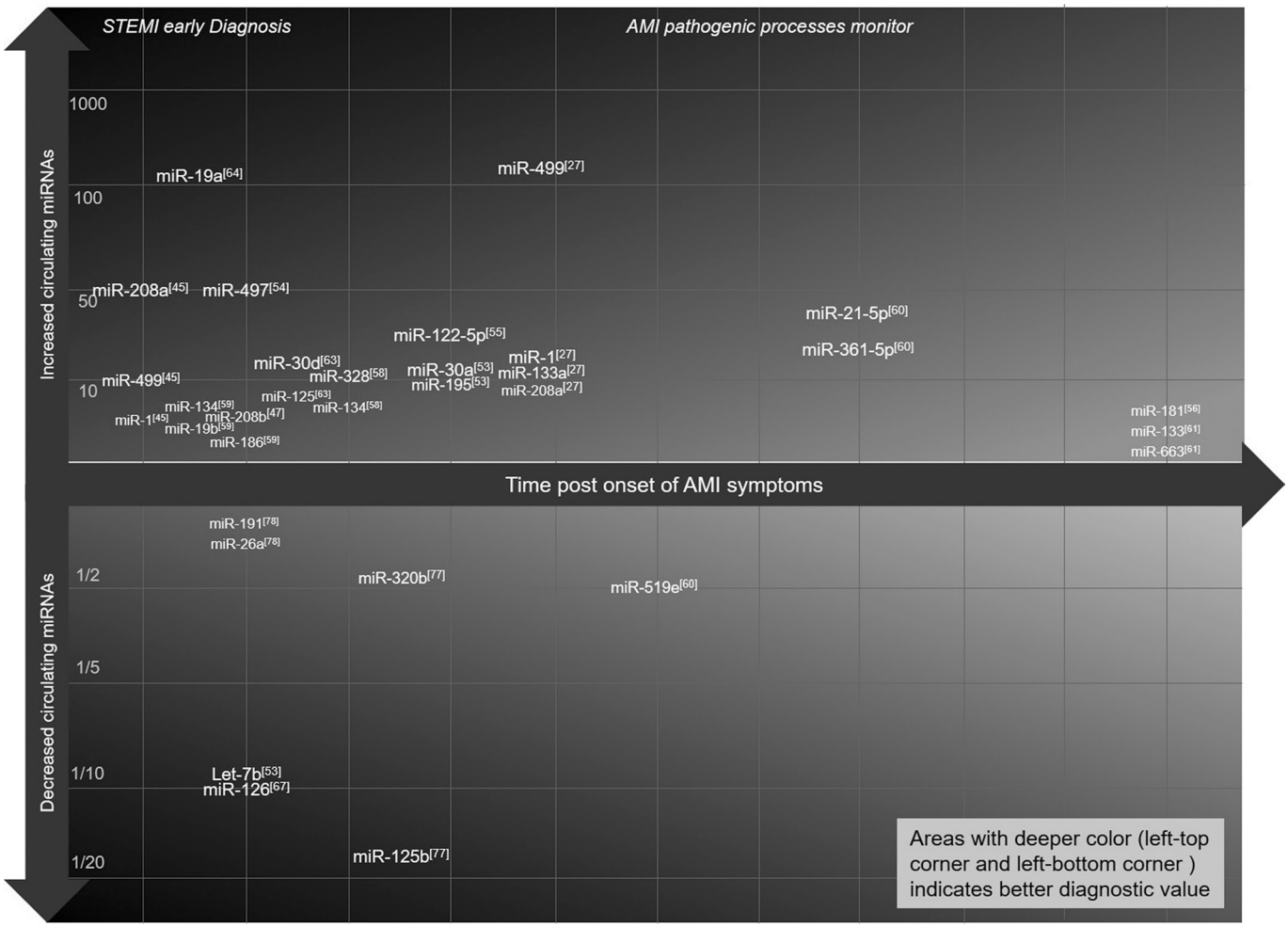

Figure 1. Building a miRNA release spectrum after AMI. With current and future information on circulating miRNAs after the onset of AMI, we can build a miRNA release spectrum that contains detailed messages on when and how much miRNA is released into the circulation after AMI. With this spectrum, physicians can make extremely early diagnosis of STEMI or understand the status of an AMI patient that is either suffering from a STEMI or enduring a NSTEMI.

195, with special kinetics post AMI were observed. These two miRNAs increased significantly at only 8 h post AMI and rapidly dropped back to baseline[53]. Circulating miR-122-5p also showed similar kinetics to miR-30a and miR-195, which peaked at 8 h post AMI[54, 55]. However, circulating miR-122-5p did not show a quick drop at 12 h post AMI, but miR-30a and miR-195 did. Another circulating miRNA with unique kinetics post AMI was circulating miR-181a; its level in the circulation increased from 6 h post AMI and reached peak at 24 h post AMI[56]. These results suggested an option that various miRNAs with diverse releasing kinetics could be integrated together and work as monitors of the pathogenic processes of AMI. miR-328 was found increased by over 10 fold in the plasma of AMI patients in a small sample cohort[57], and a large sample cohort (carried out later) further validated the over 10-fold increase of miR-328a in the plasma of AMI patients and proposed that miR-134 is another circulating miRNA that has potential in AMI diagnosis[58]. Although another report also suggested a rise in circulating miR-134, both studies showed that only an approximately 5-fold increase was observed post AMI[58, 59]. Atherosclerosis-related miR-21-5p and miR-361-5-p in the circulation were increased in AMI patients as well as in patients with ischemic stroke[60]. Novel circulating miRNA were also identified to differentiate STEMI from NSTEMI. Circulating miR-1291 showed a significant increase in NSTEMI compared to STEMI, whereas circulating miR-663b was 2-fold higher in STEMI than in NSTEMI[61]. In addition, circulating miR-486 and miR-150 also varied from STEMI to NSTEMI[62]. Also, circulating miR-125b-5p and miR-30d-5p distinguished AMI from UA[63]. These data suggested that a combination of these circulating miRNAs could provide a biomarker signature to differentiate STEMI from NSTEMI and UA. Circulating miR-19a and miR-19b also showed modest increases in the plasma of AMI patients[59, 64]. Interestingly, the circulating level of miR-22, a miRNA participating in cardiac hypertrophy[65], is also elevated in the blood of AMI patients[66].

Multiple novel circulating miRNAs that decreased in AMI patients have also been identified. Circulating let-7b and

Table 1. Circulating miRNA that are crucial for cardiac event prediction after AMI. Altered circulating levels of miRNAs that predicts cardiac death or left ventricular remodeling after AMI.

Cardiac event	Sample type	Altered miRNA	AUC/OR
Cardiac death after AMI	Plasma	miR-133a[46]	AUC: 0.57, 95% CI: 0.52 to 0.62
		miR-208b[46]	AUC: 0.57, 95% CI: 0.50 to 0.63
		miR-499[96]	OR: 1.70, 95% CI: 1.31 to 2.20
	Serum	miR-155[99]	Approximately 4-fold higher
		miR-380[99]	Approximately 3-fold higher
		miR-145[101]	AUC: 0.707
		ratio of miR-122-5p/miR-133b[102]	OR: 1.52, 95% CI: 1.10 to 2.08
Left ventricular remodeling after AMI	Plasma	miR-16[110]	OR: 15.9, 95% CI: 2.63 to 95.91
		miR-27a[110]	OR: 4.18, 95% CI: 1.36 to 12.83
		miR-208b[111]	OR: 17.91, 95% CI: 2.07 to 98.81
		miR-34a[111]	OR: 4.18, 95% CI: 1.36 to 12.83
		miR-21[112]	OR: 1.119, 95% CI: 1.039 to 1.205
		miR-146a[112]	OR: 2.127, 95% CI: 1.507 to 3.003
		miR-150[110] (down)	OR: 0.08, 95% CI: 0.01 to 0.48
		miR-101[110] (down)	OR: 0.19, 95% CI: 0.04 to 0.97
	Serum	miR-155[113]	*P* value= 0.026

AUC, area under the receiver operator characteristic curve; OR, odd ratio; CI, confidence interval.

miR-126 were found to be dramatically decreased to 1/10 in the plasma of AMI patients from as early as 4 h post onset of AMI[53, 67]. Moreover, the serum level of miR-126 was also decreased in AMI patients[68]. Since both let-7b and miR-126 play critical roles in heart development and heart diseases, it is of great importance to further investigate the biological significance of the decrease of these two circulating miRNAs[69-73]. Circulating miR-519e-5p and miR-99a were also decreased to approximately 50% in AMI patients[60, 74]. In addition, plasma miR-145 was found to be reduced in both NSTEMI and STEMI patients and patients with heart failure[75]. With the fast development of high-throughput miRNA detection technologies, additional novel decreased circulating miRNAs were easily identified in AMI patients[76-78]. Circulating miR-320b and miR-125b were found to be decreased with microarray assay in the plasma of AMI patients, and these reductions were further validated in a cohort of 178 Chinese AMI patients[77]. Another microarray-based study showed that plasma miR-26a and miR-191 were decreased in AMI patients, which is in line with a previous report suggesting that serum miR-26a and serum miR-191 were decreased in AMI patients[68, 78]. Notably, miR-155 and miR-126, two miRNAs critical for vascular biology[69, 70, 79], were both decreased in the plasma of patients post off-pump coronary artery bypass graft, suggesting a potential monitoring function of miR-155 and miR-126 in cardiac surgery[51]. Taken together, these data suggested that by building up a thorough network of circulating miRNAs post AMI, it is possible to diagnose STEMI rapidly and monitor the pathogenic processes of AMI and thus to organize personalized therapeutic schedules for patients with a risk of AMI.

Long non-coding RNAs and circular RNAs

Recently, non-coding RNA other than miRNAs, such as long non-coding RNAs and circular RNAs, have drawn tremendous attention from scientists in the cardiovascular biology field[80-82]. Circulating forms of these non-coding RNA are also potential biomarkers for cardiovascular diseases[19, 83]. Here, we summarize recent research on non-coding RNAs (other than miRNAs) as diagnostic biomarkers of AMI.

The first study on circulating lncRNAs tested the expression levels of five lncRNAs in the blood cells of 414 patients and 86 healthy controls[84]. Four out of the five lncRNAs, hypoxia inducible factor 1A antisense RNA 2 (aHIF), cyclin-dependent kinase inhibitor 2B antisense RNA 1 (ANRIL), potassium voltage-gated channel, KQT-like subfamily, member 1 opposite strand/antisense transcript 1 (KCNQ1OT1) and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), are differentially expressed in AMI patients and more importantly, MALAT1, ANRIL, KCNQ1OT1 and MI associated transcript (MIAT) were able to distinguish STEMI from NSTEMI[84]. Two more lncRNAs, Zinc finger antisense 1 (ZFAS1) and Cdr1 antisense (CDR1AS), were identified with altered expression levels in the whole blood of AMI patients[85]. Another study showed alterations of over 5000 lncRNAs in the whole blood of Chinese Uyghur AMI patients[86]. In addition, lncRNA Urothelial carcinoma-associated 1 (UCA1), which is detectable in plasma, decreased in AMI patients at two hours after the onset of symptoms[87]. Although these studies provided excellent scientific significance, the sensitivity of these lncRNAs as biomarkers was not comparable to the miRNAs identified as diagnostic biomarkers for AMI. The expression of ZFAS1, CDRAS and MIAT were also affected in a MI mice model, and attenuation of MIAT abrogated the fibrogenesis induced by MI[85, 88]. CircRNAs are a covalently closed circular form of non-coding RNA that presents in various organisms[89, 90]. Due to their specific structure, circRNAs have great potential

as biomarkers in disease diagnosis[91]. CircRNA Cdr1as was elevated in myocardial tissues from MI mice, suggesting that circRNAs may also have potential as diagnostic biomarkers for AMI[92]. In addition, a circRNA microarray was applied to detect altered circRNAs in MI mice, which further provided bases for the application of circRNAs as biomarkers[93].

In summary, several attempts to use non-coding RNAs, especially miRNAs, as diagnostic biomarkers for AMI have become milestones in biomarker identification. Researchers and clinicians are paying more attention to uniting the protocols for sample collection and management. Thus, specific novel non-coding RNAs with specific diagnostic values can be expected in the future. Nonetheless, a handful of circulating miRNAs have already shown better qualities than traditional biomarkers, such as cTn. Further kinetic characterization of these miRNAs will provide detailed information for AMI diagnosis.

Non-coding RNAs as prognostic biomarkers post AMI

Non-coding RNAs as prognostic biomarkers for cardiac death post AMI

Since miRNAs are relatively stable due to various regulatory mechanisms[94, 95], researchers are not satisfied with using circulating miRNAs as only diagnostic biomarkers for AMI. Hence, ever since their identification, efforts have been put into using circulating miRNAs as prognostic biomarkers post AMI.

Among the first group of circulating miRNAs identified in AMI patients, miR-133a and miR-208b were first associated with mortality[46]. High levels of circulating miR-133a and miR-208b were found to be associated with all-cause mortality at 6 months in a 444-patient cohort[46]. The association between increased circulating miR-208b levels and mortality was subsequently validated by other AMI cohorts[96, 97]. Moreover, high plasma levels of miR-499 were also associated with 30-d, 4-month, 1-year, 2-year and 6-year mortality[96-98]. Based on a miRNA array, increased levels of serum miR-155 and miR-380 were strongly associated with cardiac death[99]. More importantly, miR-192, miR-194 and miR-34 were significantly higher in the serum collected from a group of patients who developed ischemic heart failure after AMI onset[100]. In addition, high levels of serum miR-145 were also associated with cardiac death and heart failure in post AMI patients[101]. Recently, it was proposed that the ratio of serum miR-122-5p/133b measured at the time of cardiac catheterization was a strong predictor of cardiac death[102]. Although future investigations for the validation of these miRNAs as prognostic biomarkers post AMI are necessary, it is undeniable that aberrant levels of circulating miRNAs provided predictive information on adverse cardiovascular events post AMI, such as cardiac death and heart failure.

Non-coding RNAs as prognostic biomarkers for cardiac function post AMI

Despite improvements in reperfusion rates and secondary preventive medications post AMI, cardiac dysfunction, especially left ventricular dysfunction, developed at a relatively high rates[103, 104]. Thus, it is of special importance to identify biomarkers that predict cardiac dysfunction in patients who suffered from AMI and subsequently provide medical suggestions for these patients. Based on the valuable information behind circulating non-coding RNAs in both diagnostic and prognostic levels for AMI patients, increasing studies have focused on the prognostic value of circulating non-coding RNAs for cardiac function post onset of AMI.

In addition to the roles in AMI diagnosis and cardiac death prediction post AMI, high serum levels of miR-133a were found to be associated with decreased myocardial salvage, larger infarcts and graver reperfusion injury in AMI patients post reperfusion[105]. In addition, elevated plasma levels of miR-133a were associated with coronary artery stenosis in patients with coronary heart disease[106]. Circulating miR-1, miR-208b and miR-499 were found to be negatively associated with left ventricular ejection fraction (LVEF) in patients treated with percutaneous coronary intervention[96]. In addition to miRNAs, high levels of circulating lncRNA MALAT1 also predicted poor LVEF in AMI patients four months post reperfusion[84]. Circulating lncRNA were also proposed to have roles in cardiac fibrosis post infarction[88, 107]. Left ventricular (LV) remodeling is considered to be a predominate cause of heart failure in AMI patients[108]. By large-scale screening, several plasma miRNAs, especially decreased plasma miR-150, were found to be strongly associated with LV remodeling[109]. It was further characterized that a panel of 4 circulating miRNAs, miR-16/miR-27a/miR-101/miR-150, predicted LV remodeling after AMI with a net reclassification improvement of 66%[110]. In addition, increased circulating levels of miR-208b, miR-34a, miR-21 and miR-155 were all associated with LV remodeling after AMI[111-113]. Importantly, a circular RNA, MICRA, was identified recently as a circulating biomarker that predicts LV dysfunction, which expanded our understanding of circular RNAs[114].

Taken together, circulating non-coding RNAs showed promising roles as prognostic biomarkers post AMI. Future validations of the previous findings in larger cohorts and standardizations of detection schemes could further promote the recognition and application of non-coding RNAs as biomarkers for risk stratification of AMI patients.

Non-coding RNAs as risk predictive biomarkers for AMI

Two studies with unique significance based on large biobanks identified circulating miRNAs that predict future myocardial infarction in healthy individuals[115, 116]. Nineteen circulating miRNAs of 820 participants of the Bruneck cohort were quantified, and the association between levels of these circulating miRNAs and myocardial infarction incidence were estimated. In the end, researchers found that increased levels of circulating miR-126 and decreased levels of circulating miR-223 and miR-197 were associated with incidence of myocardial infarction in apparently health participants[115]. Based on the *HUNT* (The Nord-Trøndelag Health Study) report, a combination of 5 miRNAs, miR-106-5p/miR-424-5p/let-7g-5p/miR-

144-3p/miR-660-5p, correctly predicted 77.6% incidence of myocardial infarction in apparently health participants. More importantly, by adding this miRNA combination to the Framingham Risk Score, the AUC increased significantly from 0.72 to 0.91[116]. These two illuminating studies indicated a potential use of miRNAs as biomarkers to predict heart attack for apparently healthy people. With the popularization of physical examinations and the development of personalized medicine, the establishment of miRNAs as biomarkers to predict the incidence of heart attacks is evolutionary meaningful.

Conclusion and perspectives

Former genomic 'garbage' has now proven itself as a powerful regulator in every biological process. The identification of each type of non-coding RNAs has led a revolution not only in our understanding of the molecular network but also in clinical applications. Multiple miRNAs have exhibited excellent properties as biomarkers for cancers, neurological diseases and cardiovascular diseases[117-121]. Cardiac-specific miR-208a is no doubt the most promising STEMI biomarker thus far. Not only because the specificity and sensitivity of miR-208a are outstanding but also because the kinetics of miR-208a release showed superiority over the 'gold standard' cTn: 1) miR-208a can be detected within 2 h, which is earlier than cTn, and allows extremely early diagnosis of AMI; and 2) miR-208a declined to baseline within 24 h, which enables the detection of minor cardiac events post major infarction. In addition, based on existing reports, we are able to build a miRNA release spectrum (Figure 1) after AMI, which provides quantitative and time-lapse monitoring of AMI progress. With this spectrum, we are able to customize personal medical care, which prevents further damage.

Despite what researchers have accomplished, validations of non-coding RNAs with dramatic changes and swift responses to the onset of AMI in larger cohorts are imperatively needed. Meanwhile, the establishment of standardized detection methods and release kinetics of novel non-coding RNAs are equally important. To finally facilitate the clinical applications of non-coding RNAs as biomarkers for AMI, future studies should focus on the following: 1) patient information, especially the detailed time of symptom onset, which helps identify extremely early biomarkers for STEMI; 2) inclusion of multiple examination time points, which enables long-term monitoring of the course of NSTEMI or UA; and 3) collaboration to increase cohort size and unify detection methods, which improves the applicability of certain biomarkers to a wider population. Meanwhile, it is of significance to further analyze the predictive value of non-coding RNAs for incident myocardial infarction of apparently healthy people.

Even though several animal models have been utilized to describe the accurate release kinetics of these non-coding RNAs that may serve as biomarkers for AMI, elaborate release kinetics that reflect the authentic release kinetics of AMI patients are still not available. A nonhuman primate AMI model may provide infusive results because 1) nonhuman primates are so close to human beings that they share highly conserved genetic regulation networks; thus, all kinds of non-coding RNA, even lncRNA, could be exploited. 2) As a big animal model, primates have enough blood for time-lapse sampling. Thus, it is of great potential to utilize a primate AMI model to further explore the applications of non-coding RNAs as biomarkers for AMI.

In summary, circulating non-coding RNAs, especially miRNAs, displayed numerous advantages as biomarkers and built a multi-level nexus that illustrates that the biological nature of AMI is a promising prospect for AMI diagnosis and prognosis.

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