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Review

Circulating microRNAs to predict heart failure after acute myocardial infarction in women

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ABSTRACT

Left ventricular remodeling after acute myocardial infarction affects cardiac function and increases the risk of developing heart failure. Despite the emergence of biomarkers associated with remodeling, the ideal biomarker to accurately predict the risk of developing heart failure after acute myocardial infarction is still to be discovered. Female and male hearts cope differently with ischemic stress, leading to different consequences on cardiac morphology and function. As biomarkers reflect the pathogenesis of remodeling, utilization of sex-specific biomarkers might improve risk stratification. Expressed in cardiac and inflammatory cells, microRNAs regulate several biological pathways triggering the remodeling process. In addition, circulating microRNAs are associated with the risk of developing heart failure after acute myocardial infarction, hence their biomarker potential. Interestingly, multiple microRNAs display sex-specific expression profiles as they can be modulated by sexual hormones and escape X-inactivation, for those located on the X-chromosome. This review article aims to discuss the potential of circulating microRNAs to predict heart failure after acute myocardial infarction in a sex-specific manner.

1. Introduction

Cardiovascular disease (CVD) is the first cause of mortality Worldwide [1]. Half of deaths are imputable to coronary artery disease (CAD) which kills as many men as women [1,2]. Among CAD, acute myocardial infarction (AMI) plays a major role and is associated with a high risk of developing left ventricular (LV) remodeling (LVR) leading to cardiac dysfunction and heart failure (HF). Identification of patients at high risk of LVR represents an unmet clinical need and could aid reducing the incidence of post-AMI HF. Indeed, being able to stratify patients according to their risk of developing adverse outcomes after AMI would allow tailoring healthcare to each individual, optimizing the use of imaging technologies, novel drugs, and planning a close follow-up with frequent re-hospitalization in high-risk patients. Novel biomarkers of outcome after AMI are required to aid in moving towards implementation of personalized medicine.

Multiple specificities linked to sex have been shown in AMI risk factors, presentation features and prognosis [3–5]. Male and female hearts do not equally respond to ischemic stress leading to sex-related differences in the consequences of AMI, notably related to the changes in cardiac morphology and function [6]. As biomarkers reflect the underlying disease process, sex-specific biomarkers of LVR have the potential to improve risk stratification of patients and allow a gender-based personalized medicine.

Non-coding RNAs (ncRNAs) among which microRNAs (miRNAs) emerged as putative regulators and potential biomarkers of LVR [7]. Interestingly, miRNAs show sex-specific expression profiles due either to their escape of X-inactivation for those located on the X-chromosome or to modulation by sexual hormones [8,9]. This review presents the sex-disparities in AMI and LVR and discusses the potential of miRNAs as sex-specific predictors of LVR development following AMI.

2. Sex-disparities in AMI

Analysis of patient cohorts and in vivo experimental studies revealed multiple sex-disparities in AMI patients related to risk factors, pathophysiology, diagnosis and prognosis. Women with AMI are older than men and present more comorbidities and risk factors, particularly

Abbreviations: CVD, cardiovascular disease; CAD, coronary artery disease; AMI, acute myocardial infarction; LV, left ventricular; LVR, left ventricular remodeling; ncRNA, non-coding RNA; miRNA, microRNA; HF, heart failure; ICM, ischemic cardiomyopathy; BNP, Brain natriuretic peptide; NT-proBNP, N terminal prohormone of brain natriuretic peptide; AUC, area under the receiver operating characteristic curve; AIC, Akaike information criterion; lncRNA, long non-coding RNA; IL, interleukin; ECs, endothelial cells; ER, estrogen receptor

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diabetes and hypertension [5,10]. Furthermore, angiographic studies showed that female patients present less extensive CAD [11], more plaque erosion [12] and non-occlusive CAD (15% versus 8%) than their male counterparts [13]. Although chest pain is the predominant symptom of AMI in both sexes, atypical symptoms are more common among women [3,4,14]. Moreover, women are less often diagnosed with ST-segment elevation myocardial infarction than men (27% versus 37%) [15]. Women have longer ischemic time (i.e. delay between chest pain onset and reperfusion) and treatment times than men, especially among those aged < 60 years old [16]. The higher mortality rate in women after AMI has been mainly assigned to an older age at event time and accumulation of comorbidities [15,17]. Nevertheless, despite a matching for age and risk factors in *ISAR-RISK* and *ART* studies, women still had higher 1-year mortality [18]. The *VALIANT* study including > 10,000 patients with myocardial infarction and diagnosed for HF or asymptomatic systolic dysfunction showed higher risk of HF and combined outcome of cardiovascular death or HF hospitalization among women, although this risk appeared to be independent from differences in LVR between women and men [5]. Thus, whether different outcomes after AMI between women and men are direct consequences of different LVR is unclear and most probably include other important parameters such as ischemic time and comorbidities.

3. Sex-disparities in LVR

Animal models showed that male and female hearts do not evenly respond to ischemic stress. Females had smaller infarct size, less necrosis and apoptosis, better contractility and better LV function recovery [19]. In addition, coronary occlusion in hypertensive female rats led to concentric hypertrophy without thinning and dilation of the infarct zone, whereas males were more prone to eccentric LV hypertrophy with thinning and dilation of the infarct zone [20]. On the other hand, males had a delayed healing process, which predisposes to ventricular rupture and exaggerated LVR [21].

In human, and depending on the study cohorts, between fifteen to 30% of AMI patients develop LVR, with comparable incidence among men and women [22,23]. Post-mortem analyses revealed that men had 10 times higher apoptosis in the infarct border zone compared to women [24]. In another study addressing the association between sex, reperfusion and LVR, angioplasty was more efficient in women who had a better myocardial recovery, a smaller infarct size and less microvascular deterioration [25]. In a group of patients with end-stage HF, sex-disparities in LVR were dependent on the aetiology of HF [6]. Indeed, while no gender-biased differences were observed in patients with idiopathic cardiomyopathy, heart weight and LV mass index was greater in men than women with ischemic cardiomyopathy (ICM). This difference was assigned to fundamental cellular remodeling, with men having 2-fold more cardiomyocytes hypertrophy [6]. Thus, LVR differs between women and men and this may be reflected in biomarker levels.

4. Sex-disparities in biomarkers of LV remodeling

Brain natriuretic peptide (BNP) and its N-terminal fraction NT-proBNP have been widely studied for their ability to diagnose HF and predict LVR after AMI, yet their potential to act in a sex-specific manner is still unclear. Sex affects the circulating levels of these peptides, with women having higher levels independently of age [26–28]. This is mainly due to stimulatory effects of estrogens and lower hemoglobin levels in women [28,29]. Cardiac troponins are secreted at lower levels in women compared to men [30], presumably because of a lower mass of the female left ventricle [31]. Nevertheless, a recent study showed that higher cardiac troponin levels in men persisted even after adjustment with LV mass [32]. Cardiac troponins were shown to be associated with LVR in several patient cohorts, although the influence of sex on this association was not thoroughly addressed [33,34].

Among other potential biomarkers of LVR, both galectin 3 and the interleukin (IL) 33 receptor ST2 (suppression of tumorigenicity 2) showed sex-biased levels. Community studies showed that women had higher levels of galectin 3 leading to the utilization of sex-specific cut-offs for the analyses [35,36]. Conversely, women have been reported to have less ST2 than men and this difference was attributed to female sex-hormones [37]. Despite these differences, the association between these biomarkers and LVR has not been addressed separately in men and women. Recently, a novel female-specific biomarker of LVR after AMI has been reported. This biomarker is a messenger RNA encoding the cyclin dependent kinase inhibitor 1C, a regulator of cell proliferation [38]. This finding supports the potential of RNA molecules as sex-specific biomarkers of outcome after AMI.

5. miRNAs as biomarkers of LVR

The RNA family can be dichotomized into protein-coding RNAs and ncRNAs. Non-coding RNAs have been further classified into small (< 200 nucleotides) and long (> 200 nucleotides) RNAs. Small RNAs include the well-known miRNAs which are widely expressed in the cardiovascular system and are involved in numerous pathophysiological processes through down-regulation of gene expression [7,39]. Circulating miRNAs are mostly present in exosomes and are highly stable, hence their potential as cardiovascular biomarkers [7,40]. Circulating profiles of cardiac-enriched miRNAs vary after AMI, yet an added diagnostic value over cardiac troponins could not be demonstrated [41].

Several studies reported associations between circulating miRNA levels and LVR after AMI (Table 1). Levels of cardiac-enriched miR-208 and miR-499 were correlated with LV function after AMI [42,43], although miR-1 and miR-133a did not show significant associations [44,45]. In addition, a few miRNAs not known to be enriched in the heart (e.g. miR-34a/-21/-146/-150/-194) have been shown to be associated with LVR and HF after AMI [46–48]. Interestingly, some studies reported the incremental value of panels of miRNAs compared to single miRNAs to predict LVR after AMI [43,48,49]. Whether these miRNAs can be used as sex-specific predictors of LVR has not been properly addressed, notably due to low number of women in AMI cohorts limiting the statistical power of the analyses.

The potential of miRNAs as sex-specific biomarkers of LVR could originate from the capacity of X-linked miRNAs to escape the X chromosome inactivation as well as their modulation by sexual hormones. In mouse, the largest proportions of somatic sex-biased miRNAs have been found in heart and liver [51]. Sexual dimorphisms in miRNAs has been studied in both human and murine hearts with and without ICM [52]. In human, 3 miRNAs were sexually dimorphic in ICM and 15 in normal heart. No miRNA showed sexual dimorphism both in normal and ICM hearts suggesting that the profile of sexual dimorphic miRNAs changes under ischemic stress condition. ICM-and sex-associated miRNAs were predicted to be involved in pathways important for cardiac homeostasis such as cardiac muscle growth, angiogenesis, apoptosis, and cation transport [52].

6. X chromosome –linked miRNAs

X-chromosome encodes more miRNAs than most of the autosomes. Based on miRBase miRNA archive [www.mirbase.org 2018], 118 miRNAs are annotated on the human X-chromosome and only 4 on the Y chromosome. The function of the majority of these miRNAs remain to be elucidated. It is known that 15% and 3% of the X-linked genes escape X inactivation respectively in human and mouse [53]. In diploid cells, females have two copies of the X chromosome and males have one copy. In order to compensate sex-biased differences in gene dosage, one of the two X chromosomes in females is randomly inactivated and the genes from this inactive X chromosome are silenced [54]. This inactivation involves the long non-coding RNA (lncRNA) Xist which coats the X chromosome and leads to DNA methylation [54]. Among the X-

Table 1
Association of miRNAs with LVR after AMI.

miRNA	Cardiac enrichment	Time of measurement (post-AMI)	Number of patients	Assessment of LVR (month post-AMI)	Association with LVR	Predictive value and correlation	Ref
miR-208b	Yes	Admission	359	6	Positive	AUC 0.780	[43]
miR-34a	No	Admission	359	6	Positive	AUC 0.738	[43]
miR-208b-34a combination		Admission	359	6	Positive	AUC 0.81	[43]
miR-208b	Yes	Admission	362	4	Negative	AUC 0.69	[42]
miR-499	Yes	Admission	362	4	Negative	AUC 0.64	[42]
miR-150	No	3–4 days	90	4–6	Negative	AUC 0.74	[47]
miR-146a	No	5 days	198	12	Positive	AUC 0.818	[48]
miR-21	No	5 days	198	12	Positive	AUC 0.719	[48]
miR-16/27a/101/150 combination	No	Prior to discharge	150	6	Negative miR-150/101 Positive miR-16/27a	Δ AIC (versus clinical model) 6.83 ($p = .005$)	[49]
miR-194	No	Median 18 days	58	12	Positive	Correlation coefficient = 0.33	[46]
miR-155	No	5 days	20	6	Positive	Correlation coefficient = 0.49	[50]

AUC, area under the receiver operating characteristic curve; AIC, Akaike information criterion.

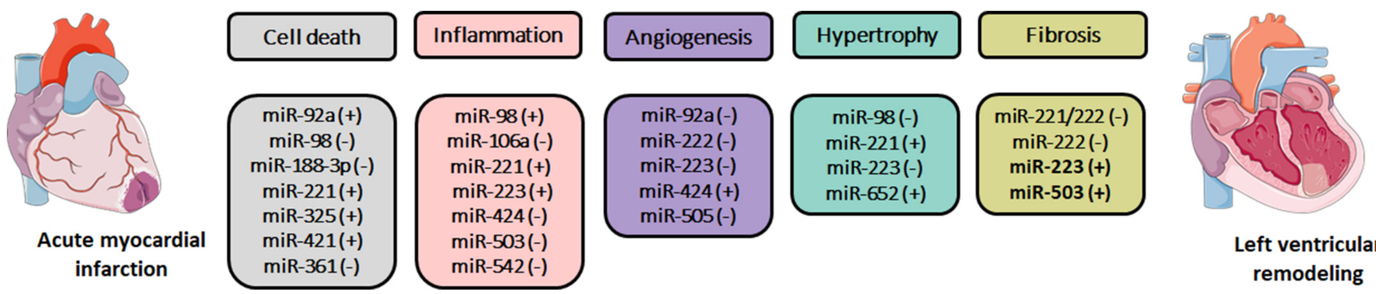

Fig. 1. Implication of X-linked miRNAs in processes triggering LVR after AMI. + signs indicate a stimulatory effect of miRNAs on biological processes; − signs indicate an inhibitory effect.

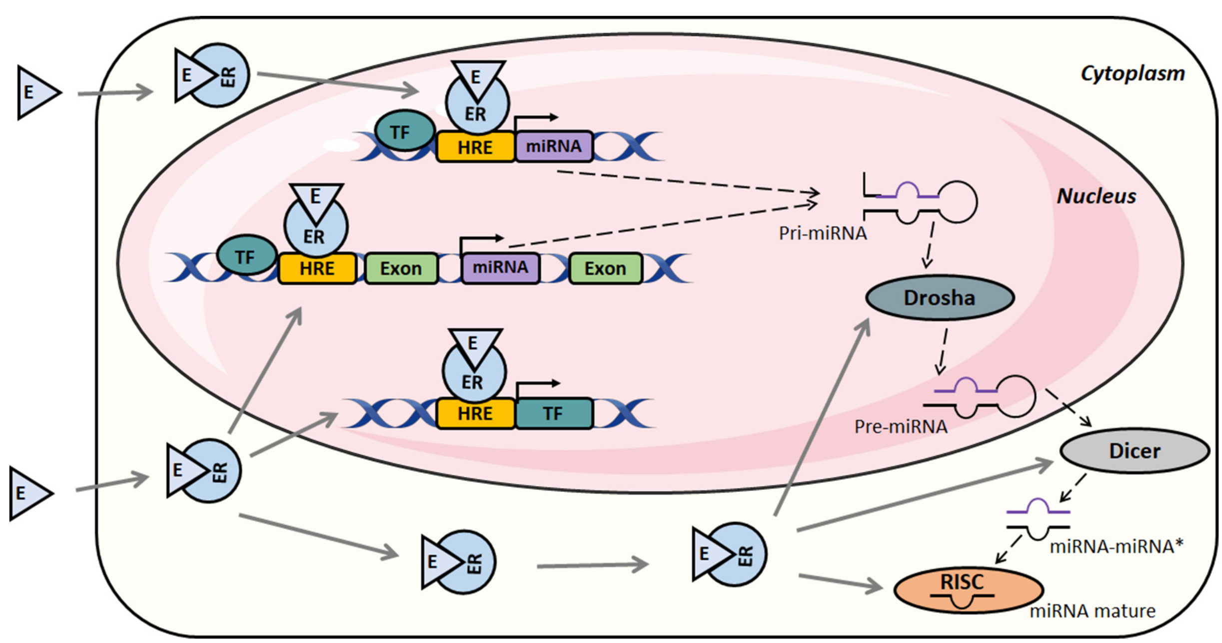

Fig. 2. Modulation of miRNAs by estrogen. E, estrogen; ER, estrogen receptor; HRE, hormone response element; RISC, RNA-induced silencing complex; TF, transcription factor.

linked miRNAs, many were found to escape X chromosome inactivation [8]. These miRNAs could therefore be responsible for sex-disparities in physiological and disease conditions. X-linked miRNAs have been shown to be involved in the different biological processes triggering LVR such as cell death, inflammation, angiogenesis, cardiomyocyte hypertrophy, and fibrosis (Fig. 1).

6.1. Cell death

Inhibition of X-linked miR-92a in pigs undergoing myocardial

Table 2
Association of miRNAs with different biological pathways leading to LVR after AMI.

miRNA	Mechanism	Potential target	Cell type/animal model	Reference
miR-92a	Induction of cardiomyocytes apoptosis	–	Porcine I/R model	[55]
	Inhibition of angiogenesis	Integrin subunit α5	Human endothelial cells Murine limb ischemia and MI model	[72]
miR-361	Induction of mitochondrial fission	Prohibitin (PHB1)	Murine cardiomyocytes Murine MI model	[56]
miR-421	Induction of mitochondrial fission	Pink1	Murine cardiomyocytes Murine I/R model	[57]
miR-188	Inhibition of autophagy	ATG7	Murine cardiomyocytes subjected to anoxia/reperfusion Murine I/R model	[58]
miR-325	Induction of autophagy	Apoptosis repressor with caspase recruiting domain (ARC)	Murine cardiomyocytes subjected to anoxia/reperfusion Murine I/R model	[59]
miR-221	Inhibition of autophagy	P27-CDK2-mTOR axis	H9c2 cardiomyocytes cell line Neonatal rat cardiomyocytes Transgenic mice	[60]
	Dendritic cells apoptosis, differentiation and maturation	$P27^{kip1}$ protein	Human and murine dendritic cells	[64]
	Induction of hypertrophy	P27	TAC mice Cultured cardiomyocytes	[73]
	Inhibition of fibrosis	TGF-β signaling genes (JNK1, TGFβR, ETS-1)	Rat cardiac fibroblasts Angiotensin II-mediated pressure overload mice	[77]
miR-98	Inhibition of apoptosis	Fas and caspase-3	Neonatal rat cardiomyocytes treated with H_2O_2 Murine MI model	[61]
	Inhibition of hypertrophy	Cyclin D2	Angiotensin II-mediated pressure overload mice Neonatal rat cardiomyocytes	[76]
	Inhibition of IL-10 production and endotoxin tolerance in macrophages	IL-10 mRNA	HEK-293cell line RAW.264.7 cell line	[65]
miR-223	Immune cells activation, differentiation, proliferation and survival Macrophage polarization Cytokine production	Granzyme B, IKKα, STAT3	In vitro/in vivo models	[62]
	Inhibition of angiogenesis	β1 integrin	Human umbilical vein endothelial cells Murine hindlimb ischemia model	[69]
	Inhibition of hypertrophy Reduction of intracellular calcium and contractility	Cardiac troponin I interacting kinase (TNNI3K)	Neonatal rat cardiomyocytes TAC model	[75]
	Induction of fibrosis Cardiac fibroblasts proliferation, migration and differentiation	RASA-1	Rat cardiac fibroblasts Rat MI model	[78]
miR-155	Induction of dendritic cells apoptosis Differentiation of monocytes to dendritic cells	$P27^{kip1}$ protein	Human and murine dendritic cells	[64]
miR-424	Induction of angiogenesis	Culin-2	Human endothelial cells subjected to hypoxia Murine ischemia models	[68]
miR-505	Inhibition of endothelial cells migration and tube formation	Fibroblast growth factor-18 (FGF-18)	Endothelial cells	[70]
miR-222	Inhibition of endothelial cells proliferation and migration	Signal transducer and activator of transcription 5A (STAT5A)	Endothelial cells	[71]
	Inhibition of fibrosis	TGF-β signaling genes (JNK1, TGFβR, ETS-1)	Cardiac rat fibroblasts Angiotensin II-mediated pressure overload mice	[77]
miR-652	Induction of hypertrophy	Jagged-1	TAC mice	[74]
miR-503	Induction of fibrosis Induction of cellular proliferation and collagen production in fibroblasts	Apelin-13	TAC mice Neonatal murine cardiac fibroblasts	[79]
miR-126-3p	Anti-atherogenic	Spred-1/VCAM-1	ApoE−/− mice Human umbilical vein endothelial cells	[83]
	Induction of myocardial apoptosis	Caspase-3	Rat I/R model H9c2 cell line	[84]
miR-106a/-106b/-24/-27a/-27b	Induction of fibrosis	MAPK/ERK1/2 pathway	TAC model Rat fibroblasts Cardiomyocytes cell line	[85]
miR-23a	Induction of concentric remodeling Induction of mitochondrial structural and respiratory damage	PGC-1α	Postmenopausal and ovariectomized mice Cultured cardiomyocytes	[87]

I/R, ischemia/reperfusion; MI, myocardial infarction; TAC, transverse aortic constriction.

ischemia/reperfusion reduced infarct size and apoptosis, and improved cardiac function [55]. MiR-421 and miR-361 had opposite effects on cardiomyocyte apoptosis upon myocardial ischemia by modulating mitochondrial fission [56,57]. Overexpression of miR-188-3p in an ischemia-reperfusion model attenuated cardiomyocytes death through autophagy [58]. This effect involved a lncRNA named autophagy promoting factor which was found to interact directly with miR-188-3p and modulate its activity [58]. MiR-325 was upregulated upon ischemia/reperfusion and its overexpression in cardiomyocytes increased autophagic death and infarct size [59]. Moreover, cardiac-specific overexpression of miR-221 led to HF in mice which exhibited hypertrophic heart with excessive interstitial fibrosis, apoptosis and altered cardiac function [60]. This effect implicated an inhibition of cardiomyocyte autophagy through activation of mTOR pathway [60]. Moreover, miR-98 was found to exert an anti-apoptotic effect after AMI through modulation of Fas/Caspase 3 apoptotic pathway [61]. Taken together, these data show that X-linked miRNAs play a key role in modulating cell death after AMI and could account for the difference in infarct size between women and men.

6.2. Inflammation

The X-linked miR-223 has been extensively studied and plays a prominent role in inflammation, as well as in diabetes, insulin-resistance and stem cell differentiation [62]. MiR-221 regulates dendritic cells and T lymphocytes proliferation through the inhibition of cyclin inhibitor proteins [63,64]. MiR-98 is upregulated in activated macrophages and inhibits IL-10 production [65]. MiR-106a, miR-424, miR-503, and miR-542 are involved in monocytes differentiation [66]. Data from HUNT-study addressing the ability of miRNAs to predict the risk of 10 years fatal AMI in an healthy population identified a combination of 5 miRNAs among which the 2 X-linked miR-106a and miR-424 [67]. Interestingly, in this population, miR-424 was associated with the endpoint specifically in men [67].

6.3. Angiogenesis

Hypoxia induced the expression of the X-linked miR-424 in endothelial cells, leading to an increase in vascular endothelial growth factor expression, cell migration and vessel formation [68]. On the opposite, overexpression of miR-223 abrogated endothelial cells (ECs) proliferation, migration and sprouting through preventing growth factor signaling [69]. MiR-505, which is upregulated in the plasma of hypertensive patients, inhibits ECs migration and vessel formation by targeting the proangiogenic fibroblast growth factor 18 [70]. MiR-222, which was downregulated in ECs upon treatment with the inflammatory proangiogenic mediators IL-3 and basic fibroblast growth factor, reduced ECs proliferation and migration through down-regulation of the transcription factor signal transducer and activator of transcription 5A [71]. MiR-92a controls angiogenesis in mice and pigs subjected to ischemia [55,72].

6.4. Hypertrophy

X-linked miR-221 promoted cardiac hypertrophy by down-regulating the hypertrophic suppressor p27 [73]. Inhibition of miR-652 in mice subjected to pressure overload reduced hypertrophy, apoptosis, fibrosis, and preserved angiogenesis, effects mediated by modulation of the Notch1 ligand Jagged1 [74]. MiR-223 was downregulated in both hypertrophic neonatal rat cardiomyocytes and hypertrophic murine heart [75]. It was observed that miR-223 directly targets the cardiac troponin I-interacting kinase to modulate cardiomyocytes hypertrophy [75]. In another study, knocking down miR-98 increased angiotensin II-induced cardiac hypertrophy, an effect partially attributed tocyclin D2 downregulation of [76].

6.5. Fibrosis

Expression of the X-linked miRNA cluster 221/222 negatively correlated with the extent of fibrosis in myocardial biopsies from patients [77]. Inhibition of both miRNAs in mice subjected to angiotensin II-mediated pressure overload increased fibrosis and induced LV dysfunction, an effect involving the transforming growth factor β signaling [77]. MiR-223 regulates fibrosis after AMI through stimulation of cardiac fibroblasts proliferation, migration and differentiation [78]. In a transverse aortic constriction model as well as in angiotensin II-treated cardiac fibroblasts, miR-503 promoted fibrosis through inhibition of apelin13, a crucial protein for cardiac fibroblasts activation [79].

7. Estrogen-modulated miRNAs

Estrogen binds to estrogen receptors (ER) ERα and ERβ and the recently discovered G-protein coupled ER (GPER) [19]. Cells of the cardiovascular system such as ECs, vascular smooth muscle cells and cardiomyocytes express ERs which suggests the involvement of estrogen in cardiovascular pathophysiology. Estrogen plays a pivotal role in cardioprotection against ischemic stress: decreased infarct size, decreased cardiomyocyte death, improved neovascularization, regulation of inflammation [19]. Estrogen affects miRNAs biogenesis through downregulation of *AGO2* and upregulation of *DICER1*and *DROSHA* [80,81]. At the transcriptional level, estradiol seems to modulate the expression of miRNAs through either direct binding of ERα on the regulatory regions of the miRNA, or by modulating the expression of the mRNA-encoding genes that harbor intronically miRNAs, or lastly by modulating the expression of the transcription factors that control the expression of miRNAs [9] (Fig. 2). Estrogen-bound ERα binds to estrogen response elements on DNA and induce the expression of miR-21, miR-23a, and miR-221/222 [9,82].

Few data show the involvement of miRNAs in the cardioprotective effects of estrogen. MiR-126-3p is modulated through the cycle phases in menstruating females suggesting a regulation by estrogens [83]. Furthermore, the anti-thrombotic effect of estrogen is abrogated after inhibition of miR-126-3pin ApoE−/− mice [83]. This effect was proposed to involve a regulation of ECs proliferation and migration and inhibition of monocytes infiltration by miR-126-3p [83]. In another study, miR-126-3p enhanced apoptosis in female rats undergoing myocardial ischemia-reperfusion injury, and its inhibition reduced infarct size [84]. Following pressure overload in mice, miR-106a/-106b/-24/-27a/-27b were found to be upregulated only in male hearts and contribute to fibrosis through MAPK/ERK1/2 signaling pathway regulation [85]. This sex-biased modulation of fibrosis was mediated by estrogen through ERβ activation [85]. Moreover, miR-23a is involved in ageing-associated concentric remodeling which is more common among women [86,87]. Estrogen deficiency during menopause leads to mitochondrial respiration inefficiency, which is mediated by the downregulation of peroxisome proliferator-activated receptor-γ co-activator 1-α bymiR-23a [87].

8. Conclusion and future directions

Personalizing healthcare after AMI is required to decrease the risk of developing LVR and HF and to improve life quality. Novel biomarkers might be useful in this regard. However, LVR and outcome after AMI show important differences between women and men, implying the discovery of sex-specific biomarkers. Since they escape X-chromosome inactivation and are modulated by sex hormones, miRNAs appear to be a reservoir of such sex-specific biomarkers.

Although the miRNAs summarized in this article and in Table 2 have been shown to be associated with different biological pathways leading to adverse remodeling after AMI (e.g. cell death, inflammation, angiogenesis, hypertrophy, and fibrosis), whether targeting one or several of them is a suitable strategy to prevent the development of LVR still needs to be demonstrated. In addition, since miRNAs are known to act both intracellularly and through paracrine mechanisms, it will be insightful to determine whether they act at a local or systemic level on pathways leading to LVR. This could inform about the desired mode of administration of miRNA-targeting drugs. The identification of sex-specific miRNAs associated with outcome after AMI motivates the search for novel sex-specific therapeutic strategies based on miRNAs.

Evaluation of the additive prognostic impact on novel biomarkers such as miRNAs on classical markers is paramount and requires specific statistical methods that have been deployed in some but not all studies. Care should be taken to avoid model overfitting due to the multiplication of explanatory variables in prediction models. The issue of sex-specificity raised in this review article has to be carefully taken into consideration and requires proper sample size calculations to reach a sufficient study power.

Long non-coding RNAs represent the majority of ncRNAs. They are involved in cardiac development and disease [88,89], have been associated with post AMI outcome [90,91], can escape X-inactivation [92], and are regulated by estrogen in cancer cells [93]. Therefore, studying the sex-biased expression of lncRNAs after AMI and their functional role in LVR may lead to the discovery of novel sex-specific biomarkers of LVR.

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Declarations of interest

None.

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