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At the heart of programming: the role of micro-RNAs

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Review

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Abstract

Epidemiological and experimental observations tend to prove that environment, lifestyle or nutritional challenges influence heart functions together with genetic factors. Furthermore, when occurring during sensitive windows of heart development, these environmental challenges can induce an 'altered programming' of heart development and shape the future heart disease risk. In the etiology of heart diseases driven by environmental challenges, epigenetics has been highlighted as an underlying mechanism, constituting a bridge between environment and heart health. In particular, micro-RNAs which are involved in each step of heart development and functions seem to play a crucial role in the unfavorable programming of heart diseases. This review describes the latest advances in micro-RNA research in heart diseases driven by early exposure to challenges and discusses the use of micro-RNAs as potential targets in the reversal of the pathophysiology.

Origins of heart diseases

The heart is the first organ to form during embryogenesis.[1] Its development is a highly regulated process relying on the intervention of various factors that orchestrate cardiac morphogenesis, myogenesis, contractility and metabolism. Mammalian heart undergoes considerable maturation *in utero*, such that the majority of cardiomyocytes, present shortly after birth, beat for a lifetime.[2,3] Thus, an early challenge altering cardiomyocytes maturation, endowment and growth *in utero* can give rise to coronary artery disease,[4] cardiomyopathy,[5] myocarditis,[6] congenital malformations[7] and valvular disease,[8] which can impact lifelong cardiac functions and lead to heart failure. By affecting at least 26 million people,[9] heart failure is a worldwide leading cause of death. Heart failure corresponds to the incapacity of the heart to maintain an adequate circulation of blood in the bodily tissues. Heart failure can be caused by inherited disorders or develop after birth, and the reason behind this remains, most of the time, unknown. Mutations in a variety of genes have been associated with heart diseases in human.[10,11] In addition, the use of animal models based on gene mutations suggests a multiplicity of pathways affecting cardiomyocytes such as transcriptional control,[12] calcium homeostasis,[13] force generation and transmission,[14] as well as metabolism.[15] The use of fast and cost-effective technologies, genetic testing based on the entire exome or genome sequencing[16] revealed a high number of variants which have little effect on cardiac health conditions. A number of polymorphisms have been suggested as a risk factor for heart diseases, however, most of these variants represent susceptibilities that require additional mutations or injury to cause the phenotype of disease. As such, polymorphisms in the adrenergic pathway,[17] G protein-coupled receptor kinases,[18] in the renin–angiotensin–aldosterone system[19,20] have been described.

Besides genetic causes of heart failure, environment,[21–24] nutrition and lifestyle[25–27] have a major impact on heart function. Diet, obesity, diabetes and alcohol consumption (in a dose-dependent manner[28–30]) are particularly of high concern in heart disease etiology. Given the worldwide epidemic of obesity and metabolic disorders, strong efforts are being made to gain insight into the mechanisms of cardiovascular health influenced by nutrition. The important role of nutrition on cardiac functions is reflected by the model of mice fed through their long-term feeding with high-fat diet which results in cardiac hypertrophy and fibrosis[31–33] associated with lipotoxicity.[34] Interestingly enough, correlations between myocardial lipid accumulation and cardiac dysfunction have been noted in humans. When comparing healthy lean individuals to individuals with moderate obesity, an increase in triglyceride accumulation precedes ventricular hypertrophy.[35] Experience of stress such as long-term stress (i.e. work related) as well as acute stress (e.g. experienced during an earthquake,[36] a terrorist attack[37] or an industrial accident[38]) triggers coronary heart disease,[39] myocardial infarction or stroke. Those factors linked to environment, nutrition and lifestyle have stronger effects on heart when they occur early during development.

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Early exposure to environmental challenges induces cardiac disorders

Since the work of Professor D.J. Barker and the hypothesis of the Developmental Origins of Health and Disease (DOHaD) providing a framework to assess the effect of early nutrition and growth on long-term health, a bulk of data identified the developmental period as a phase when the fetus integrate information from the fetal milieu allowing the organism to adapt to change later in life. The fetus learns to adapt to the environment it expects to encounter once outside of the womb. Such 'programming' is a normal, adaptive component of development by which the fetus is predisposed to inhabit an environment with expected resources. When fetal conditions do not match the environment later during life, the child or the adult can develop non-adapted physiological response to the environment. As such, a challenge during fetal life can therefore modify the developmental trajectory and change the developmental 'predictive adaptive' response to the adverse *in utero* environment into maladaptive in adulthood if conditions (e.g. diet and lifestyle) change. Given that turnover of human cardiomyocytes is limited over a lifetime, the heart is particularly sensitive to challenges that perturb the intrauterine environment. In addition to acute effects that may drive long-lasting cardiac dysfunction,[40] early developmental exposure to environmental challenges can induce changes that may impact cardiac functions only later in life (Fig. 1). Insults during infancy, gestational and periconceptional periods are associated with an increased risk of heart diseases in offspring. Fetal hypoxia is one of the most common consequences of complicated pregnancies, occurring during preeclampsia, placental insufficiency or infection. In sheep, a large animal model in which the timing of cardiomyocyte maturation is similar to human, prenatal hypoxia can promote fetal growth restriction associated with a reduction in the total number of cardiomyocyte.[41] In perturbed intrauterine environments such as fetal hypoxia,[42] placental insufficiency and malnutrition,[43,44] adaptations made by the fetus cause permanent changes in tissue structure and function, with depressed cardiac performance and cardiomyopathies that persist into adulthood.[45,46] Those defects have been associated with left ventricular hypertrophy, altered myocardial contractility, endothelial dysfunction,[41] susceptibility to ischemia reperfusion injury[47] and premature cardiac ageing phenotype.[48] Several underlying mechanisms have been proposed, including an increase in beta(2)-adrenoreceptor and the G(s)alpha/G(i)alpha ratio, and a decrease in heat shock protein 70 and endothelial nitric oxide synthase in the left ventricle,[49] or increased expression of insulin-like growth factor 2 (*IGF-2*) and its receptor *IGF-2R in utero* growth,[50] as well as up-regulated *IGF-2R-Gαq* signaling in low-birthweight lamb.[51] In the context of exposure to nutritional excess during perinatal life such as maternal obesity and hyperglycemia[52] as well as child obesity, impaired cardiac function,[53] are induced later in life. These exposures change the programming of cardiac metabolism, inducing excessive lipid accumulation in myocardial cells[54,34] and defects in cardiac insulin signaling.[53]

In the early origin of cardiac dysfunctions, the existence of sensitive developmental windows of exposure had been only

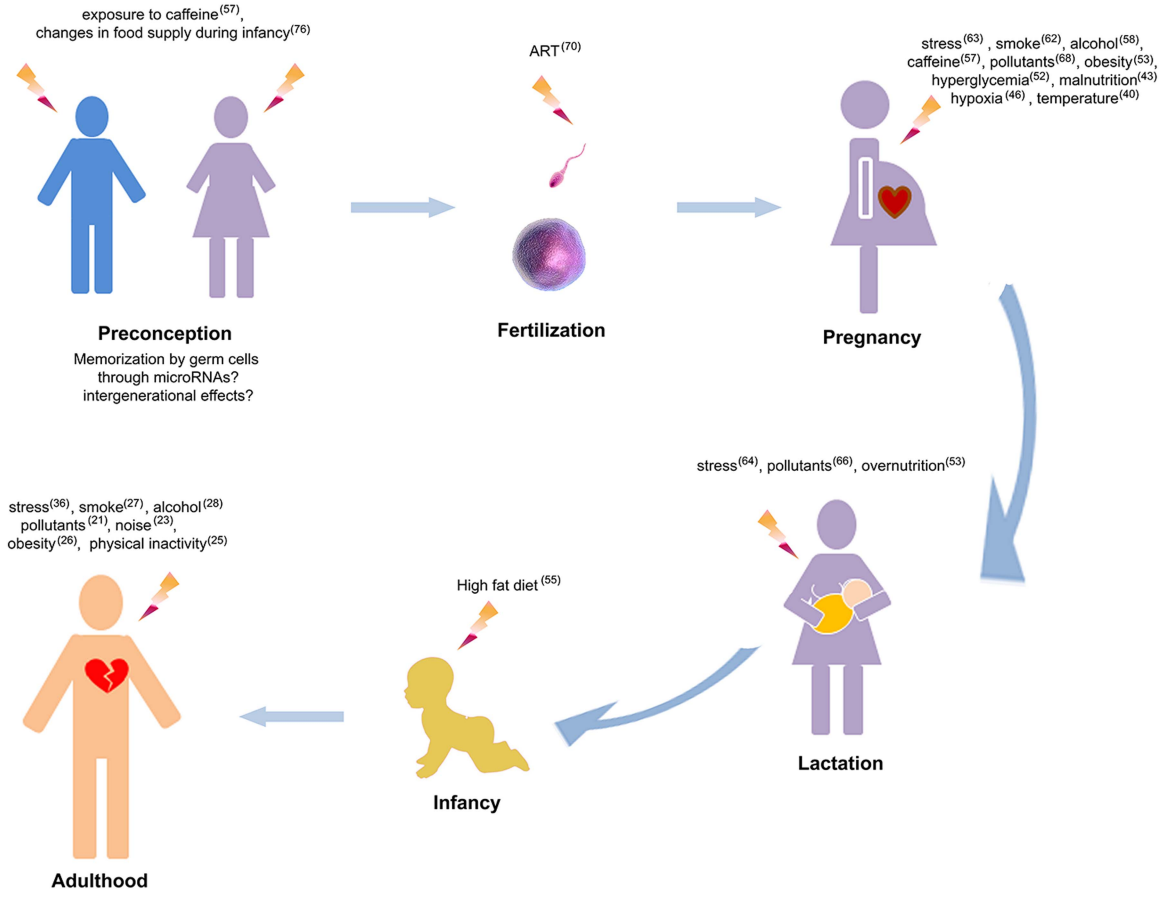

Fig. 1. Lifelong environmental challenges that alter heart functions. Numbers indicate the references of studies associating environmental challenges and cardiac alterations. ART, assisted reproductive technologies.

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addressed in a few studies which highlighted the impact levels according to the time of exposure. In the case of high-fat diet, adult cardiac alterations including increased heart rate were described when the exposure occurred after weaning.[55] Another study which compared *in utero* and post-weaning period of exposure to a high-fat high-sugar diet showed that exposure in the post-weaning period has a more profound effect on offspring weight gain and glucose tolerance than maternal overnutrition.[56] The analyses of metabolic alterations suggest that post-weaning period is critical in the altered programming of offspring health by nutrition. These data emphasize the importance of optimizing early life nutrition in offspring of both obese and lean mothers. However, the effects of those exposures were studied on rodent where postnatal period correspond developmentally to the late gestation period in human. The critical developmental window of exposure thus, remains to be investigated in human. In the case of caffeine, mice exposed *in utero* to an equivalent to two to four cups of coffee at an early embryonic stage, develop a greater risk of dilated cardiomyopathy in adulthood. When the exposure occurs at a later embryonic stage, that is to say when germ cells develop, inter-generational (in F2 and F3) hypertrophic cardiomyopathy is induced.[57] During this critical developmental period, the high sensitivity of the heart to toxicants is observed in the response to low doses of the toxicant. Indeed, some factors can have no impact at a determined dose level in adulthood whereas it can trigger profound effects when the exposure occurs early in life, such as alcohol. While in adulthood the effects of alcohol consumption on cardiac health depends on the dose, during pregnancy, even relatively low doses of alcohol consumed can be detrimental to long-term cardiac health in the offspring by inducing ventricular hypertrophy and fibrosis in adulthood.[58] Despite public health warnings, younger women continue to smoke during pregnancy.[59] Gestational exposure to nicotine induces higher risk of perinatal[60] and obstetric complications.[61] Fetal exposure to nicotine induces alteration in the cardiac conduction system with disrupted heart rate and electrical conduction[62] which has been suggested as an underlying mechanism for sudden death. A number of studies showed that fetal heart is sensitive to maternal stress.[63] Stress experienced postnatally, during maternal separation, increases risk of heart diseases in animals[64] (e.g. increased heart rate response) and humans[65] (e.g. increased risk of developing coronary heart disease) as observed in children born in Helsinki between 1934 and 1944 and who were separated from their parents. The developing cardiovascular system is a sensitive target of many environmental pollutants, including dioxins,[66,67] and a plasticizer, the Bisphenol A (BPA)[68] which induce long-term alterations in offspring heart such as hypertrophy. Furthermore, when associated with a second hit during life (like unbalanced diet), prenatal exposure to toxicant has been shown to produce a more pronounced phenotype in adulthood. For example, when coupled with postnatal overfeeding, BPA treatment produced a stronger phenotype with significant increase in inter-ventricular septal thickness indicating that BPA pre-treatment alters the trajectory of cardiac function differentially from overfeeding alone that may be adaptive *v.* maladaptive.[69]

Assisted reproductive technologies (ARTs) are widely used in infertility treatment. Emerging evidence indicates that ART is a risk factor for heart diseases in offspring.[70,71] Hypotheses attribute the effect of ART on cardiovascular health to embryo manipulation in suboptimal culture conditions or ART-related fetal insults, or other parental factors. For instance, the advanced parental age was suggested to be a risk factor of heart malformation in the offspring.[72,73] Strikingly, parental exposures not only influences cardiac health at an inter-generational level, but also at a trans-generational level.[74] While mother contribution is well described through the transmission of biomolecules (nutrients or hormones), environmental influences (temperature) or behavior (anxiety) to their offspring, the paternal contribution has been for a long time not considered and under debate. Recently, increasing evidence is pointing out the role of paternal contribution to offspring health.[75] For example, the Overkalix cohort study (in Sweden) showed that men who had experienced famine before puberty were less likely to have grandsons with cardiovascular disease than men who had plenty to eat.[76] In inter- and trans-generational transmission of acquired traits, epigenetic marks have been highlighted as underlying molecular bases. The discovery of epigenetic mechanisms including micro-RNAs[77] that induce specific phenotypes without change in DNA sequence improved our understanding of DOHaD field while for many years the early developmental period was considered to be controlled by the genetic program. Indeed, a single genome gives rise in development to over 100 different types of cells. The same genome is present in all of these cells but their functions are remarkably different. This is achieved through different epigenetic programming in each of these cell types. As such, the early epigenome adds powerful layers of diversity to the biologic predisposition generated by the genome.

Micro-RNAs in heart development and diseases

Heart development is orchestrated by epigenetic processes. The major epigenetic features include DNA methylation, post-translational histone modifications and non-coding RNAs, including small non-coding RNAs (e.g. piRNAs and micro-RNAs). In close interaction with DNA methylation and histone post-translational modifications, non-coding RNAs regulate gene expression. These mechanisms regulate the critical steps of heart development involving coordinated cellular proliferation, migration, differentiation and programmed cell death, structural remodeling,[78] and the control of metabolic homeostasis through the regulation of glucose and lipid metabolism, and insulin signaling.[79] Recent studies have revealed important roles for micro-RNAs in heart development[80] and disease[81–83] (Table 1).

Micro-RNA biogenesis and mode of action

While only 1–2% of the genome encode for proteins, the main part gives rise to non-coding RNAs (ncRNAs) including micro-RNAs. Micro-RNAs originate from sequences disseminated throughout the genome, from introns or intergenic regions. Mature micro-RNAs are small nucleotide sequences (19–24 nucleotides in length). Some micro-RNAs are involved in pathways that are conserved throughout phylogeny while micro-RNA diversity correlates with speciation. The number of micro-RNA and targets of micro-RNAs reveals morphological complexities observed in animals.[84] Importantly, given that ~60% of the human genes are under their control, micro-RNAs are master regulators at the post-transcriptional level[85] and play important roles in many biological processes, including development, differentiation, proliferation, apoptosis, metabolism and tissue remodeling.

Micro-RNA biogenesis is based on a series of steps that go from transcription of primary micro-RNAs (pri-micro-RNAs) to

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Table 1. Micro-RNAs associated to cardiac pathophysiology

	HF	ARRH	CAD	CHD	VALV	FIBRO	HYPER	MI	DIA	MC
Mir-1	164,165	166,167	168	112,169	170	171	172	173, 174	116	
Mir-7	165				175					
Let-7	176		177	178	170,179	180				
Mir-9		181				182	183		184	
Mir-10			185							
Mir-15								144		
Mir-16	176									
Mir-17	176		186		175					
Mir-17-92		187	188	189,190			187			
Mir-18b	191				175					
Mir-19	191	181,192	193				194	195	116,196	197
Mir-20										198
Mir-21	164,176	199	200		179,201	202	202	200	203	204,205
Mir-22	206					207	208			
Mir-23	176				209		210			
Mir-24	210					211	210	211		
Mir-25	212									
Mir-26		213			214,215	216	217	218		
Mir-27	176	219		220,221			222,223		116	
Mir-29	165,176			224	225	226	227		116	
Mir-30	176	228		229	170,214	230	231	232	116	
Mir-33	233					233				
Mir-34			234		225	235	235	236	116,237	
Mir-92	176		238,239	240						
Mir-93			241							205
Mir-98					242		222			243
Mir-99		244		245	225					
Mir-100	246									
Mir-101						247	248			
miR-103					242					
mir-106b-25		249								205
Mir-107	176									
Mir-122	176		250	221	251	252		253		
Mir-122-370			250							
Mir-124			234							
Mir-125b	165,176			254	170,255	256			116	
Mir-126	257		258		179			173,259		
Mir-128					170					
Mir-130	176				251	260				
Mir-132		261	193			261		262		
Mir-133	263	264	234	265	170,255	230	266	253	116	
Mir-134-3135b			234					267		
Mir-140	176		193,239							
Mir-141					268				269	
miR-142			193		170					
Mir-143			270				271			

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Table 1: (*Continued*)

Mir-144									272	
Mir-145		181,273	168,177				274	232		
Mir-146	275	181,276	277		225			278	116	205
Mir-148					279					280
Mir-149			281,282							
Mir-150		276	193				283	284	116	
Mir-152		181								
miR-154			186							
Mir-155	176		177			285	286		116	205,280
Mir-162		181								
Mir-181	165,176			287				288	196	
Mir-182			239							
Mir-185							289			
Mir-186			193							
Mir-188								290		
Mir-191								218		
miR-192		244								
Mir-193	291				225					
miR-194					225					
Mir-195	176,210			214	214		210	292	293	
Mir-196a				220						
Mir-197			294							
Mir-199	176,210		186				295	296	116,237	
Mir-200	297				225				298	
Mir-203					299					
Mir-204					300					
Mir-206		301	302			303	304		305	
Mir-208	139	306	277,307			308	306	292,309		310
Mir-210			193					311	116,237	
Mir-212		312						262	116	205
Mir-212-132							262			
Mir-214	165,210	244			215	313	210	314	116	
miR-216									237	
Mir-221			315				316	317	116	318
Mir-222		181	315	319						318
Mir-223			294						237	
miR-301					225					
miR-302					242					
Mir-320	176							320	116	
Mir-328		181,321				322	323	267		
MiR-329					242					
miR-339			186							
Mir-340			186							
Mir-342	165	244								
Mir-350							324			
Mir-361			200					200		
Mir-365								253		
Mir-370			307							

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Table 1: (*Continued*)

Mir-373							203		203	
Mir-374		181								
Mir-374b*					215					
Mir-375		276		224				325		
Mir-378	165						326		116	
Mir-379					327					
miR-380					242					
Mir-409		328								
Mir-421				221						
Mir-423	329				170				116	
Mir-424	176		282							
Mir-432		181,328								
Mir-433				319						
Mir-451	176		330		255		331			
Mir-454		181	186							
miR-455			332							
Mir-466					333					
Mir-483		334							335	
Mir-486					251,300			284		
miR-487					242					
miR-490					242					
Mir-493		181								
Mir-494					255			336		
Mir-499		337	277	220				253,338	116	310
Mir-500					299					
Mir-505					225,299					
Mir-511										205
miR-513					225					
miR-516					225					
Mir-519	297		200							
miR-520	297									
Mir-545			186							
Mir-574			339							
miR-575					225					
MiR-558	297									
miR-582					242					
Mir-584			340							
Mir-585			186							
Mir-590		341	330			341		296		
Mir-602										
miR-622	297									
miR-624			186							
miR-630					225					
Mir-634		181								
miR-636					225					
Mir-646					299					
miR-650									237	
Mir-663								232		

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Table 1: (*Continued*)

Mir-664		181								
miR-665										
Mir-718					225,251					
Mir-765			281,282							
Mir-873				342				343		
miR-874					242					
Mir-939					215,299					
miR-940				344						
Mir-1193					299					
miR-1201				221						
Mir-1233	291									
Mir-1273e					299					
Mir-1257			332							
miR-1275				221						
Mir-1291								232		
miR-1972					225					
Mir-2861								345		
miR-3138					225					
Mir-3174					299					
Mir-3613					333					
miR-3663					225					
Mir-4298					299					
Mir-4454					255					
Mir-4484					255					

HF, heart failure; ARRH, arrhythmia; CAD, coronary artery disease; CHD, congenital heart disease; VALV, valvular disease; FIBRO, fibrosis; HYPER, hypertrophy; MI, myocardial infarction; DIA, diabetic heart disease; MC, myocarditis.
Non-exhaustive list of micro-RNAs that have been described in animal and/or human models of cardiac diseases. Orange color squares indicate micro-RNAs that were reported in specific cardiac disease. The reference of the study highlighting the involvement of micro-RNA in specific cardiac disease is indicated in each orange square.

the biologically active, mature micro-RNAs (Fig. 2). First, DNA sequences are transcribed into pri-micro-RNAs mainly through the action of RNA polymerase II,[86] and to a less extent by RNA Polymerase III.[87] The transcribed pri-micro-RNAs are then cleaved by DROSHA and its cofactor DiGeorge critical region 8 (DGCR8) in the nucleus generating micro-RNA precursors about 60–70 nt called pre-micro-RNAs.[88] These pre-micro-RNAs shuttle into the cytoplasm by interacting with the nuclear pore complex Exportin-5.[89] Once in the cytoplasm, the hairpin structures, known as pre-micro-RNAs, undergo further processing by the DICER–TAR RNA-binding protein 2 (TRBP) complex to produce fully processed RNA duplexes (around 22 nucleotides in length) comprising the mature micro-RNAs and the micro-RNAs* (also known as passenger strands).[90] Each micro-RNA strand is incorporated into an RNA-induced silencing complex (RISC) comprising an Argonaute (AGO) protein that binds to the target mRNA and degrades the passenger strand.[91] The mature micro-RNA guides the RISC to target sequences located mainly in the 3'UTR of the target messenger RNA leading to an inhibition of its translation or to its degradation. In addition to their classical roles, micro-RNAs regulate gene expression through promoter targeting and translational activation.[92,93] Binding to the 5'UTR and to exon sequence have also been described.[94] Interestingly, the micro-RNA biogenesis machinery is regulated by hypoxia, hormonal and dietary changes.[95–97] More recently, extracellular, circulating micro-RNAs have been described as highly stable, and as potential blood-based biomarkers for diseases,[98] including heart diseases. We will focus this review on the involvement of micro-RNAs in heart health and disease and especially their involvement in heart disease programming.

Micro-RNAs regulate cardiac development and function

Advances in micro-RNA analysis such as next generation high depth sequencing techniques have highlighted their critical role in heart functions. As revealed by conditional knock out of Dicer in cardiac tissue, defects in micro-RNA biogenesis affect both embryonic development and postnatal cardiac maintenance and function.[99–102] One important role of micro-RNAs in heart development and function is linked to their ability to regulate the cardiac transcriptional pathways that maintain a restricted and specific pattern of gene expression.[103] Experimental studies on animals and analyses of human samples address specific roles of different micro-RNAs.

Several clinical and experimental studies have described the importance of dysregulation of micro-RNAs in the origin of cardiac disorders (Table 1), such as coronary artery disease,[104] cardiac fibrosis and hypertrophy.[105] Among them, a few micro-RNAs, including miR-1, miR-133, miR-208 and miR-499 which regulate cell proliferation, differentiation and apoptosis in cardiac tissue from the early developmental stages, have been described as

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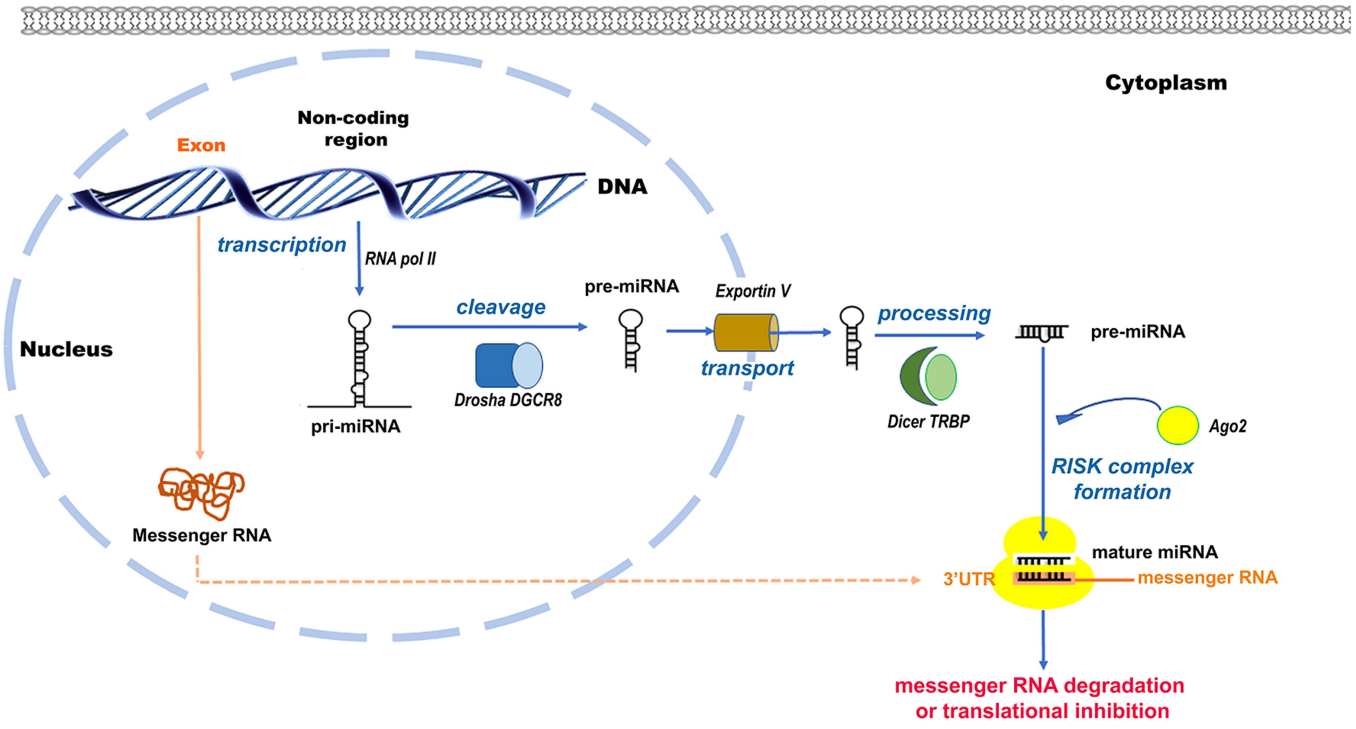

Fig. 2. Micro-RNAs biogenesis. Micro-RNAs biogenesis involves different steps. Pri-micro-RNAs are transcribed from inter- and intra-genic regions. They are then processed into pre-micro-RNAs and double-stranded micro-RNAs. The mature single-stranded micro-RNAs binds to the UTR ends of targets messenger RNAs (mRNAs) to regulate their levels.

key players in heart disease development. Their alterations have been reported in cardiac hypertrophy, myocardial infarction, cardiac arrhythmia and heart failure.[106] MiR-1, the first micro-RNA that has been implicated in heart development, exerts its action through the targeting of multiple pathways. For instance, miR-1 negatively regulates proliferation and mediates cell cycle withdrawal by targeting heart and neural crest derivatives expressed 2 (*HAND2*),[107] cell division cycle 42 (*CDC42*)[108] and the serine/threonine kinase *PIM-1*.[109] MiR-1 levels are also key player in cardiomyocyte differentiation and cell fate decision by down-regulating Notch ligand delta 1 (*DLL1*).[110] In addition, miR-1 regulates contractility of cardiomyocyte by controlling calcium homeostasis[111] and electrical conduction.[112] Indeed, it down-regulates Iroquois Homeobox 4 and 5, *IRX4* and *IRX5* which are involved in the regulation of the cardiac repolarisation gradient[113] and genes that are involved in gap junction and iron channel such as *GJA1*,[114] or the cardiac L-type calcium channel gene *CACNA1C* (*CAV1.2*).[115] MiR-1 has also displayed its important role in diabetic cardiac dysfunction. In a mouse model of streptozotocin-induced diabetes, miR-1 down-regulation may be involved in the development of cardiac hypertrophy.[116] qA study performed on diabetic patients' cohorts highlights the potential of serum miR-1 as a biomarker of myocardial steatosis.[117]

Furthermore, micro-RNAs have been highlighted as sensitive biomarkers of cardiac dysfunction and prognostic markers for diseases. Indeed, changes in their profile in diabetic individuals with normal ejection fraction are detected before clinical manifestations of heart diseases,[118,119] and are dynamic in response to therapeutic treatment (i.e. diabetic cardiac microangiopathy).[120] Just as gene polymorphism, micro-RNAs polymorphism can represent risk for heart diseases. For instance, meta-analyses performed on a total of 13 related studies involving 8120 patients and 8364 controls suggest that polymorphism in miR-146a (rs2910164), microR-196a2 (rs11614913) and miR-499 (rs3746444) are associated with coronary heart disease risk.[121]

Micro-RNAs at the origins of cardiac disorders induced by environment, lifestyle and diet

Deregulation of micro-RNAs profile has been suggested as a potential mechanism at the origin of heart diseases induced by environment and lifestyle.[122] In cardiac alterations induced by fetal hypoxia, a few micro-RNAs have been identified. Among these, miR-210 was highlighted at the origin of fetal rat cardiomyocytes death induced by hypoxia through the suppression of glucocorticoid receptor (*NR3C1*).[123] MiR-210 is regulated by the binding of hypoxia-inducible factor 1-alpha (HIF-1-α) to its promoter, and due to its consistent and powerful response to hypoxia, miR-210 is termed as the master micro-RNA regulating the cellular response to hypoxia.[124,125] Besides miR-210, other micro-RNAs such as miR-2285, miR-34, miR-192, miR-449, miR-200 families and miR-199a-214 cluster, have been associated with hypoxia, for example in high-altitude adaptation[126] or in pathological condition.[127] Changes in micro-RNA profile have been proposed as underlying mechanisms in the cardiac alterations driven by maternal exposure to dietary challenges, through the deregulation of cell death, growth and proliferation in the fetal heart.[128] In animals exposed to high-fat diet, a number of pathways altering cardiomyocyte metabolism have been described. For instance, mice exposed to high-fat diet exhibit cardiac lipotoxicity through the dysregulation of a major cellular sensor of energy availability, AMP-activated protein kinase (*AMPK*), and its upstream regulators, the calcium-binding protein 39 (*CAB39*) and the liver kinase B1 (*LKB1*).[129] MiR-451 has been shown to regulate this LKB1/AMPK pathway and cardiac lipotoxicity through the targeting of *CAB39*.[129] Similarly, dysregulated glycogen synthase

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kinase 3 (*GSK3B*) and glucose transporter 4 (*GLUT4*), involved in the insulin signaling pathway, have been associated with alterations in miR-29c, miR-21a-3p, miR-29c-3p, miR-144–3p and miR-195a-3p levels in the heart of animals exposed to high-fat diet.[130] Exposure to maternal hyperglycemia, induces cardiovascular dysfunctions in offspring. Evidence suggests that those dysfunction are due to altered levels of enhancer of zeste homolog 2 (EZH2) driven by miR-101 in fetal endothelial cells.[131] Interestingly, miR-101 and EZH2 have been highlighted in other models of fetal programming of adult diseases (e.g. infertility) driven by early exposure to endocrine disruptors.[132] Not only *in utero* exposure affects cardiac micro-RNAs in short term,[128] but also in long term.[133] As such, in mice, a maternal obesogenic diet during gestation and lactation induces miR-133a alteration in the offspring heart at 8 weeks of age associated with cardiac hypertrophy.[133] Furthermore, as highlighted by a recent study, the impact of *in utero* exposure to dietary challenges on long-term cardiac function depends on the timing of the exposure during development.[134] In this study, the comparison between prenatal exposure to maternal obesity and/or postnatal exposure to a Western diet on micro-RNA expression profiles showed that many more cardiac micro-RNA implicated in various cardiac pathologies[134] are altered in response to a relatively short period of postnatal overnutrition, rather than by a longer period of prenatal overnutrition.[134] Furthermore, cardiac micro-RNAs not only regulate functions, but also regulate metabolism at the body level. Indeed, miR-208 which cardiac levels are increased in high-fat diet mice, regulates the mediator complex subunit 13 (Med13) involved in the regulation energy balance in the heart.[135] Cardiac inhibition of miR-208 is sufficient to confer resistance to obesity in high-fat diet mice.[135] This observation highlights a novel role of cardiac micro-RNA, as a hormone-like controller on whole-body metabolism. In the effects driven by *in utero* exposure to environmental toxicants (such as BPA) on cardiac remodeling, a study performed in monkeys highlighted the involvement of miR-205 and miR-224.[68] The cellular pathways involved have been more detailed in a model of cardiomyocyte cell line exposed to a persistent organic pollutant, the polychlorinated biphenyls (PCBs). As revealed in this *in vitro* model, the deregulation of micro-RNAs involved in cardiomyocyte differentiation is a potential underlying mechanism in PCB driven cardiac dysfunction.[136]

Micro-RNAs, a target for the reversal of heart disease programming?

Given their key function in gene regulation, micro-RNAs provide promising therapeutic targets.[137] Advances in micro-RNA chemistry and delivery technologies allowed the development of powerful tools for *in vivo* regulation of micro-RNAs.[138] In the treatment of post-myocardial infarction, cardiac remodeling and dysfunction, hypertrophy, heart failure, atherosclerosis and myocarditis,[139,140] animal models of *in vivo* delivery of micro-RNA mimics or anti-miRs show the potential of micro-RNA based therapy. For instance, the inhibition of micro-RNAs (miR-128,[141] miR-92a,[142] miR-26a,[143] miR-15[144] or miR-34[145] families) involved in cardiomyocyte cell death induced by myocardial ischemia reduces infarct size after ischemia-reperfusion and augments the recovery of heart function. Pharmacological inhibition of miR-140 which is involved in mitochondrial fission reduces infarct size after acute myocardial infarction in mice.[146] Inhibition of miR-21[147] or miR-25[148] prevents heart failure development in mice by restoring cardiac function, reducing fibrosis and normalizing cardiomyocyte cell size. Conversely, micro-RNAs such as miR-210[149] which protects cardiomyocytes and vasculature, when injected intra intramyocardially, reduce cell death and improve cardiac function and angiogenesis after acute myocardial infarction.[150] Research into the role of micro-RNAs in heart disease holds great promise for future therapeutic applications. However, many questions on their delivery and duration of action in human remain. Thus, modification in lifestyle and diet remains the first choice in the micro-RNAs modulation. Interestingly, exercise training improves cardiac autonomic control, cardiac function and arrhythmogenesis in rats with preserved ejection fraction heart failure.[151] Recently, physical exercise has been shown to modulate cardiac micro-RNAs which are possibly involved in exercise mediate cardioprotection. Modification in these micro-RNAs levels driven by exercise can be detected in the blood, representing potential biomarkers of cardiorespiratory fitness.[152] Apoptosis-related micro-RNAs and their downstream proteins in heart can be influenced by swimming training.[153] Circulating micro-RNA levels (miR-1, miR-133 and miR-206) are elevated with marathon running[154] and with moderate exercise in pathological conditions like myocardial infarction (miR-1 and miR-214) which are associated with the normalization of Ca^{2+} handling and left ventricular compliance in infarcted hearts.[155]

Recent evidence showed that hydrogen sulfide (H_2S) has the potential to protect the heart against diseases.[156,157] H_2S is a gaseous mediator along with nitric oxide and carbon monoxide, and is produced endogenously from cysteine metabolism in mammalian tissues. Low plasma levels of H_2S have been described in type 2 diabetic patients,[158] in high-fat diet treated mice[159] and streptozotocin-treated rats.[158] Recent evidence showed that H_2S has the potential to protect the heart against diseases.[156,157] Exogenous H_2S treatment mitigates cardiomyopathy induced by diabetes and protects the heart from I/R injury. Interestingly, H_2S has been demonstrated to regulate micro-RNAs[160] in cardiomyocyte cell lines. The preconditioning of myocardial I/R with H_2S decreases miR-1-mediated apoptosis.[161] However, in the context of early programming of heart diseases, little is known about the potential of micro-RNAs in the reversal of the pathology. In a rat model of adult cardiac hypertrophy induced by maternal undernutrition, specific cardiac micro-RNA profiles are exhibited and are associated with genes involved in inflammation and cardiovascular development. When the offspring is treated with growth hormone, the cardiac hypertrophy is reversed,[162] accompanied by an up-regulation of cardiac let-7 highlighting the potential of let-7 micro-RNA family in the reversal of cardiac pathophysiology induced by maternal undernutrition. Interestingly, recent study showed that short caloric restriction in adulthood can restore cardiac function in mice that were exposed postnatally to overnutrition.[163] However, the role of micro-RNAs in the reversal of cardiac alteration programming by nutritional approach remains to be investigated.

Future perspective

How environmental challenges during early life can alter and shape offspring cardiac functions through alterations in micro-RNAs is an intense area of research. However, several questions still need to be elucidated. While evidence exists for the influence of early life insults on micro-RNAs and pathophysiology in adipose tissue, brain, liver and pancreas, evidence for the existence of a causative link between environmental challenges,

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nutritional constraints, or lifestyle challenges, and micro-RNAs and developmental programming of cardiovascular diseases is still limited. Furthermore, the sensitive developmental windows of exposure and the role of micro-RNAs in gender differences need to be clarified for the different types of challenges. Finally, the targeting of micro-RNAs through nutritional, exercise or pharmacological approaches would provide valuable information that would allow better advice for early prevention, and promote appropriate changes to maximize later life health benefits.

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Conflicts of Interest. None.

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