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Review

miR-1: A comprehensive review of its role in normal development and diverse disorders

Amin Safa [a], Zahra Bahroudi [b], Hamed Shoorei [c], Jamal Majidpoor [d], Atefe Abak [e], Mohammad Taheri [f,*], Soudeh Ghafouri-Fard [g,*]

[a] Institute of Research and Development, Duy Tan University, Da Nang, 550000, Viet Nam
[b] Department of Anatomical Sciences, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Department of Anatomical Sciences, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran
[d] Department of Anatomy, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[e] Department of Medical Genetic, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[f] Urogenital Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[g] Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciecnes, Tehran, Iran

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ABSTRACT

MicroRNA-1 (miR-1) is a conserved miRNA with high expression in the muscle tissues. In humans, two discrete genes, *MIRN1-1* and *MIRN1-2* residing on a genomic region on 18q11.2 produce a single mature miRNA which has 21 nucleotides. miR-1 has a regulatory role on a number of genes including heat shock protein 60 (HSP60), Kruppel-like factor 4 (KLF4) and Heart And Neural Crest Derivatives Expressed 2 (HAND2). miR-1 has critical roles in the physiological processes in the smooth and skeletal muscles as well as other tissues, thus being involved in the pathogenesis of a wide range of disorders. Moreover, dysregulation of miR-1 has been noted in diverse types of cancers including gastric, colorectal, breast, prostate and lung cancer. In the current review, we provide the summary of the data regarding the role of this miRNA in the normal development and the pathogenic processes.

1. Introduction

MicroRNA-1 (miR-1) is a conserved miRNA with high expression in the muscle tissues particularly the heart muscle and is involved in the development of this tissue [1,2]. Being encoded by a genomic region on 18q11.2, the miR-1 subfamily comprises 2 discrete genes, *MIRN1-1* and *MIRN1-2* which code for the same mature miRNA which has 21 nucleotides [3]. It has a regulatory role on a number of genes such as heat shock protein 60 (HSP60) and Kruppel-like factor 4 (KLF4) at the post transcriptional level [4,5]. Moreover, Heart And Neural Crest Derivatives Expressed 2 (HAND2), a transcription factor (TF) that stimulates ventricular cardiomyocyte development, has been identified to be targeted by miR-1 [3]. Meanwhile, miR-1 has been shown to be targeted by a number of muscle differentiation regulators, such as serum response factor, MyoD and MEF2 [3]. Investigations in animal models have revealed that miR-1 enhances myogenesis through modulating histone deacetylase-4, a suppressor of muscle gene expression [6]. In addition to its critical roles in the physiological processes in the smooth and skeletal muscles, it regulates several functions in other tissues, thus being involved in the pathogenesis of a wide range of disorders. In the current review, we summarize the data regarding the role of this miRNA in the normal development and the pathogenic processes.

2. miR-1 in normal development

Numerous studies have reported the role of miR-1 in developmental processes. Consistent with its role in the development of heart tissue, Trhriz et al. have reported over-expression of miR-1 in the course of cardiac differentiation of embryonic stem cells in mice. Cdk9 has been shown to mediate up-regulation of miR-1 to induce myoblast apoptosis [7]. Moreover, Dai et al. have shown the role of this miRNA the proliferative ability and differentiation of skeletal muscle satellite cells. This miRNA has been shown to target the 3′UTR of Pax7 and HDAC4. This miRNA promotes bovine skeletal muscle satellite cell myogenic differentiation inhibiting expression of these genes [8]. A significant portion of predicted miR-1 targets have been enriched in RNA metabolism. The

* Corresponding authors.
E-mail addresses: mohammad_823@yahoo.com (M. Taheri), S.ghafourifard@sbmu.ac.ir (S. Ghafouri-Fard).

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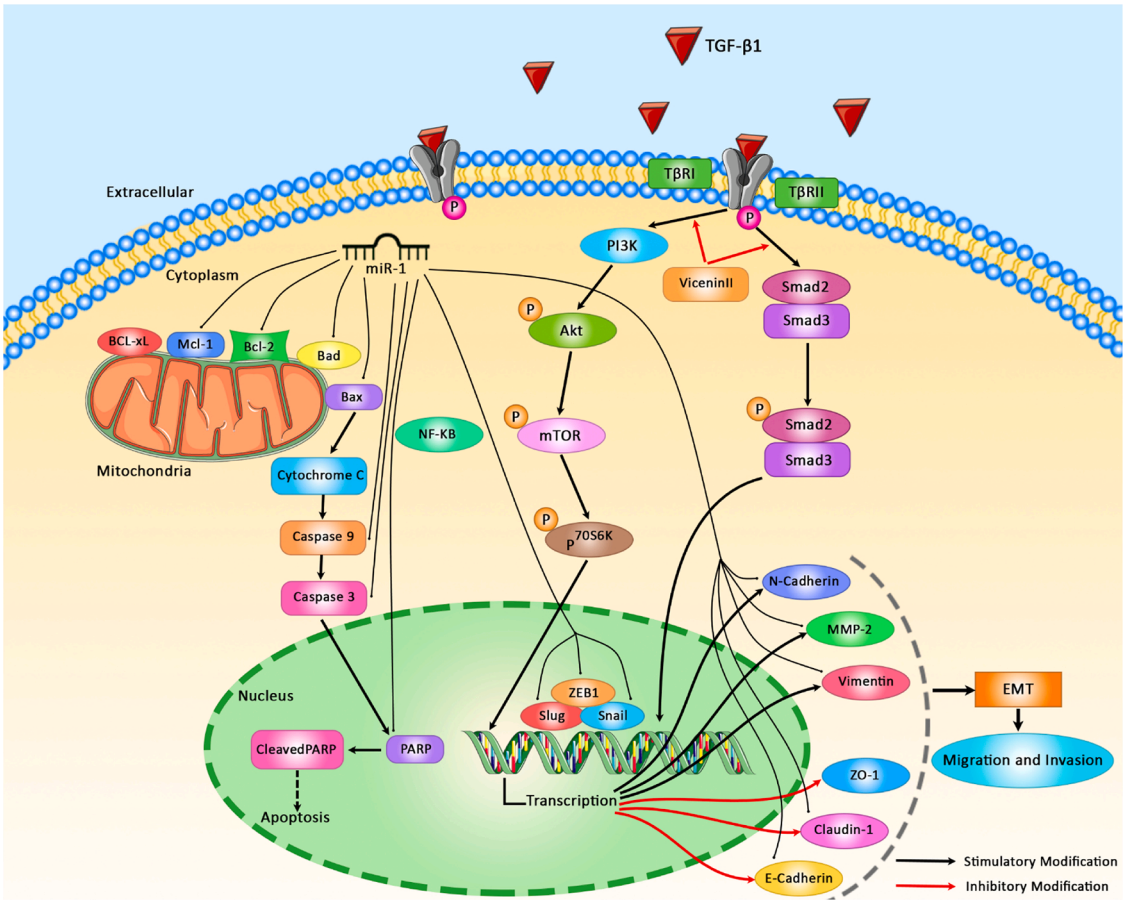

Fig. 1. Schematic illustration of the impact of miR-1 on PI3K/AKT/mTOR/NFκB Pathway.

splicing factor Srsf9 has been recognized as another target of miR-1 during myogenesis [9]. Nakamura et al. have used a microarray-based technique to assess miRNA expression during tooth development. They demonstrated a distinctive signature for miR-1 in the developing tooth. Expression of this miRNA in the tooth germ has been increased until embryonic day 16.5, then being reduced progressively on postnatal days 1 and 3. This miRNA has been shown to be present at the cervical ring of the dental epithelium. Connexin (Cx) 43 has been identified as a target of miR-1. Reduction of miR-1 level has decreased proliferation rate of cells but accelerated the rate of ATP release. Collectively, their investigations showed that miR-1 modulates expression of Cx43 to influence cell proliferation rate in the course of dental epithelial cell

Table 1
Summary of the results of studies that assess the functional roles of miR-1 during development of different tissues.

Samples	Cell Lines	Target	Pathway	Function	Ref
GEO database	SF2	CX43	–	Expression of miR-1 was increased in the course of tooth development. miR-1 by modulating Cx43 could modulate cell proliferation during dental epithelial cell differentiation.	[10]
–	C2C12, AB1 ES	Cdk9, P53, P21, MyoD, Srf, Mef2	–	Cdk9 by modulation of miR-1 and myogenic transcription factors could regulate differentiation and apoptosis of myoblast cells.	[7]
Skeletal muscle satellite cells	–	Pax7, HDAC4, MHC	–	miR-1 via inhibiting the Pax7/HDAC4 axis could have a role in the proliferation and differentiation of skeletal muscle satellite cells.	[8]
Mouse	C2C12	Srsf9	–	miR-1 by targeting Srsf9 could promote C2C12 differentiation.	[9]
–	NSCs	Hes1, Nestin, Cyclin-D1, β-tubulin-III, GFAP	UCA1	UCA1/miR-1 axis by targeting Hes1 could regulate neural stem cell differentiation.	[16]
Goat	–	HDAC4	–	miR-1 by inhibiting HDAC4 in skeletal muscle satellite cells could promote muscle development.	[17]
–	NHAs	CCL2, GFAP, S100β, IL-6, TNF-α, Vimentin	H19	H19/miR-1-3p/CCL2 axis might participate in modulating NHA activation and proliferation.	[18]
–	293 T, H1299, NB4, C2C7, NIH3T3,	Zfp281, ZNF281	–	miR-1 by targeting the ZNF281/Zfp281 axis could be involved in counteracting muscle differentiation.	[19]
–	BMSCs	TLR1, Runx2, OPN	–	Down-regulation of miR-1 by regulating the Runx2/OPN axis and inhibiting TLR1 could promote osteogenic restoration of bone marrow mesenchymal stem cells.	[11]
Duck	–	THBS1, Bcl-2, FAS	aplacirc_013267	Aplacirc_013267 by sponging apla-miR-1-13 and regulating THBS1 could promote the apoptosis of follicular granulosa cells.	[20]
Bactrocera dorsalis	–	Bdtra, TRA	–	During the embryonic developmental stages, miR-1-3p by suppressing Bdtra expression could induce male sex determination.	[15]

Table 2
Summary of studies which reported up-regulation of miR-1 in human/animal disorders.

Type of Disease	Samples	Cell Lines	Target	Pathway	Function	Ref
Myocardial Infarction (MI)	Mouse	NMVCs	CX43, Kir2.1	–	Metformin (200 mg/kg/d for 4 weeks) by regulating miR-1 could ameliorate cardiac conduction delay in mice.	[21]
Acute Myocardial Infarction (AMI)	AMI (n = 44), normal controls (n = 18)	–	–	–	Changes in miR-1 levels in plasma could be used as diagnostic/prognostic indicators of adverse ventricular remodeling.	[25]
Viral Myocarditis	Mouse	HL-1	Cx43	–	Astragalus root dry extract via regulating the miR-1/Cx43 axis could present strong cardioprotective effects on viral myocarditis.	[26]
Myocardial Steatosis	Mouse/human; serum samples from uncomplicated type 2 diabetes (n = 78) and normal control (n = 12)	HL-1	–	–	Serum miR-1 could be used as a reflection of myocardial steatosis in uncomplicated type 2 diabetes.	[27]
Multiple Sclerosis (MS)	MS (n = 36), healthy controls (n = 33)	Th17, Th1, Th2, Treg	ETS1, RORC, CSF2, AHR, IL-10, MAF, CXCL3, CSF2, IL-23R	–	Overexpression miR-1-3p by targeting ETS1 could affect the differentiating process of Th17 in MS patients.	[22]
Sepsis	Mouse	HL-1, Cardiomyocytes	Caspase-3, caspase-9, Cytochrome-3, HSPA-4, MMP, ROS, NF-kB	RMRP	The lncRNA RMRP through the miR-1-5p/HSP70 route could prevent mitochondrial dysfunction and cardiomyocyte apoptosis in LPS-induced sepsis mice.	[23]
Pulmonary Arterial Hypertension (PAH)	Rat	–	KCNA5	–	miR-1 by targeting KCNA5 could reduce the activity and expression of Kv channels and also induce pulmonary artery smooth muscle cell hypertrophy.	[28]
PAH	–	PASMCs	SOD1, GJA1, CAV2, KLF4	–	miR-1 by regulating endothelial genes could induce endothelial dysfunction in rat pulmonary arteries.	[29]
ST-Segment Myocardial Infarction (STEMI)	Non-left ventricular (LV) remodeling (n = 58), LV remodeling (n = 22)	–	–	–	miR-1 is increased in the remodeling group. Therefore, miR-1 could be involved as a predictive factor of LV remodeling post- STEMI.	[30]
Polymyositis/ Dermatomyositis associated with Interstitial Lung Disease (PM/DM-ILD)	PM/DM (n = 22), healthy controls (HC) (n = 30), systemic lupus erythematosus (n = 11)	–	–	–	Increased miR-1 level in serum could be used as a marker for observing disease activity and forecasting treatment response in PM/DM.	[31]
Acute Chest Pain (ACP)	AMI (n = 174), non-AMI (n = 176), non-ACP (n = 100)	–	–	–	The increased concentration of miR-1 in the AMI and non-AMI group relative to the non-APC group could be used as a diagnostic and prognostic method.	[32]
Non-Alcoholic Fatty Liver Disease (NAFLD)	Mouse	Huh7, 293 T, THP-1, HUVECs	NF-kB, KLF4	–	Hepatocyte-derived extracellular vesicles via the miR-1/KLF4/NF-kB pathway could promote endothelial inflammation and facilitate atherogenesis.	[18]
Cerebral Palsy (CP)	Rat	N2A	BDNF, Caspase-3	MALAT1, PI3K/Akt	Vitamin B1 and B12 by increasing BDNF via the MALAT1/miR-1 axis could contribute to alleviating neuron apoptosis and nerve damage in CP.	[24]

differentiation [10]. Down-regulation of miR-1 expression in bone marrow mesenchymal stem cells (BMSCs) has led to attenuation of their proliferation, suppression of Caspase 3 activity, and over-expression of osteogenic genes Runx2 and OPN expression while down-regulation of TLR1 expression. TLR1 has been identified as a target of miR-1. miR-1 silencing in BMSCs of fractured rats has enhanced bone density and ALP activity and increased expressions of type I collagen and BMP-2, indicating the role of miR-1 silencing in enhancement of osteogenic differentiation and bone healing [11]. This miRNA is also involved in mediation of the effects of a certain circular RNA (circRNA) on granulosa cells. The circRNA aplacirc_13267 enhances apoptosis of duck granulosa cell through the apla-miR-1-13/THBS1 axis [12]. In addition, miR-1 participate in the regulation of the autophagy process via modulation of a number of conserved Rab GTPase-activating proteins [13]. Notably, IFNB-mediated regulation of Mir1 and its effects on the reduction of TBC1D15, a RAB GTPase-activating protein possibly contributes in the pathogenesis of Parkinson's disease [14]. Finally, Peng et al. have shown the role of miR-1-3p in male sex determination in an Oriental fruit fly. This miRNA inhibits expression of Bdtra, a necessary factor in female sex determination [15]. Fig. 1 shows the influence of miR-1 on PI3K/AKT/mTOR/NFκB Pathway.

Table 1 shows the outcomes of studies that assess the functional roles of miR-1 during development of different tissues.

3. Up-regulation of miR-1 in disorders

Consistent with diverse roles of miR-1, expression of this miRNA has been dysregulated in various disorders. Lv et al. have shown up-regulation of miR-1 in H_2O_2 exposed cardiomyocytes and in mice model of myocardial infarction (MI). This up-regulation was accompanied by down-regulation of the potassium channel 2.1 (Kir2.1) and CX43, prolongation of the PR and QT intervals, delay in action potential period and decrease in conduction pace. Notably, metformin could amend these effects through suppressing miR-1 expression [21]. Li et al. have assessed levels of miR-1-3p in peripheral blood mononuclear cells, cerebrospinal fluid and different population of T cells obtained from healthy subjects and multiple sclerosis (MS) patients. They reported up-regulation of this miRNA in MS patients during relapse phase in

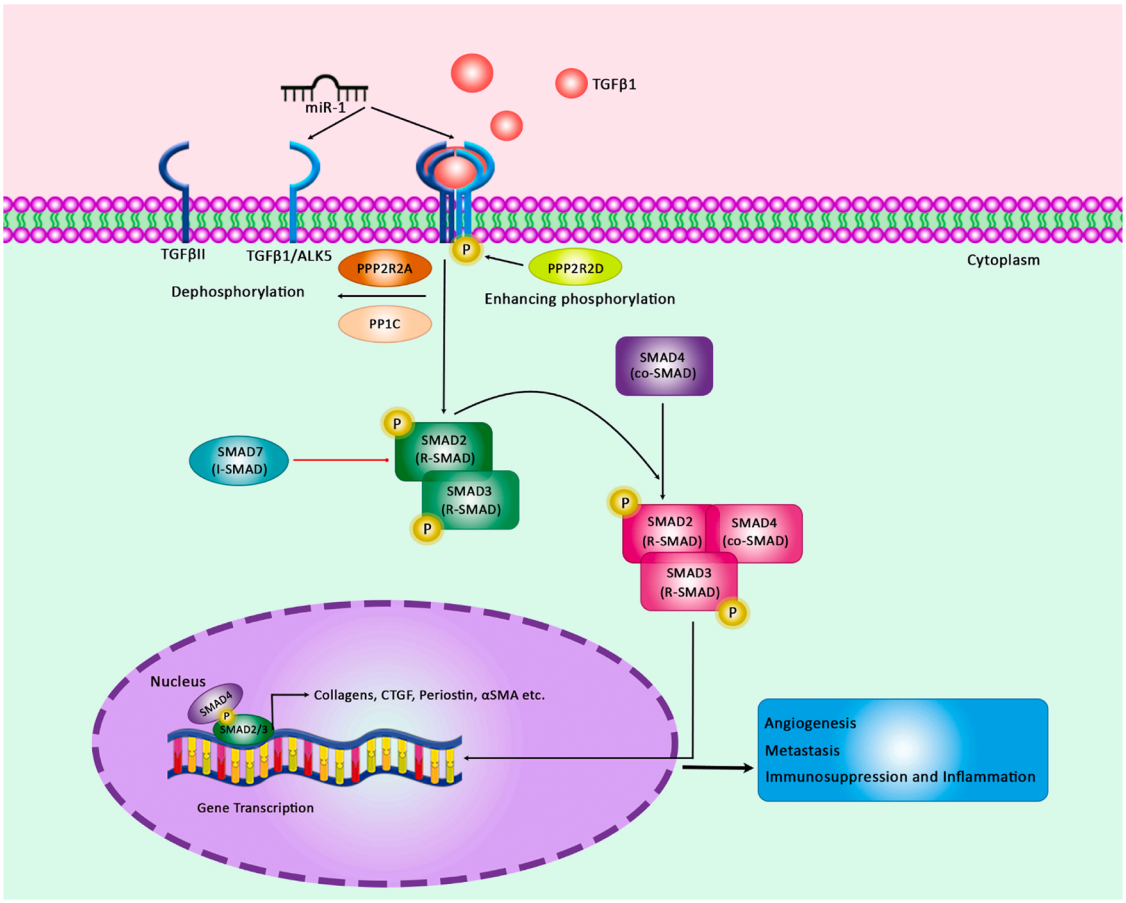

Fig. 2. Schematic illustration of modulation of the TGF-β1 signaling pathway by miR-1. This miRNA targets TGF-βR1/ALK5 and inhibits the TGF-β signaling pathway, thus participating in cardiac hypertrophy.

correlation with MS severity. Up-regulation of this miRNA in naïve CD4+T cells enhanced differentiation of Th17 cells. miR-1-3p regulates differentiation Th17 cells through modulating expression of ETS1 [22]. Han et al. have shown the role of miR-1-5p in attenuation of the protective effect of HSPA4 against lipopolysaccharide-associated mitochondrial injury and apoptosis. The lncRNA RMRP axis has been shown to serve as a sponge for miR-1-5p. RMRP suppresses lipopolysaccharide-induced apoptosis of cardiomyocytes and mitochondrial injury through inhibiting the impact of miR-1-5p on HSPA4 [23]. Jiang et al. have confirmed the role of this miRNA in liver steatosis. They observed that steatotic hepatocyte secrete miR-1-containing extracellular vesicles that enhance endothelial inflammation and induce atherogenesis through inhibition of KLF4 and induction of NF-κB [18]. Deprivation/reoxygenation reduces MALAT1 and BDNF levels and enhance the miR-1 levels. These effects have been ameliorated by vitamin B1 and B12 administration. These vitamins decreased miR-1 expression through MALAT1, enhanced BDNF levels and induced PI3K/Akt pathway via the MALAT1/miR-1 axis, therefore precluding neuron apoptosis and modifying nerve damage in cerebral palsy rats [24]. Table 2 shows the outcomes of experiments which reported up-regulation of miR-1 in human/animal disorders.

4. Down-regulation of miR-1 in disorders

Contrary to studies which reported up-regulation of miR-1 in acute myocardial infarction (AMI) [21,25], Pinchi et al. have confirmed down-regulation of this miRNA in postmortem hearth samples of AMI patients compared with sudden cardiac death and controls [33]. Wu et al. have judged the effects of Wenxin Granules on prevention of fatal arrhythmia by modulating gap junctions and miR-1 after MI in a rat model constructed by coronary artery ligation. Wenxin Granules preserved the configuration of the gap junctions and their fundamental Cx43 levels by modulating miR-1 [34]. miR-1 has a vital role in the maintenance of cardiac rhythms [35] and its suppression may cause cardiac hypertrophy and arrhythmia [36]. Fig. 2 displays involvement of miR-1 in cardiac hypertrophy.

Up-regulation of this miRNA prohibited T3 -associated cardiomyocyte hypertrophy and decreased HADC4 expression in cardiomyocytes. Expression of this miRNA has also been decreased in cardiac tissues of hyperthyroid animals [37]. miR-1 has also been down-regulated in persons with symptomatic heart failure in association with the severity of this condition. Expression level of this miRNA has been suggested as a biomarker for predicting heart failure exacerbation [38]. Besides, miR-1-3p has been shown to decrease expression SFRP1, thus enhancing bone formation and mass and counteracting with the pathogenesis of osteoporosis [39]. Expression of miR-1 has also been decreased after sciatic nerve damage, leading to over-expression of BDNF, and enhancement of proliferation and migration of Schwann cells. This finding might facilitate design of novel therapeutic modalities for management of peripheral nerve injury [40]. Table 3 reviews the results of studies which reported down-regulation of miR-1 in human/animal disorders.

5. miR-1 expression in cancers

The bulk of evidence points to the tumor suppressor role of this miRNA. Peng et al. have reported decreased levels of miR-1 in breast cancer cells. Over-expression of this miRNA has blocked cell

Table 3
Outlines of studies which reported down-regulation of miR-1 in human/animal disorders.

Type of Disease	Samples	Cell Lines	Target	Pathway	Function	Ref
Myocardial Infarction (MI)	Rat	–	PKC, CX43, Cx45, 44/42 MAPK, ELK-1, SRF	–	Wenxin Granules (WXKL) by regulating miR-1 and PKC can preserve the configuration of gap junctions and their constituent Cx43.	[34]
Acute Myocardial Infarction (AMI)	Serum samples from normal controls (n = 18), AMI (n = 19), Sudden Cardiac Death (n = 25)	–	CD15, IL-15, CX43, MCP-1, tryptase, troponin-C, troponin-I	–	A low level of miR-1 in serum specimens of AMI patients could be used as a marker for diagnosing sudden cardiac death from AMI.	[33]
Cardiomyocyte Hypertrophy	Rat	NRCMs	ANP, BNP, α-actin, HDAC4	–	Overexpression of miR-1 by reducing HDCA4 could inhibit T3-induced hypertrophy in cardiomyocytes.	[37]
Cardiomyocyte Hypertrophy	Rat	NRVCs	CDK6, ANF, B-MHC	CDKs-Rb	miR-1 via down-regulating CDK6 and inactivating the Rb pathway could inhibit hypertrophic phenotype in cardiomyocytes.	[41]
Symptomatic Heart Failure (SHF) with Left Ventricular Hypertrophy (LVH)	SHF (n = 59) and normal controls (n = 17)	–	–	–	miR-1 and galectin-3 level in SHF patients with LVH could be associated with anatomic alterations of the left ventricle.	[42]
SHF	Blood sample from SHF (n = 61)	–	NT-proBNP	–	Down-regulation of miR-1 could be used as a biomarker for predicting HF exacerbation.	[38]
Acute HF with Asymptomatic Type 2 Diabetic (DM)	Serum samples from normal controls (n = 45), DM + coronary artery disease (CAD) (n = 45), HF + DM (n = 45), DM (n = 45)	–	NT-proBNP, Galectin-3	–	miR-1 could be useful in predicting the onset of HF in asymptomatic T2DM patients.	[43]
Osteoporosis (OS)	Mouse/human; OS (n = 29), non-OS (n = 20)	mBMSCs	SFRP1, ALP, RUNX2, TRAP, PPARγ	MAPK, Wnt, TGF-β/BMP	miR-1-3p by targeting SFRP1 could regulate the differentiation of mesenchymal stem cells to prevent OS.	[39]
Bone and Joint Diseases	Ossification of the posterior longitudinal ligament (OPLL, = 52), non-OPLL (n = 16)	–	CX43, COL I, OCN, ALP, RUNX2, NF-kBp65, OCN, IL6, TNFα, BMP2	MALAT1	MALAT1/miR-1 axis by targeting CX43 could mediate OPLL.	[44]
Osteoarthritis (OST)	Mouse/human; 20 pairs of OST and neighboring normal tissues	–	Ihh	–	miR-1 by down-regulating Ihh expression could protect the articular cartilage from osteoarthritis-induced degeneration.	[18]
Viral Myocarditis (VMC)	Mouse	–	Bax, Bcl-2, Caspase-9, Kcnd2, Irx5, Kcnj2, Kir2.1	–	miR-1 by modulating the expressions of apoptosis-associated genes could ameliorate cardiac function and reduce cardiomyocyte apoptosis in VMC mice.	[45]
Pulmonary Arterial Hypertension (PAH)	Rat	LHCN-M2	TGF-βR1, ALK-5	TGF-β	miR-1 via targeting TGF-βR1 and reducing TGF-β signaling could be involved in the cardiac hypertrophy.	[46]
Keloid	Keloid tissues (n = 11), normal skin (n = 8)	HKFs, HSFs	TM4SF1, Fibronectin	AKT/ERK	miR-1-3p by targeting TM4SF1 via regulating AKT/ERK signaling could inhibit proliferation and migration in keloid.	[47]
Atrial Fibrillation (AF)	Post-operative AF (POAF = 24) and non-OAF (n = 24)	–	–	–	A reduction of the miR-1 level in the AF could participate in the development of POAF.	[48]
Peripheral Nerve Injury	Rat	SC	BDNF	–	miR-1 by targeting BDNF could regulate Schwann cell proliferation and migration after peripheral nerve damage.	[40]
Hypoxia-induced Neuronal Injury	–	Neuro-2a	HSP-70, Bax, Cyt C, MMP, Caspase-3	–	miR-1 by targeting HSP-70 could have a role in hypoxia-induced apoptotic injury to neuro-2a cells via the intrinsic apoptotic pathway.	[49]

proliferation, migration and invasion and stimulated cell apoptosis. The tumor suppressor effects of this miRNA have been exerted through targeting Bcl-2. Notably, such inhibitory effects on tumor volume and weight have been verified in nude mice. Moreover, up-regulation of miR-1 has increased the toxic effects of paclitaxel and cisplatin on breast cancer cells [50]. Although miR-1 has been shown to be decreased in gastric cancer samples by independent investigations [51–53], Liu et al. have shown its up-regulation in serum specimens of patients with this kind of malignancy [54]. Loss of miR-1 has resulted in the over-expression of PD-L1 in sorafenib-resistant hepatoma cells. Mechanistically, miR-1 has been shown to target PD-L1. Down-regulation of miR-1 in these cells has been attributed to over-expression of Nuclear factor E2-related factor 2 (NRF-2) [55]. Mutant ACTB mRNA 3′-UTR has been shown to be over-expressed in hepatocellular carcinoma (HCC) samples. This mutation facilitates its interaction with miR-1 and miR-29a and destruction of these miRNAs via AGO2, enhancing HCC cells migration and invasion by increasing expression of miR-1 target gene MET and miR-29a target gene MCL1 [56]. Wu et al. have reported down-regulation of miR-1 in colorectal cancer tissues and cell lines compared with neighboring non-cancerous tissues. Up-regulation of this miRNA has resulted in suppression of colony endurance and proliferation, and induction of apoptosis upon irradiation. This miRNA increases Bax and E-cadherin levels and down-regulates Bcl-2, MMP2 and MMP9 expressions. Moreover, miR-1 has improved the sensitivity of cancer cells to radiotherapy [57]. In breast cancer cells, diverse studies have demonstrated various routes for contribution of miR-1 in the carcinogenic process. For instance, miR-1 has been shown to defeat proliferation of cancer stem cells through modulation of EVI-1 [58]. In addition, miR-1 can inhibit evolution of triple-negative breast cancer through inhibition of Slug expression [59]. Finally, miR-1 modulates apoptotic processes, then sensitizing breast cancer cells to paclitaxel and cisplatin [50]. Besides, the role of some lncRNAs such as RMRP and MALAT1 in the pathogenesis of cancer is mediated through sponging miR-1 [60,61]. This miRNA has direct or indirect interactions with several cancer-related molecules such as VEGF, MET, c fos, c jun, BCL 2, Bax and Bcl-2, thereby influencing cancer course via different mechanisms.

Table 4
Summary of studies which reported down-regulation of miR-1 in cancers (ANT: adjacent normal tissue).

Type of Cancer	Samples	Cell Lines	Target	Pathway	Function	Ref
Gastric Cancer (GC)	–	GES-1, HGC-27, SGC-7901, MGC-803, MKN-28	MMP-7, VEGF, Sorcin, E-cadherin, N-cadherin	–	Overexpression of miR-1 by targeting the MMP-7/VEGF axis could inhibit the mobility and migration of GC cells.	[51]
GC	90 pairs of GC and ANTs	GES-1, SGC7901, MKN28, AGS, NCIN87, BGC823, HGC27	VEGFA, EDN1, MET	–	miR-1 by suppressing the expression of VEGF-A and EDN1 could inhibit proliferation, migration, and tube formation of endothelial cells.	[52]
GC	48 pairs of GC and ANTs	AGS, SGC-7901	MET, Survivin	–	miR-1 by targeting MET could inhibit GC cell proliferation and migration.	[53]
GC	–	SGC7901/ADM, SGC7901/VCR, SGC7901	Sorcin, c-fos, c-jun, BCL-2, Bax, Bcl-2, MDR1/P-gp, MRP-1	–	miR-1 by inhibiting sorcin via promoting the accumulation of intracellular drugs and apoptosis of cells could reverse multidrug resistance in GC cells.	[62]
GC	62 pairs of GC and ANTs	GES-1, AGS, MGC803	STC2	–	miR-1-3p by down-regulating STC2 could inhibit the progression of GC.	[63]
Gastric Intestinal Metaplasia (IM)	Mouse	GES-1, AGS, MKN45, AZ521, HCT-116	HDAC6, HNF4α, CDX2, MUC2, KLF4	–	miR-1 by mediating HDAC6/HNF4α loop could promote bile acids (BA)-induced gastric IM.	[64]
Medulloblastoma (MDB)	Mouse/human; MDB (N = 10), normal cerebellar samples (n = 5)	Daoy, D283 med, D341	YY1, E-cadherin, Vimentin, Fibronectin, α-SMA	HOTAIR	HOTAIR by sponging miR-1 and targeting YY1 could promote MDB growth, migration, and invasion.	[65]
Liver cancer	Mouse	Hep3B, HepG2, HepG2-SR, Hep3B-SR	PD-L1, P-gp, MRP1	NRF-2	NRF-2/miR-1 axis by up-regulating PD-L1 could promote tumorigenic properties and enhance drug resistance in sorafenib-resistant hepatoma.	[55]
Breast Cancer (BCa)	Mouse/human; 47 pairs of BCa and ANTs	MCF-7, ZR-7530	Bcl-2, Bip, E-Cadherin, Claudin-1, Bax, Bad, Mcl-1, ZEB-1, PARP, Caspase-7, Caspase-9	ERK1/2, AKT	Overexpression of miR-1 by targeting apoptotic pathways could increase the sensitivity of BCa cells to paclitaxel and cisplatin.	[50]
BCa	Mouse/human; 21 pairs of BCa and adjacent normal tissue	MDA-MB-231	EVI-1, E-cadherin, N-cadherin	–	miR-1 by down-regulating EVI-1 expression could inhibit BCSCs proliferation and promote apoptosis.	[58]
BCa	Mouse/human; 139 pairs of BCa and adjacent normal tissue	MCF-10A, MDA-MB-231, Hs578 T, MDA-MB-468	Slug, AgO2	MALAT1	MALAT1 via the miR-1/slug axis could promote triple-negative breast cancer development.	[59]
BCa	–	HBL-100, MCF-7, MDA-MB-231, MDA-MB-435S	MALAT1, CDc-42, Vimentin, E-cadherin, MMP-9,	–	MALAT1 by competitively binding miR-1 with cdc42 could induce migration and invasion of human breast cancer cells.	[66]
Colorectal Cancer (CRC)	53 pairs of CRC and ANTs	FHC, HCT116, CCL244, SW480, HT29, Lovo	Bax, Bcl-2, E-cadherin, MMP2, MMP9	–	Up-regulation of miR-1 by inducing cell apoptosis and the synergic inhibition of aggressive phenotypes could enhance the radiosensitivity of CRC cells.	[57]
CRC	GEO database	–	–	–	miR-1-3p via multiple biological approaches could suppress CRC progression.	[67]
CRC	111 pairs of CRC and adjacent normal tissue	HMrSV5, HCT-116, CL-187, ClonA1, HT-29, SW-620	VEGF, VEGFR-2	–	miR-1 by targeting VEGF could inhibit the progression of colon cancer.	[68]
CRC	28 pairs of CRC and ANTs	–	–	–	Downregulation of miR-1 expression could as a biomarker for CRC.	[69]
CRC	Mouse	HCT-116, SW480, SW620, HT-29, CaCO2, HEK293	HIF-1, Smad3, HK2, MCT4	–	miR-1 via the Smad3/HIF-1 axis could regulate glucose metabolism and controlling tumorigenesis in CRC.	[70]
CRC	Mouse/human; 75 pairs of CRC and adjacent normal tissue	LDL-1, WiDr, SW480, COLO21	P62, LC3I, LC3II, PTBP1, PKM2, PKM1	–	PTBP1-associated miR-1 could induce growth inhibition through autophagy and overturn the Warburg effect in colorectal tumors.	[71]
Prostate cancer (PCa)	20 pairs of PCa and ANTs	RWPE-1, C4-2, 22Rv1, LNCaP, PC3, 293 T	CDK4	PCA3	LncRNA PCA3 via the miR-1/CDK4 axis could regulate glycolysis, viability, and apoptosis in PCa.	[72]
PCa	20 pairs of PCa and ANTs	PC3, LNCap, DU145, RWPE-1, C4-2	KRAS, caspase-3, BAX, bcl-2, PARP	MALAT1	MALAT1 by up-regulating miR-1 and downregulating KRAS could suppress PCa.	[73]
PCa	TCGA database	–	PAICS, CDH1, TWIST1, ZWINT, KIAA0101, SRC, AR	–	miR-1 could aid the clinical diagnosis of PCa.	[74]
PCa	PCa recurrent group (n = 27); non-recurrent (n = 51)	–	–	–	Down-regulation of miR-1 could function as an important independent predicative factor for PCa recurrence.	[75]
PCa	Mouse/human; 32 pairs of PCa and ANTs	DU145, PC3, LNCap, 22Rv1, RasB1	TWIST1	EGFR	EGFR/miR-1 axis by activating TWIST1 could promote PCa bone metastasis.	[76]
PCa		22RV1, LNcaP		–		[77]

(*continued on next page*)

Table 4 (*continued*)

Type of Cancer	Samples	Cell Lines	Target	Pathway	Function	Ref
	Mouse/human; 124 pairs of PCa and ANTs		E2F5, PFTK1, CDK2, CDK4		miR-1-3p by repressing E2F5 and PFTK1 could modulate prostate cancer cell aggressiveness.	
PCa	–	RWPE2, PC-3, DU-145, 22RV1, LNCaP	CORO1C, E-cadherin, N-cadherin, Vimentin, Slug Snail	MALAT1	Knockdown of MALAT1 by sponging miR-1-3p could inhibit migration, invasion, and EMT in prostate cancer cells.	[78]
Esophageal Squamous Cell Carcinoma (ESCC)	Mouse/human; 8 pairs of ESCC and ANTs	TE1, TE13, EC9706, ECA109, KYSE140, KYSE150, KYSE450, Het-1A	Fibronectin-1	Wnt, TGF-β, MAPK, p53	Downregulation of miR-1 could suppress cell proliferation and migration and promotes ESCC cell apoptosis.	[79]
ESCC	74 pairs of ESCC and ANTs	TE-1	PIK3CA, Akt, surviving	Akt	miR-1 by suppressing the PI3K3A/Akt/survivin axis could enhance sensitivity to gefitinib and also inhibit tumorigenicity of ESCC.	[80]
Non-small-cell lung carcinoma (NSCLC)	38 pairs of NSCLC and ANTs	A549, Calu1, H1299, H460, BEAS-2B	ANXA2, CDK4, CDK6, CCND1	RMRP	RMRP/miR-1-3p axis by upregulating ANXA2 expression could promote cell proliferation and invasion in NSCLC.	[60]
NSCLC	Plasma samples from NSCLC (n = 47) and normal group (n = 41)	–	–	–	The decrease of miR-1 expression in blood samples could help distinguish NSCLC patients from healthy subjects.	[81]
NSCLC	Bronchoalveolar lavage cell (BAL) and sputum from NSCLC (n = 30) and cancer-free group (n = 30)	–	–	–	The decrease of miR-1 could be used for early detection of NSCLC.	[82]
Lung Cancer	–	A549, 95D	SDF-1, CXCR4, Bcl-xL, NF-kB	–	Regulation of miR-1 on SDF-1 biogenesis in cancer-associated fibroblasts could increase tumor progression, metastasis, and resistance to therapy via paracrine.	[83]
Bladder Cancer (BLC)	48 pairs of BLC and ANTs	EJ, J82, T24, UM-UC-3, SV-HUC-1	Glutaminase	–	miR-1-3p by targeting the glutaminase could inhibit the proliferation, migration, and invasion of BLC cells.	[84]
BLC	BLC (n = 18), normal samples (n = 6)	5637, T24, UM-UC-3	CCL2	–	miR-1-3p by targeting CCL2 could suppress proliferation and invasion of BLC cells.	[85]
BLC	34 pairs of BCL and ANTs	SV-HUC-1, 5637, T24, J82, UM-UC-3	SFRP1	–	miR-1-3p by targeting SFRP1 could suppress the proliferation, invasion, and migration of BCL cells.	[86]
BLC	Bladder transitional cell carcinoma (TCC) (n = 43); normal bladder transitional cell (NBTC) (n = 36)	TCC J82, T24, SV-HUC-1, HEK293 T	HuR, E-Cadherin, vimentin, caspase-3, PARP, Bcl-2, Bax,	HOTAIR	miR-1 via HuR/HOTAIR axis could inhibit cell proliferation, migration, invasion, and promoted cell apoptosis in BCL.	[87]
Osteosarcoma (OS)	Dog	–	MET, MCL-1	–	The decrease of miR-1 expression associated with higher MET expression could be used as a biomarker for canine OS treatment.	[88]
OS	34 pairs of OS and adjacent normal tissues	SAOS-2, U2OS, NHOst	VEGFA	–	miR-1 by targeting VEGFA could inhibit cell growth, migration, and invasion in OS Cells.	[89]
OS	Mouse/human; OS (n = 41), normal bone tissue (n = 12)	MG-63, U-2OS	c-MET	–	EGCG via regulating miR-1/c-MET interaction could suppress OS cell growth.	[90]
OS	Mouse	MG63, Saos2, G292, hFOB1.19	PAX3, p21, p53, p73	–	miR-1 could induce arrest in the G0/G1 phase and suppress cell proliferation in OS.	[91]
Oral Squamous Cell Carcinomas (OSCC)	OSCC (n = 381), normal tissue (n = 35)	SAS, GNM, Fadu, HSC3, SCC4, OECM-1, Ca9-22, OC3, NHOK	Slug, E-cadherin	–	miR-1 by targeting the Slug could enhance tumorigenicity and invasiveness in OSCC.	[92]
Head & Neck Squamous Cell Carcinoma (HNSCC)	22 pairs of HNSCC and adjacent normal epithelial	FaDu, SAS, HSC3	EGFR, c-MET, AKT, Erk1/2	MAPK	Down-regulation of miR-1by targeting EGFR and c-MET could enhance cancer cell aggressiveness in HNSCC.	[93]
Pancreatic Ductal Adenocarcinoma (PDAC)	43 pairs of PDAC and ANTs	–	–	–	Abnormal alterations of miR-1 in PDAC could determine the prognosis of patients with PDAC by noninvasive methods.	[94]
GC and BCa	Mouse	MGC-803, MKN45, MKN74, AGS, GES-1, HGC-27, A375, CCC-ESF, MCF-7	CDK4, TWF1, WASF2, CNN3, CORO1C, TMSB4X	–	miR-1 by down-regulating target genes expression could inhibit tumor growth and metastasis of breast and gastric cancers.	[95]
Mesothelioma	–	CRL-2081, CRL-5820, CRL-5826, CRL-5915, CRL-5946,	PIM-1	–	miR-1 by down-regulation of PIM1could partake in cell proliferation, invasion, and migration in mesothelioma.	[96]

(*continued on next page*)

Table 4 (*continued*)

Type of Cancer	Samples	Cell Lines	Target	Pathway	Function	Ref
Cervical Cancer (CC)	Mouse/Human;57 pairs of CC and adjacent normal tissues	ACC-Meso-1, ACC-Meso-4, NPL HPV-C33A, HPV18+Hela, HPV16+Siha	G6PD	–	miR-1 by targeting G6PD could suppress the development and progression of high-risk papilloma virus associated infected cervical cancer.	[97]
Nasopharyngeal Carcinoma (NPC)	NPC (n = 26), non-NPC (n = 18)	5−8 F, CNE-2, HONE-1, SUNE-1, NPE	Slug, Bcl-2, Caspase-3	MALAT1	MALAT1 by modulating miR-1/slug axis could regulate radioresistance in NPC.	[61]
Clear Cell Renal Cell Carcinoma (Ccrcc)	41 pairs of ccRCC and ANTs	HK-2, ACHN, 786-o, SN12PM6, CAKI-1, OS-RC-2	CDK4, CDK6, Caprin1, Slug, β-Tubulin, N-cadherin, Vimentin, E-cadherin, Rb	–	The decrease of miR-1 expression could inhibit ccRCC cell proliferation and interferes with cell cycle regulation and metastasis.	[98]
Renal Cell Cancer (RCC)	Mouse/human; 58 pairs of RCC and ANTs	HK-2, OS-RC-2, CAKI-1, 769-P, ACHN, A498, 786-O	Fibronectin-1, E-cadherin, Slug	–	Overexpression of miR-1-3p by reducing fibronectin-1 could inhibit EMT in RCC.	[99]
Thyroid Cancer (TC)	26 pairs of TC and adjacent normal tissues	Nthy-ori 3-1, TPC-1, FTC-133, B-CPAP, SW579	CCND2	HOTAIR	HOTAIR via miR-1/CCND2 axis could promote the development and progression of TC.	[100]
–	Mouse	MDA-MB-435, MCF-7, MNSCs BCNSCs	LRPPRC, MINOS1, GPD2	–	Overexpression of miR-1 by targeting the MINOS1/GPD2 axis could mediate mitochondria damage in cancer stem cells.	[101]

Table 4 provides a summary of the results of researches which gauged the tumor suppressor role of miR-1.

6. Discussion

Numerous lines of evidence have shown the important roles of miRNAs in the developmental processes. These transcripts can regulate expression of several targets at the post-transcriptional phase. Accordingly, they are involved in the pathogenesis of diverse human disorders. miR-1 has a particular situation in this regard. While initial studies indicated its specific expression in muscle tissues, additional investigations demonstrated its widespread expression in different tissues including dental epithelial cells and hepatocytes. The diverse function of miRNAs in the physiological and pathological events can be explained by its diverse targets. This miRNA has been shown to target several genes including HSP60, KLF4, HAND2, Srsf9, Pax7, HDAC4 and TLR1. Notably, the seed sequence of miR-1 is the same as another miRNA, namely miR-206 [8], indicating similar targets for these miRNAs. Most notably, miR-1 has functional interactions with some long non-coding RNAs (lncRNAs) namely HOTAIR, MALAT1, UCA1 and H19, more emphasizing on consideration of the functional networks between different kinds of transcripts. Construction of TF/miR-1/lncRNA networks using the available high throughput data would facilitate identification of the role of this miRNA in diverse pathological and physiological processes. It is worth mentioning that such functional networks might have tissue-specific roles.

miR-1 has been regarded as a tumor suppressor gene in various tissues. Such effects have been exerted through modulation of a number of oncogenes such as Bcl-2. In addition to its roles in suppression of cancer, its levels have been shown to foresee the occurrence of some side effects of anti-cancer drugs. For instance, doxorubicin-induced cardiotoxicity can be predicted by assessment of circulating levels of miR-1 [102]. Levels of this miRNA can also be used as diagnostic/prognostic biomarkers for a range of disorders including cancer [54], and adverse outcomes of MI [25]. Moreover, miR-1 expression in heart tissue had the appropriate accuracy in differentiation of patients with AMI from sudden cardiac death [33].

miR-1 can be regarded as a target for manipulation of inflammatory processes. This miRNA has a prominent role in inhibition of KLF4 and induction of NF-κB [18]. NF-κB has been shown to activate expression of several pro-inflammatory proteins such as cytokines and chemokines, thus contributing in the control of inflammasome. Moreover, this nuclear factor regulates survival, function and differentiation of several immune cells. Therefore, NF-κB is involved in the pathogenesis of numerous inflammatory conditions [103]. Since dysregulation of miR-1 can partake in the pathogenesis of inflammatory conditions, this miRNA might serve as a therapeutic targets in these disorders. In addition, Klf4 up-regulation is involved in the activation of epithelial cytokines and consequent development of esophageal squamous cell carcinoma in animal models [104]. Thus, miR-1-mediated regulation of KLF4 might be important in the carcinogenic processes as well. Another layer of regulatory role of miR-1 on NF-κB in the context of cancer has been represented by the effects of this miRNA on the expression of SDF-1 and SDF-1-mediated enhancement of cancer cell proliferation and chemoresistance through involvement of NF-κB [83].

Modulation of expression of this miRNA might be regarded as a therapeutic option in some disorders. For instance, intravenous injection of antagomiR-1 following middle cerebral artery occlusion has been shown to ameliorate neurological impairment and decrease infarction size, brain edema, and blood-brain barrier permeability [105]. Moreover, metformin has been shown to amend cardiac conduction defect through modulation of expression of miR-1 [21]. Besides, Astragalus Root dry extract has been demonstrated to inhibit arrhythmia and preserve CVB3-induced Cx43 expression by influencing expression of miR-1 [26].

Taken together, miR-1 has diverse roles in the developmental processes and is involved in the development of diverse disorders particularly MI and cancer. In addition, it has been considered as a potential marker and therapeutic target in these conditions. Further in vivo investigation of miR-1-targetted therapeutic modalities would facilitate translation of this wealth of basic science data into clinical application.

Declaration of Competing Interest

The authors report no declarations of interest.

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References

[1] Y. Mishima, C. Stahlhut, A.J. Giraldez, miR-1-2 gets to the heart of the matter, Cell 129 (2) (2007) 247–249.

[2] Y. Zhao, J.F. Ransom, A. Li, V. Vedantham, M. von Drehle, A.N. Muth, T. Tsuchihashi, M.T. McManus, R.J. Schwartz, D. Srivastava, Dysregulation of cardiogenesis, cardiac conduction, and cell cycle in mice lacking miRNA-1-2, Cell 129 (2) (2007) 303–317.

[3] Y. Zhao, E. Samal, D. Srivastava, Serum response factor regulates a muscle-specific microRNA that targets Hand2 during cardiogenesis, Nature 436 (7048) (2005) 214–220.

[4] Z.X. Shan, Q.X. Lin, C.Y. Deng, J.N. Zhu, L.P. Mai, J.L. Liu, Y.H. Fu, X.Y. Liu, Y. X. Li, Y.Y. Zhang, S.G. Lin, X.Y. Yu, miR-1/miR-206 regulate Hsp60 expression contributing to glucose-mediated apoptosis in cardiomyocytes, FEBS Lett. 584 (16) (2010) 3592–3600.

[5] C. Xie, H. Huang, X. Sun, Y. Guo, M. Hamblin, R.P. Ritchie, M.T. Garcia-Barrio, J. Zhang, Y.E. Chen, MicroRNA-1 regulates smooth muscle cell differentiation by repressing Kruppel-like factor 4, Stem Cells Dev. 20 (2) (2011) 205–210.

[6] J.F. Chen, E.M. Mandel, J.M. Thomson, Q. Wu, T.E. Callis, S.M. Hammond, F. L. Conlon, D.Z. Wang, The role of microRNA-1 and microRNA-133 in skeletal muscle proliferation and differentiation, Nat. Genet. 38 (2) (2006) 228–233.

[7] V. Tarhriz, K.D. Wagner, Z. Masoumi, O. Molavi, M.S. Hejazi, H. Ghanbarian, CDK9 regulates apoptosis of myoblast cells by modulation of microRNA-1 expression, J. Cell. Biochem. 119 (1) (2018) 547–554.

[8] Y. Dai, Y.M. Wang, W.R. Zhang, X.F. Liu, X. Li, X.B. Ding, H. Guo, The role of microRNA-1 and microRNA-206 in the proliferation and differentiation of bovine skeletal muscle satellite cells, In Vitro Cell. Dev. Biol.-Anim. 52 (1) (2016) 27–34.

[9] K.K. Bjorkman, M. Buvoli, E.K. Pugach, M.M. Polmear, L.A. Leinwand, miR-1/206 downregulates splicing factor Srsf9 to promote C2C12 differentiation, Skeletal Muscle 9 (1) (2019) 1–12.

[10] T. Nakamura, T. Iwamoto, H.M. Nakamura, Y. Shindo, K. Saito, A. Yamada, Y. Yamada, S. Fukumoto, T. Nakamura, Regulation of miR-1-mediated connexin 43 expression and cell proliferation in dental epithelial cells, Front. Cell Dev. Biol. 8 (2020) 156.

[11] J. Wang, X. Zhao, X. Wang, M. Liu, W. Wan, Low expression of miR-1 promotes osteogenic repair of bone marrow mesenchymal stem cells by targeting TLR1, Eur. Rev. Med. Pharmacol. Sci. 24 (7) (2020) 3492–3500.

[12] Y. Wu, H. Xiao, J. Pi, H. Zhang, A. Pan, Y. Pu, Z. Liang, J. Shen, J. Du, The circular RNA aplacirc_13267 upregulates duck granulosa cell apoptosis by the apla-miR-1-13/THBS1 signaling pathway, J. Cell. Physiol. 235 (7-8) (2020) 5750–5763.

[13] C. Nehammer, P. Ejlerskov, S. Gopal, A. Handley, L. Ng, P. Moreira, H. Lee, S. Issazadeh-Navikas, D.C. Rubinsztein, R. Pocock, Interferon-β-induced miR-1 alleviates toxic protein accumulation by controlling autophagy, eLife 8 (2019).

[14] P. Ejlerskov, D.C. Rubinsztein, R. Pocock, IFNB/interferon-β regulates autophagy via a MIR1-TBC1D15-RAB7 pathway, Autophagy 16 (4) (2020) 767–769.

[15] W. Peng, S. Yu, A.M. Handler, Z. Tu, G. Saccone, Z. Xi, H. Zhang, miRNA-1-3p is an early embryonic male sex-determining factor in the Oriental fruit fly Bactrocera dorsalis, Nat. Commun. 11 (1) (2020) 1–11.

[16] J. Zheng, D. Yi, Y. Liu, M. Wang, Y. Zhu, H. Shi, Long nonding RNA UCA1 regulates neural stem cell differentiation by controlling miR-1/Hes1 expression, Am. J. Transl. Res. 9 (8) (2017) 3696.

[17] M. Sui, Q. Zheng, H. Wu, L. Zhu, Y. Ling, L. Wang, F. Fang, Y. Liu, Z. Zhang, M. Chu, The expression and regulation of miR-1 in goat skeletal muscle and satellite cell during muscle growth and development, Anim. Biotechnol. (2019) 1–8.

[18] F. Jiang, Q. Chen, W. Wang, Y. Ling, Y. Yan, P. Xia, Hepatocyte-derived extracellular vesicles promote endothelial inflammation and atherogenesis via microRNA-1, J. Hepatol. 72 (1) (2020) 156–166.

[19] S. Nicolai, M. Pieraccioli, A. Smirnov, C. Pitolli, L. Anemona, A. Mauriello, E. Candi, M. Annicchiarico-Petruzzelli, Y. Shi, Y. Wang, ZNF281/Zfp281 is a target of miR-1 and counteracts muscle differentiation, Molecular Oncol. 14 (2) (2020) 294–308.

[20] W. Wu, Y. Zhao, E. Gao, Y. Li, X. Guo, T. Zhao, W. He, H. Zhang, LncRNA DLEU2 accelerates the tumorigenesis and invasion of non–small cell lung cancer by sponging miR-30a-5p, J. Cell. Mol. Med. 24 (1) (2020) 441–450.

[21] L. Lv, N. Zheng, L. Zhang, R. Li, Y. Li, R. Yang, C. Li, R. Fang, A. Shabanova, X. Li, Metformin ameliorates cardiac conduction delay by regulating microRNA-1 in mice, Eur. J. Pharmacol. (2020), 173131.

[22] J. Shengnan, X. Dafei, J. Hua, F. Sunfu, W. Xiaowei, X. Liang, Long non-coding RNA HOTAIR as a competitive endogenous RNA to sponge miR-206 to promote colorectal cancer progression by activating CCL2, J. Cancer 11 (15) (2020) 4431.

[23] Y. Han, Y. Cai, X. Lai, Z. Wang, S. Wei, K. Tan, M. Xu, H. Xie, lncRNA RMRP prevents mitochondrial dysfunction and cardiomyocyte apoptosis via the miR-1-5p/hsp70 axis in LPS-induced sepsis mice, Inflammation (2020) 1–14.

[24] E.-Y. Li, P.-J. Zhao, J. Jian, B.-Q. Yin, Z.-Y. Sun, C.-X. Xu, Y.-C. Tang, H. Wu, Vitamin B1 and B12 mitigates neuron apoptosis in cerebral palsy by augmenting BDNF expression through MALAT1/miR-1 axis, Cell Cycle 18 (21) (2019) 2849–2859.

[25] U. Grabmaier, S. Clauss, L. Gross, I. Klier, W. Franz, G. Steinbeck, R. Wakili, H. Theiss, C. Brenner, Diagnostic and prognostic value of miR-1 and miR-29b on adverse ventricular remodeling after acute myocardial infarction–the SITAGRAMI-miR analysis, Int. J. Cardiol. 244 (2017) 30–36.

[26] Y. Wang, J. Li, L. Xuan, Y. Liu, H. Ge, J. Gu, C. Wei, M. Zhao, Astragalus root dry extract restores connexin43 expression by targeting miR-1 in viral myocarditis, Phytomedicine 46 (2018) 32–38.

[27] D. de Gonzalo-Calvo, R. Van Der Meer, L. Rijzewijk, J. Smit, E. Revuelta-López, L. Nasarre, J. Escola-Gil, H. Lamb, V. Llorente-Cortes, Serum microRNA-1 and microRNA-133a levels reflect myocardial steatosis in uncomplicated type 2 diabetes, Sci. Rep. 7 (1) (2017) 1–14.

[28] G. Mondejar-Parreño, M. Callejo, B. Barreira, D. Morales-Cano, S. Esquivel-Ruiz, L. Moreno, A. Cogolludo, F. Perez-Vizcaino, miR-1 is increased in pulmonary hypertension and downregulates Kv1. 5 channels in rat pulmonary arteries, J. Physiol. 597 (4) (2019) 1185–1197.

[29] G. Mondejar-Parreño, M. Callejo, B. Barreira, D. Morales-Cano, S. Esquivel-Ruiz, M. Filice, L. Moreno, A. Cogolludo, F. Perez-Vizcaino, miR-1 induces endothelial dysfunction in rat pulmonary arteries, J. Physiol. Biochem. 75 (4) (2019) 519–529.

[30] Q. Ma, Y. Ma, X. Wang, S. Li, T. Yu, W. Duan, J. Wu, Z. Wen, Y. Jiao, Z. Sun, Circulating miR-1 as a potential predictor of left ventricular remodeling following acute ST-segment myocardial infarction using cardiac magnetic resonance, Quant. Imaging Med. Surg. 10 (7) (2020) 1490.

[31] Y. Sugiyama, R. Yoshimi, M. Takeno, Y. Kunishita, D. Kishimoto, R. Kamiyama, Y. Kirino, S. Ohno, H. Nakajima, miR-1 is a novel biomarker for polymyositis/dermatomyositis-associated interstitial lung disease, Mod. Rheumatol. (2019) 1–6.

[32] T. Su, X. Shao, X. Zhang, Z. Han, C. Yang, X. Li, Circulating microRNA-1 in the diagnosis and predicting prognosis of patients with chest pain: a prospective cohort study, BMC Cardiovasc. Disord. 19 (1) (2019) 5.

[33] E. Pinchi, P. Frati, M. Aromatario, L. Cipolloni, M. Fabbri, R. La Russa, A. Maiese, M. Neri, A. Santurro, M. Scopetti, miR-1, miR-499 and miR-208 are sensitive markers to diagnose sudden death due to early acute myocardial infarction, J. Cell. Mol. Med. 23 (9) (2019) 6005–6016.

[34] A. Wu, M. Zhao, L. Lou, J. Zhai, D. Zhang, H. Zhu, Y. Gao, H. Shang, L. Chai, Effect of wenxin granules on gap junction and miR-1 in rats with myocardial infarction, Biomed Res. Int. 2017 (2017).

[35] Y. Zhao, J.F. Ransom, A. Li, V. Vedantham, M. von Drehle, A.N. Muth, T. Tsuchihashi, M.T. McManus, R.J. Schwartz, D. Srivastava, Dysregulation of cardiogenesis, cardiac conduction, and cell cycle in mice lacking miRNA-1-2, Cell 129 (2) (2007) 303–317.

[36] M. Wu, D. Wu, C. Wang, Z. Guo, B. Li, Z. Zuo, Hexabromocyclododecane exposure induces cardiac hypertrophy and arrhythmia by inhibiting miR-1 expression via up-regulation of the homeobox gene Nkx2. 5, J. Hazard. Mater. 302 (2016) 304–313.

[37] G.P. Diniz, C.A. Lino, C.R. Moreno, N. Senger, M.L.M. Barreto-Chaves, MicroRNA-1 overexpression blunts cardiomyocyte hypertrophy elicited by thyroid hormone, J. Cell. Physiol. 232 (12) (2017) 3360–3368.

[38] G. Sygitowicz, M. Tomaniak, O. Błaszczyk, Ł. Kołtowski, K.J. Filipiak, D. Sitkiewicz, Circulating microribonucleic acids miR-1, miR-21 and miR-208a in patients with symptomatic heart failure: preliminary results, Arch. Cardiovasc. Dis. 108 (12) (2015) 634–642.

[39] H. Gu, S. Shi, F. Xiao, Z. Huang, J. Xu, G. Chen, K. Zhou, L. Lu, X. Yin, MiR-1-3p regulates the differentiation of mesenchymal stem cells to prevent osteoporosis by targeting secreted frizzled-related protein 1, Bone (2020), 115444.

[40] S. Yi, Y. Yuan, Q. Chen, X. Wang, L. Gong, J. Liu, X. Gu, S. Li, Regulation of Schwann cell proliferation and migration by miR-1 targeting brain-derived neurotrophic factor after peripheral nerve injury, Sci. Rep. 6 (1) (2016) 1–10.

[41] W. Yuan, C. Tang, W. Zhu, J. Zhu, Q. Lin, Y. Fu, C. Deng, Y. Xue, M. Yang, S. Wu, CDK6 mediates the effect of attenuation of miR-1 on provoking cardiomyocyte hypertrophy, Mol. Cell. Biochem. 412 (1–2) (2016) 289–296.

[42] M. Tomaniak, G. Sygitowicz, O. Błaszczyk, Ł. Kołtowski, D. Puchta, K. Malesa, J. Kochanowsk, D. Sitkiewicz, K.J. Filipiak, miR-1, miR-21, and galectin-3 in hypertensive patients with symptomatic heart failure and left ventricular hypertrophy, Kardiol. Pol 76 (2018) 1009–1011.

[43] M.A. Al-Hayali, V. Sozer, S. Durmus, F. Erdenen, E. Altunoglu, R. Gelisgen, P. Atukeren, P.G. Atak, H. Uzun, Clinical value of circulating microribonucleic acids miR-1 and miR-21 in evaluating the diagnosis of acute heart failure in asymptomatic type 2 diabetic patients, Biomolecules 9 (5) (2019) 193.

[44] X. Yuan, Y. Guo, D. Chen, Y. Luo, D. Chen, J. Miao, Y. Chen, Long non-coding RNA MALAT1 functions as miR-1 sponge to regulate connexin 43-mediated ossification of the posterior longitudinal ligament, Bone 127 (2019) 305–314.

[45] W. Li, M. Liu, C. Zhao, C. Chen, Q. Kong, Z. Cai, D. Li, MiR-1/133 attenuates cardiomyocyte apoptosis and electrical remodeling in mice with viral myocarditis, Cardiol. J. 27 (3) (2020) 285–294.

[46] M. Connolly, B.E. Garfield, A. Crosby, N.W. Morrell, S.J. Wort, P.R. Kemp, miR-1-5p targets TGF-βR1 and is suppressed in the hypertrophying hearts of rats with pulmonary arterial hypertension, PloS One 15 (2) (2020), e0229409.

[47] M. Xu, J. Sun, Y. Yu, Q. Pang, X. Lin, M. Barakat, R. Lei, J. Xu, TM4SF1 involves in miR-1-3p/miR-214-5p-mediated inhibition of the migration and proliferation in keloid by regulating AKT/ERK signaling, Life Sci. (2020), 117746.

[48] A. Feldman, D.A.R. Moreira, C. Gun, H.T.L. Wang, M.H. Hirata, J. de Freitas Germano, G.G.S. Leite, P. Farsky, Analysis of circulating miR-1, miR-23a, and miR-26a in atrial fibrillation patients undergoing coronary bypass artery grafting surgery, Ann. Hum. Genet. 81 (3) (2017) 99–105.

[49] C.-Y. Chang, T.-N. Lui, J.-W. Lin, Y.-L. Lin, C.-H. Hsing, J.-J. Wang, R.-M. Chen, Roles of microRNA-1 in hypoxia-induced apoptotic insults to neuronal cells, Arch. Toxicol. 90 (1) (2016) 191–202.

[50] J. Peng, C. Yuan, Z. Wu, Y. Wang, W. Yin, Y. Lin, L. Zhou, J. Lu, Upregulation of microRNA-1 inhibits proliferation and metastasis of breast cancer, Mol. Med. Rep. 22 (1) (2020) 454–464.

[51] X.-Q. Lin, W. Wu, X. Chen, R.-P. Chen, F. Wu, Z.-F. Chen, E.-J. Huang, C. Chen, mir-1 inhibits migration of gastric cancer cells, Front. Biosci. (Landmark Edition) 25 (2020) 452–462.

[52] M. Xie, D.A. Dart, T. Guo, X.-F. Xing, X.-J. Cheng, H. Du, W.G. Jiang, X.-Z. Wen, J.-F. Ji, MicroRNA-1 acts as a tumor suppressor microRNA by inhibiting angiogenesis-related growth factors in human gastric cancer, Gastric Cancer 21 (1) (2018) 41–54.

[53] C. Han, Y. Zhou, Q. An, F. Li, D. Li, X. Zhang, Z. Yu, L. Zheng, Z. Duan, Q. Kan, MicroRNA-1 (miR-1) inhibits gastric cancer cell proliferation and migration by targeting MET, Tumor Biol. 36 (9) (2015) 6715–6723.

[54] R. Liu, C. Zhang, Z. Hu, G. Li, C. Wang, C. Yang, D. Huang, X. Chen, H. Zhang, R. Zhuang, T. Deng, H. Liu, J. Yin, S. Wang, K. Zen, Y. Ba, C.Y. Zhang, A five-microRNA signature identified from genome-wide serum microRNA expression profiling serves as a fingerprint for gastric cancer diagnosis, Eur. J. Cancer (Oxford, England: 1990) 47 (5) (2011) 784–791.

[55] D. Li, F.-f. Sun, D. Wang, T. Wang, J.-j. Peng, J.-Q. Feng, C. Wang, D.-j. Zhou, H. Luo, Z.-Q. Fu, Programmed Death Ligand-1 (PD-L1) Regulated by NRF-2/MicroRNA-1 Regulatory Axis Enhances Drug Resistance and Promotes Tumorigenic Properties in Sorafenib-Resistant Hepatoma Cells, Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics, 2020.

[56] Y. Li, H. Ma, C. Shi, F. Feng, L. Yang, Mutant ACTB mRNA 3′-UTR promotes hepatocellular carcinoma development by regulating miR-1 and miR-29a, Cell. Signal. 67 (2020), 109479.

[57] Y. Wu, N. Pu, W. Su, X. Yang, C. Xing, Downregulation of miR-1 in colorectal cancer promotes radioresistance and aggressive phenotypes, J. Cancer 11 (16) (2020) 4832–4840.

[58] L. Wu, T. Wang, D. He, X. Li, Y. Jiang, miR-1 inhibits the proliferation of breast cancer stem cells by targeting EVI-1, OncoTargets Ther. 11 (2018) 8773.

[59] C. Jin, Q. Lu, Y. Lin, L. Ma, Reciprocal regulation of Hsa-miR-1 and long noncoding RNA MALAT1 promotes triple-negative breast cancer development, Tumor Biol. 37 (6) (2016) 7383–7394.

[60] Y. Wang, X. Luo, Y. Liu, G. Han, D. Sun, Long noncoding RNA RMRP promotes proliferation and invasion via targeting miR-1-3p in non–small-cell lung cancer, J. Cell. Biochem. 120 (9) (2019) 15170–15181.

[61] C. Jin, B. Yan, Q. Lu, Y. Lin, L. Ma, The role of MALAT1/miR-1/slug axis on radioresistance in nasopharyngeal carcinoma, Tumor Biol. 37 (3) (2016) 4025–4033.

[62] L.M. Deng, T. Tan, T.Y. Zhang, X.F. Xiao, H. Gu, miR-1 reverses multidrug resistance in gastric cancer cells via downregulation of sorcin through promoting the accumulation of intracellular drugs and apoptosis of cells, Int. J. Oncol. 55 (2) (2019) 451–461.

[63] J. Ke, B. Zhang, Y. Li, M. Zhong, W. Ma, H. Xue, Y. Wen, Y. Cai, MiR-1-3p suppresses cell proliferation and invasion and targets STC2 in gastric cancer, Eur. Rev. Med. Pharmacol. Sci 23 (2019) 8870–8877.

[64] N. Wang, M. Chen, Z. Ni, T. Li, J. Zeng, G. Lu, J. Wang, J. Zhang, S. Wu, Y. Shi, HDAC6/HNF4α loop mediated by miR-1 promotes bile acids-induced gastric intestinal metaplasia, Gastric Cancer (2020) 1–14.

[65] J. Zhang, N. Li, J. Fu, W. Zhou, Long noncoding RNA HOTAIR promotes medulloblastoma growth, migration and invasion by sponging miR-1/miR-206 and targeting YY1, Biomed. Pharmacother. 124 (2020), 109887.

[66] J. Chou, B. Wang, T. Zheng, X. Li, L. Zheng, J. Hu, Y. Zhang, Y. Xing, T. Xi, MALAT1 induced migration and invasion of human breast cancer cells by competitively binding miR-1 with cdc42, Biochem. Biophys. Res. Commun. 472 (1) (2016) 262–269.

[67] J.Y. Wang, J.C. Huang, G. Chen, D.M. Wei, Expression level and potential target pathways of miR-1-3p in colorectal carcinoma based on 645 cases from 9 microarray datasets, Mol. Med. Rep. 17 (4) (2018) 5013–5020.

[68] D. Zhu, Y. Sun, D. Zhang, M. Dong, G. Jiang, X. Zhang, J. Zhou, miR-1 inhibits the progression of colon cancer by regulating the expression of vascular endothelial growth factor, Oncol. Rep. 40 (2) (2018) 589–598.

[69] X. Wu, S. Li, X. Xu, S. Wu, R. Chen, Q. Jiang, Y. Li, Y. Xu, The potential value of miR-1 and miR-374b as biomarkers for colorectal cancer, Int. J. Clin. Exp. Path. 8 (3) (2015) 2840.

[70] W. Xu, Z. Zhang, K. Zou, Y. Cheng, M. Yang, H. Chen, H. Wang, J. Zhao, P. Chen, L. He, MiR-1 suppresses tumor cell proliferation in colorectal cancer by inhibition of Smad3-mediated tumor glycolysis, Cell Death Disease 8 (5) (2017) e2761-e2761.

[71] K. Taniguchi, M. Sakai, N. Sugito, M. Kumazaki, H. Shinohara, N. Yamada, T. Nakayama, H. Ueda, Y. Nakagawa, Y. Ito, PTBP1-associated microRNA-1 and-133b suppress the Warburg effect in colorectal tumors, Oncotarget 7 (14) (2016) 18940.

[72] F. Guo, Z. Cao, H. Guo, S. Li, The action mechanism of lncRNA-HOTAIR on the drug resistance of non-small cell lung cancer by regulating Wnt signaling pathway, Exp. Ther. Med. 15 (6) (2018) 4885–4889.

[73] J. Chang, W. Xu, X. Du, J. Hou, MALAT1 silencing suppresses prostate cancer progression by upregulating miR-1 and downregulating KRAS, OncoTargets Ther. 11 (2018) 3461.

[74] Z.C. Xie, J.C. Huang, L.J. Zhang, B.L. Gan, D.Y. Wen, G. Chen, S.H. Li, H.B. Yan, Exploration of the diagnostic value and molecular mechanism of miR-1 in prostate cancer: a study based on meta-analyses and bioinformatics, Mol. Med. Rep. 18 (6) (2018) 5630–5646.

[75] W. Wei, J. Leng, H. Shao, W. Wang, MiR-1, a potential predictive biomarker for recurrence in prostate cancer after radical prostatectomy, Am. J. Med. Sci. 353 (4) (2017) 315–319.

[76] Y.-S. Chang, W.-Y. Chen, J.J. Yin, H. Sheppard-Tillman, J. Huang, Y.-N. Liu, EGF receptor promotes prostate cancer bone metastasis by downregulating miR-1 and activating TWIST1, Cancer Res. 75 (15) (2015) 3077–3086.

[77] S.-M. Li, H.-L. Wu, X. Yu, K. Tang, S.-G. Wang, Z.-Q. Ye, J. Hu, The putative tumour suppressor miR-1-3p modulates prostate cancer cell aggressiveness by repressing E2F5 and PFTK1, J. Exp. Clin. Cancer Res. 37 (1) (2018) 1–15.

[78] X. Dai, Z. Liang, L. Liu, K. Guo, S. Xu, H. Wang, Silencing of MALAT1 inhibits migration and invasion by sponging miR-1-3p in prostate cancer cells, Mol. Med. Rep. 20 (4) (2019) 3499–3508.

[79] Q. Wei, X. Li, W. Yu, K. Zhao, G. Qin, H. Chen, Y. Gu, F. Ding, Z. Zhu, X. Fu, microRNA-messenger RNA regulatory network of esophageal squamous cell carcinoma and the identification of miR-1 as a biomarker of patient survival, J. Cell. Biochem. 120 (8) (2019) 12259–12272.

[80] Q. Yu, Y. Liu, C. Wen, Y. Zhao, S. Jin, Y. Hu, F. Wang, L. Chen, B. Zhang, W. Wang, MicroRNA-1 inhibits tumorigenicity of esophageal squamous cell carcinoma and enhances sensitivity to gefitinib, Oncol. Lett. 15 (1) (2018) 963–971.

[81] R. Sheervalilou, H. Lotfi, M. Shirvaliloo, A. Sharifi, M. Nazemiyeh, N. Zarghami, Circulating MiR-10b, MiR-1 and MiR-30a expression profiles in lung cancer: possible correlation with clinico-pathologic characteristics and lung cancer detection, Int. J. Mol. Cell. Med. 8 (2) (2019) 118.

[82] R. Sheervalilou, A.M. Khamaneh, A. Sharifi, M. Nazemiyeh, A. Taghizadieh, K. Ansarin, N. Zarghami, Using miR-10b, miR-1 and miR-30a expression profiles of bronchoalveolar lavage and sputum for early detection of non-small cell lung cancer, Biomed. Pharmacother. 88 (2017) 1173–1182.

[83] J. Li, J. Guan, X. Long, Y. Wang, X. Xiang, mir-1-mediated paracrine effect of cancer-associated fibroblasts on lung cancer cell proliferation and chemoresistance, Oncol. Rep. 35 (6) (2016) 3523–3531.

[84] C. Wang, Y. Li, Y.-w. Li, H.-b. Zhang, H. Gong, Y. Yuan, W.-t. Li, H.-y. Liu, J. Chen, HOTAIR lncRNA SNPs rs920778 and rs1899663 are associated with smoking, male gender, and squamous cell carcinoma in a Chinese lung cancer population, Acta Pharmacol. Sin. 39 (11) (2018) 1797–1803.

[85] W. Wang, F. Shen, C. Wang, W. Lu, J. Wei, A. Shang, C. Wang, MiR-1-3p inhibits the proliferation and invasion of bladder cancer cells by suppressing CCL2 expression, Tumor Biol. 39 (6) (2017), 1010428317698383.

[86] A. Shang, M. Yang, F. Shen, J. Wang, J. Wei, W. Lu, W. Wang, C. Wang, C. Wang, MiR-1-3p suppresses the proliferation, invasion and migration of bladder cancer cells by up-regulating SFRP1 expression, Cell. Physiol. Biochem. 41 (3) (2017) 1179–1188.

[87] D. Yu, C. Zhang, J. Gui, RNA-binding protein HuR promotes bladder cancer progression by competitively binding to the long noncoding HOTAIR with miR-1, OncoTargets Ther. 10 (2017) 2609.

[88] L. Leonardo, P. Laura, B.M. Serena, miR-1 and miR-133b expression in canine osteosarcoma, Res. Vet. Sci. 117 (2018) 133–137.

[89] J. Niu, Y. Sun, Q. Guo, D. Niu, B. Liu, miR-1 inhibits cell growth, migration, and invasion by targeting VEGFA in osteosarcoma cells, Dis. Markers 2016 (2016).

[90] K. Zhu, W. Wang, Green tea polyphenol EGCG suppresses osteosarcoma cell growth through upregulating miR-1, Tumor Biol. 37 (4) (2016) 4373–4382.

[91] R. Fujii, E. Osaka, K. Sato, Y. Tokuhashi, MiR-1 suppresses proliferation of osteosarcoma cells by up-regulating p21 via PAX3, Cancer Genomics-Proteomics 16 (1) (2019) 71–79.

[92] C.-Y. Peng, Y.-W. Liao, M.-Y. Lu, C.-H. Yu, C.-C. Yu, M.-Y. Chou, Downregulation of miR-1 enhances tumorigenicity and invasiveness in oral squamous cell carcinomas, J. Formos. Med. Assoc. 116 (10) (2017) 782–789.

[93] K. Koshizuka, T. Hanazawa, I. Fukumoto, N. Kikkawa, R. Matsushita, H. Mataki, K. Mizuno, Y. Okamoto, N. Seki, Dual-receptor (EGFR and c-MET) inhibition by tumor-suppressive miR-1 and miR-206 in head and neck squamous cell carcinoma, J. Hum. Genet. 62 (1) (2017) 113–121.

[94] Q. Cheng, L.H. Han, H.J. Zhao, H. Li, J.B. Li, Abnormal alterations of miR-1 and miR-214 are associated with clinicopathological features and prognosis of patients with PDAC, Oncol. Lett. 14 (4) (2017) 4605–4612.

[95] C. Liu, S. Zhang, Q. Wang, X. Zhang, Tumor suppressor miR-1 inhibits tumor growth and metastasis by simultaneously targeting multiple genes, Oncotarget 8 (26) (2017) 42043.

[96] V.J. Amatya, A.S. Mawas, K. Kushitani, M.M. Mohi El-Din, Y. Takeshima, Differential microRNA expression profiling of mesothelioma and expression analysis of miR-1 and miR-214 in mesothelioma, Int. J. Oncol. 48 (4) (2016) 1599–1607.

[97] T. Hu, Y.-F. Chang, miR-1 inhibits progression of high-risk papillomavirus-associated human cervical cancer by targeting G6PD, Oncotarget 7 (52) (2016) 86103.

[98] H. Xiao, J. Zeng, H. Li, K. Chen, G. Yu, J. Hu, K. Tang, H. Zhou, Q. Huang, A. Li, MiR-1 downregulation correlates with poor survival in clear cell renal cell carcinoma where it interferes with cell cycle regulation and metastasis, Oncotarget 6 (15) (2015) 13201.

[99] J. Liu, Y. Huang, Q. Cheng, J. Wang, J. Zuo, Y. Liang, G. Yuan, miR-1-3p suppresses the epithelial-mesenchymal transition property in renal cell cancer by downregulating Fibronectin 1, Cancer Manage. Res. 11 (2019) 5573.

[100] W. Di, Q. Li, W. Shen, H. Guo, S. Zhao, The long non-coding RNA HOTAIR promotes thyroid cancer cell growth, invasion and migration through the miR-1-CCND2 axis, Am. J. Cancer Res. 7 (6) (2017) 1298.

[101] S. Zhang, C. Liu, X. Zhang, Mitochondrial damage mediated by miR-1 overexpression in cancer stem cells, Mol. Ther.-Nucleic Acids 18 (2019) 938–953.

[102] R.O.-C. Vagner, L.R. Ferreira, S.M. Ayub-Ferreira, M.S. Ávila, S.M. Brandão, F. D. Cruz, M.H. Santos, C.B. Cruz, M.S. Alves, V.S. Issa, Circulating miR-1 as a

potential biomarker of doxorubicin-induced cardiotoxicity in breast cancer patients, Oncotarget 8 (4) (2017) 6994.
[103] T. Liu, L. Zhang, D. Joo, S.-C. Sun, NF-κB signaling in inflammation, Signal Transduct Target. Ther. 2 (2017) 17023.
[104] M.-P. Tetreault, M.-L. Wang, Y. Yang, J. Travis, Q.-C. Yu, A.J. Klein-Szanto, J. P. Katz, Klf4 overexpression activates epithelial cytokines and inflammation-mediated esophageal squamous cell cancer in mice, Gastroenterology 139 (6) (2010), 2124-2134.e9.
[105] A. Talebi, M. Rahnema, M.R. Bigdeli, Effect of intravenous injection of antagomiR-1 on brain ischemia, Mol. Biol. Rep. 46 (1) (2019) 1149–1155.