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REVIEW

Roles of the canonical myomiRs miR-1, -133 and -206 in cell development and disease

Keith Richard Mitchelson, Wen-Yan Qin

Keith Richard Mitchelson, Wen-Yan Qin, National Engineering Research Centre for Beijing Biochip Technology, Beijing 102206, China

Wen-Yan Qin, Medical Systems Biology Research Centre, Tsinghua University School of Medicine, Beijing 102206, China

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Correspondence to: Dr. Keith Richard Mitchelson, National Engineering Research Centre for Beijing Biochip Technology, 18 Life Science Parkway, Zhonghuan Life Science Park, Beijing 102206, China. keith_mitchelson@hotmail.com
Telephone: +86-10-61777524
Fax: +86-10-80726898

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Abstract

MicroRNAs are small non-coding RNAs that participate in different biological processes, providing subtle combinational regulation of cellular pathways, often by regulating components of signalling pathways. Aberrant expression of miRNAs is an important factor in the development and progression of disease. The canonical myomiRs (miR-1, -133 and -206) are central to the development and health of mammalian skeletal and cardiac muscles, but new findings show they have regulatory roles in the development of other mammalian non-muscle tissues, including nerve, brain structures, adipose and some specialised immunological cells. Moreover, the deregulation of myomiR expression is associated with a variety of different cancers, where typically they have tumor suppressor functions, although examples of an oncogenic role illustrate their diverse function in different cell environments. This review examines the involvement of the related myomiRs at the crossroads between cell development/tissue regeneration/tissue inflammation responses, and cancer development.

Key words: Muscle microRNAs; MiR-1; MiR-206; MiR-133a; MiR-133b; Cell development; Cancer

Core tip: The roles of the canonical muscle-associated microRNAs are reviewed, including microRNA families miR-1 and miR-133, and single miR-206, which are collectively known as the "myomiRs". The myomiRs act at the crossroads of the molecular regulation of muscle cells, linking between pathways for cell differentiation, development and maintenance, but also potentiate aberrant cell growth in numerous non-muscle cancers. Typically myomiRs are downregulated in cancers, but some myomiRs are upregulated in a few cancers, yet each dysregulation event advances tumor progression. The review examines normal and disease-linked molecular changes associated with the myomiRs, and collates the extensive literature into accessible tables.

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INTRODUCTION

MicroRNAs (miRs) are short single strand RNA molecules (typically 22 nt) which interact in a semi-complementary manner with numerous target gene mRNAs, directed by a short "seed sequence", destining the targeted mRNA for degradation or for translational inhibition, and thus an miR can downregulate the functional expression of the target gene. In this manner a single miR can influence the abundance of numerous independent gene targets, and aid in the co-ordinate regulation of members of diverse cell signalling pathways, as well as metabolic pathways and basic cell proliferation or developmental processes. Three miR families, miR-1, miR-133 and miR-206 constitute the original (canonical) myomiRs and were considered muscle specific because of their prevalence in skeletal and cardiac muscle[1-5] and for their central roles in the regulation of myogenesis, muscle development and muscle remodelling[6-8]. Although other muscle enriched miRs such as miR-499 and -208, and others with key roles in cardiac muscle development have been identified, and although the term "myomiR" is now often used to denote several miRs encoded within myosin genes, for brevity this review is restricted to discussion of the three canonical myomiRs.

In man the genes encoding the canonical myomiR are organized into three cistrons encoding partners (miR-1-2, miR-133a-1), (miR-1-1, miR-133a-2) and (miR-133b, miR-206) and are located on chromosomes 18q11.2, 20q13.33 and 6p12.2, respectively. In this review we examine the roles of the myomiRs in normal tissue development and their emerging functions in various non-muscle tissues and their influence on the progression of cancers. The dysregulation of expression of the myomiRs in cancers is often related to a significant worsening patient prognosis, *via* the deregulation of a variety of validated gene targets.

The two mature miR-1 isomers have identical sequence, as have the two miR-133a isomers. The mature miR-133 isomers are also highly similar, differing only at the 3'-terminal base, with miR-133a$_{1/2}$ terminating G-3' and miR-133b with A-3', respectively. Independent upstream enhancers have been identified for the cistronic *miR-1-2 -133a-1* genes, as well as for the cistronic *miR-1-1/-133a-2* genes which are intronic to the *C20orf166* gene[9]. These independent enhancers allow the different isomer genes to be independently expressed under cell specific regulation.

DIFFERENT ROLES OF MYOMIRS IN MUSCLE

MicroRNA-1 and -133 were initially identified during the development and differentiation of skeletal muscle[7] and cardiac muscle[2,6]. Both *miR-1/-133a* gene cistrons are canonically expressed in skeletal and cardiac muscle[5,9], whilst the *miR-133b/-206* gene cluster is expressed in developing skeletal muscle[5] but not (significantly) in cardiac muscle, defining seminal roles of miR-1 and miR-133a in muscle biogenesis, and specifically in cardiac biogenesis[2,6]. A cartoon illustrating some of the major effects of myomiRs during differentiation of embryonic tissue and during tissue regeneration is shown in Figure 1.

MiR-133a has a regulatory role from the earliest differentiation of myogenic stem cells into myoblasts[7,10] continuing throughout the growth of structurally complex muscle tissues[7,11], and has homeostatic functions for muscle maintenance and protection in mature muscle, or in muscle regeneration from muscle progenitor cells after skeletal muscle stress or injury[5]. Key studies show miR-1, -133b and -206 acting during early development of skeletal myocytes through to the homeostatic maintenance of skeletal muscle[3,4,8], with miR-133b/-206 also having functions in neuromuscular synapse development and maintenance[12], as detailed in Tables 1 and 2.

Others have noted that the canonical myomiRs act as balanced regulators, often specifying broadly opposing functions. The miRs-1 and -206 are semi-homologous with closely similar mature sequences (and identical seed sequences), and target some genes in common, as well as independent targets. The identical mature seed sequences of miRs-133a and -133b implies they would share many targets in common, yet each of these miRs appear to have distinct cellular functions, with miR-133a expression common to all muscle and miR-133b abundant in all muscle types, except cardiac muscle. Loosely, the cell signalling pathways targeted by miR-1/-206 tend to have opposing functions to the regulatory pathways targeted by miR-133a/-133b. Both miR-1/ -206 act to promote myogenic differentiation, while the miR-133 isomers maintain the undifferentiated state and promote cell growth; hence co-expression of the myomiRs likely aids maintenance of homeostasis under normal cellular conditions.

This difference in expression of the related myomiR members in cardiac muscle compared to skeletal muscle may be associated with the physiological specialization of cardiac muscle, or its greater constancy of fibre type and function. In contrast, skeletal muscles constitute a variety of differentiated fibre types and are more plastic, capable of undergoing marked changes in myofibre content and physiology related to the level of use and workload[1,3]. As understanding of the molecular

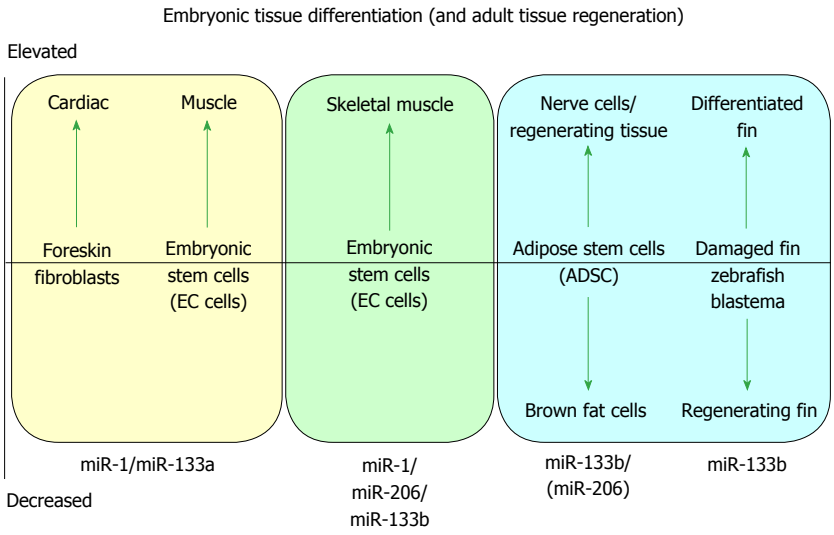

Figure 1 The roles of the myomiRs during embryonic tissue differentiation and adult tissue regeneration. Elevated levels of miR-1 and miR-133a are essential for differentiation of cardiac muscle[10,15], whilst miR-1, miR-206 and miR-133b are required for skeletal muscle differentiation[7,13]. Elevation of miR-133b levels in adipose stem cells leads to differentiation to a nerve-cell like fate[71], whilst reduction in miR-133b leads to brown fat cell differentiation[74]. Strong depletion of miR-133b and elevated Fgf allows regeneration of damaged zebrafish appendages[67,68].

regulation of muscle types have deepened, it is clear that the physiological and functional specializations are also reflected in the functions of the myomiRs.

CARDIAC MYOGENESIS

Studies with mammalian stem cells reveal broad functions for the myomiRs in the definition of primary differentiation pathways. Both miR-133 and miR-1 have roles in early cell programs leading to differentiation of muscle[2,10,13]. Pluripotent mammalian embryonic stem (ES) cells undertake cell fate decisions controlled by activation and repression of lineage-specific gene sets. These decisions are dictated by signalling networks which progressively narrow and specify the potential of ES cells as differentiation progresses. Muscle specific miR-133(a) and miR-1 both promote mesoderm formation from ES cells and suppress ectoderm and endoderm fates[2], but later during further differentiation into cardiac muscle progenitors, these miRs appear to have opposing regulatory functions[11,13]. Many non-muscle cell genes are repressed by miR-1 and miR-133 during this early ES cell differentiation program, suggesting that these two miRNAs may have general roles to regulate early ES cell-fate decisions from pluripotent cells[13], with miR-1 specifically targeting the translational repression of Dll-1 and Cdk9[10].

In vivo, the deletion of both *miR-133a1/2* genes causes lethal cardiac (ventricular-septal) abnormalities in about half of the mouse embryos or neonates, while mice deficient in only one of either miR-133a-1 or -133a-2 have phenotypically normal hearts[14]. Skeletal muscles are normal in both double and single mutant miR-133a mice (dead and surviving), implying that miR-133b can replace the absent miR-133a species in skeletal muscle and continue the regulation of normal development. In double mutant mice lacking all miR-133a, smooth muscle gene expression was activated 2-4 × and cardiomyocytes (but not cardio-fibroblasts) proliferated 2.5 × faster than normal, accompanied by increased expression of miR-133a targets, including PTBP2, CDC42, cell cycle control factors and cyclins D1, D2 and B1[14]. Recently, both adult and neonatal human foreskin fibroblasts were found capable of being reprogrammed towards cardiac muscle by exogenous expression of only several factors, myocardin, HAND2, T-box-5, GATA4, and miR-1, miR-133a and miR-499[15]. These stimulated cells expressed cardiac specific proteins and showed spontaneous contractility, emphasizing the role of these miRs in the control of specific cell development programs *via* the modulation of specific factor targets. Further, both human and mouse fibroblasts can be reprogrammed to form cardiomyocyte-like cells by overexpression of cardiac transcription factors (Gata4, Mef2c, and Tbx5 (GMT) or GMT plus Mesp1 and Myocd) along with miR-133a, which directly represses Snai1 which normally regulates EMT processes[16]. Interestingly, exogenous miR-133b can also downregulate Snai1 expression, suppressing fibroblast genes and upregulate the expression of a number of characteristic cardiac cell genes *in vitro*, yet it cannot replace miR-133a during normal heart development *in vivo*.

CARDIAC MUSCLE INJURY

Heart contractility and heart rate are stimulated during chronic pressure overload by activation of the sympathetic nervous system causing catecholamine release. The catecholamines activate β-adrenergic receptors and overstimulation is a component of heart

disease. MiR-133 directly targets adenylate cyclase VI and the catalytic subunit of PKA, both elements of the β1AR signal transduction cascade, reducing signalling[17]. Similarly carvedilol, an *in vivo* β-adrenergic blocker, improves the cardiac function in infarcted rats by restoring miR-133 expression, resulting in reduced cardiomyocyte apoptosis[18]. *In vitro* overexpression of miR-133a in cardiac cells has similar effects to carvedilol by downregulating caspase-9 and caspase-3 expression in the presence of H_2O_2. Overexpression of miR-133a also reduces ROS and malondialdehyde content, and increases SOD activity and GPx levels, protecting cardiomyocytes from apoptosis. Studies in mouse by Caré *et al*[6] also demonstrated that downregulation of both miR-133 and miR-1 are involved in cardiac hypertrophy. Specific targets of miR-133 such as RhoA, Cdc42 and Nelf-A/ WHSC2 can accumulate and contribute to the hypertrophy of cardiac myocytes during infarction.

SKELETAL MUSCLE MYOGENESIS

Liu *et al*[2,9] (2007, 2010) also established a fundamental model of differential expression of cistronic *miR-1* and *miR-133a* genes during myogenesis and differentiation of skeletal muscle, smooth muscle and cardiac muscle. The factor MEF2 controls expression of the miR-1-2/-133a-1 cistron *via* at least two MEF2 enhancer loci: one MEF2 enhancer located 3' upstream of the *miR-1-2* gene, a second intragenic MEF2 enhancer located upstream of the *miR-133a-1* gene and a third (less defined) locus far upstream that requires MyoD for expression[19]. Transcripts of *pri-miR-1-2/-133-a-1* (bi-cistron), *pri-miR-1* and *pri-miR-133a-1* genes indicate that both proximal enhancers are functional[1]. Others have emphasized the distribution of these regulatory enhancers[2] drawing attention to the differential expression of these cistronic miRs which the regulatory factor binding sites provide. The regulation of expression of the cistronic miRs by these key muscle development regulatory factors, which are themselves targets of repression by these self-same miRs, also emphasizes the precise inter-regulatory control of each of the various developmental program factors.

Notably, the 2,6-disubstituted purine reversine can induce differentiation reversal (de-differentiation) of C2C12 murine myoblast cells back into multipotent progenitor cells[20]. This occurs by inhibition of Aurora A and B protein kinases, reducing histone H3 phosphorylation, which in turn induces chromatin remodelling and restores cell multipotentency. Reversine treatment also stimulates expression of polycomb genes, Phc1 and Ezh2, leading to inhibition of expression of the muscle-specific transcription factors, myogenin, MyoD, and Myf5[21]. Concomitantly, reversine strongly inhibits miR-133a expression in C2C12 cells through the reduced expression of SRF transcription factor and by reduction of its binding to the miR-133a enhancer and by reduced epigenetic histone modifications on the miR-133a promoter, including reduced trimethylation, phosphorylation, and acetylation[22]. The co-overexpression of a miR-133a mimic along with reversine treatment prevents C2C12 myoblast de-differentiation, indicating the central role of the inhibition of miR-133a expression to the de-differentiation process. Significantly, reversine induced de-differentiation of committed cells is not limited to myoblasts, and reversine treatment can transform primary murine dermal fibroblasts into myogenic-competent cells within regenerating muscle *in vivo*[23].

Skeletal muscle myogenesis also involves the IGF signalling pathway[24], which activates muscle proliferation and differentiation *via* the PI3K/AKT pathway. The IGF pathway is regulated by miR-133-a1 which directly inhibits translation of IGF-1R protein, resulting in repression of PI3K/AKT pathway activity. IGF-1, which increases and activates IGF-1R during myogenesis by binding and inducing its phosphorylation, also indirectly activates myogenin, which in turn activates miR-133 activity. Thus miR-133 provides a negative regulation loop to monitor and control PI3K/AKT pathway activity. Similarly, miR-1 targets and reduces the activity of IGF-1 in differentiating C2C12 skeletal muscle cells and in heart muscle during cardiac failure states[25], meanwhile active IGF-1 signalling pathway downregulates miR-1 *via* repression of FoxO3a transcription factor. Thus, miR-1 also mediates the activity of the IGF-1 signal pathway and is itself feed-back regulated by the IGF-1 signal transduction cascade. Significantly, IGF-1 signalling (IGF-1 and IGF-1R) has key roles in the growth and development of many tissues[26], and also in the progression of many cancers (see later).

SKELETAL MUSCLE PLASTICITY

Skeletal muscles are plastic tissues in which the ratios of muscle fibre type (slow or fast twitch, smooth muscle, *etc*.) are to some degree responsive to remodelling through environmental input and nerve control. The muscle fibre type is maintained by the type of nerve signals received by the muscle, and transition between fast and slow twitch fibres can occur over time if nerve signals are changed from slow to fast type, and *vice versa*[27]. Similarly, prolonged workload or exercise can alter muscle fibre type and its metabolism to allow it to better respond before exhaustion. Muscle development programs regulated by miR-1 and miR-133a play important roles in muscle remodelling[4], and in hypertrophic skeletal muscle miR-1 and -133 levels are decreased[28], indicating that functional overload of muscle induces regulatory alterations which are in part influenced *via* altered miR activities.

REGULATORS OF MYOMIR EXPRESSION

Myostatin is a repressor of myogenesis, and its down-regulation allows increase of miR-1, -133a, -133b and -206 expression, activating muscle cell proliferation[29]. In contrast, myogenic factors myogenin and MyoD are well known positive regulators of myomiR expression in muscle that bind upstream of *miR-1/-133a* genes at defined enhancer regions[2,11]. SRF, MyoD and MEF2 are also direct transcriptional activators of myogenesis-related miR-1 expression in cardiac muscle[2,30]. Since downregulation of myostatin permits expression of miR-133b/-206, and MyoD and myogenin also binds the miR-206 promoter[11], suggesting that miR-206/-133b expression in muscle may also be in part controlled by MyoD/ myogenin.

The ERK1/2 signalling pathway also regulates expression of miR-133 during myogenesis in the C2C12 cell model[31], and its activity is also feedback influenced by miR-133. During myogenesis both miR-133a and -133b are upregulated, and both FGFR1 and PP2AC which function in the ERK1/2 pathway signal transduction are negatively regulated post-transcriptionally by both miRs. Inhibition of ERK1/2 pathway signalling inhibits C2C12 cell proliferation, stimulating initiation of differentiation and forming small truncated myotubes. Importantly, ERK1/2 signalling pathway activity negatively regulates expression of miR-133, providing a feedback loop between miR-133 levels and ERK1/2 signalling activity, forming an additional reciprocal mechanism for regulating myogenesis.

Recently other cellular factors have been identified that influence post-transcriptional maturation or bio-availability of myomiRs in muscle. mTOR regulates miR-1 indirectly in regenerating mouse skeletal muscle and differentiating myoblasts[32]. mTOR most likely affects MyoD protein stability, which then alters miR-1 expression through the availability of MyoD to bind its upstream enhancer. A pathway downstream of mTOR also operates in which miR-1 suppression of HDAC4 results in production of follistatin, which subsequently activates myocyte fusion. This suggests that an mTOR-miR-1-HDAC4-follistatin pathway regulates myocyte fusion during myoblast differentiation and in regenerating skeletal muscle.

King *et al*[33] (2014) demonstrated that the RNA-binding TDP-43 protein interacts with miR-1/-206 family (but not the miR-133 family) in skeletal myoblast cells, limiting their bioavailability by preventing interaction with the RISC silencing complex, noting this is the first observation of a mechanism differentiating between mature bicistronically encoded miRs, which selectively modulates the bioactivity of downstream targets of the sequestered miRs. TDP-43 accumulates in motor neurons during ALS, a neuromuscular wasting disease. Two miR-1/-206 targets, IGF-1 and HDAC-4 are elevated in both ALS-model transgenic mouse muscle and in cells modified to overexpress TDP-43. The authors suggest the decreased miR-1 (-206) activity in ALS affected muscle could alter retrograde signalling at the NMJ through the dysregulation of both HDAC-4 and MEF-2, whereby miR-1 refines synaptic function by coupling changes in muscle activity to changes in presynaptic function[34].

Factors KSRP[35], MBNL1 and RNA binding protein LIN28[36] also positively and negatively regulate miR-1 biogenesis respectively. Additionally, miR-206 binds to 3'-UTR sites of KSRP transcript to inhibit KSRP expression in skeletal muscle[37]. Independently, miR-206 and KSRP are negative regulators of utrophin A, but unexpectedly, overexpression of miR-206 in both normal and dystrophic muscle cells promotes upregulation of utrophin A, *via* the downregulation of KSRP. Thus, miR-206 appears capable of switching between direct repression of utrophin A expression and the activation of its expression through decreased KSRP, the two molecular mechanisms providing close counter-regulation of utrophin A expression.

CISTRON MIR-206 AND MIR-133B

Although the microRNA-206 and -133b are thought typical of muscle specific miRs, little is known explicitly of their functions in skeletal muscle. Cesana *et al*[38] (2011) showed that *miR-133b* gene transcript in mouse is located within the precursor of the long (spliced) non-coding RNA linc-MD1 which is expressed under the control of an upstream distal (DIST) cistronic promoter[12] (Figure 2A), while the *miR-206* gene, which is located within the intron of linc-MD1, is transcribed autonomously under control of its own proximal (PROX) promoter. In proliferating myoblasts, only primary miR-206 transcript is expressed strongly, initiated from the PROX promoter. During mouse muscle differentiation, long distance interactions bring the DIST promoter into conjunction with PROX and the polyA addition regions of linc-MD1, facilitating the co-expression of linc-MD1 RNA, as well as the primary miR-206 transcript, with the PROX promoter activated by both MyoD and myogenin binding[11]. Notably, mature linc-MD1 RNA contains binding sites for miR-133 (and miR-135) acting as a binding "sponge" to downregulate their free abundance, in turn contributing to the expression regulation of the targets of these miRs, which include key muscle transcription factors[38]. In mouse muscle, the expression of mature linc-MD1 RNA mutually excludes the expression of miR-133b, which must be excised from the linc-MD1 pre-transcript. In the rat genome, a distinct ncRNA 7H4, covering less than half of the mouse linc-MD1 precursor transcript, but closely similar to a mouse RNA AK132542 transcript, also encodes the *miR-133b* gene, suggesting a similar function to linc-MD1 may occur in rat[39].

Figure 2A uses information from Cesana *et al*[38]

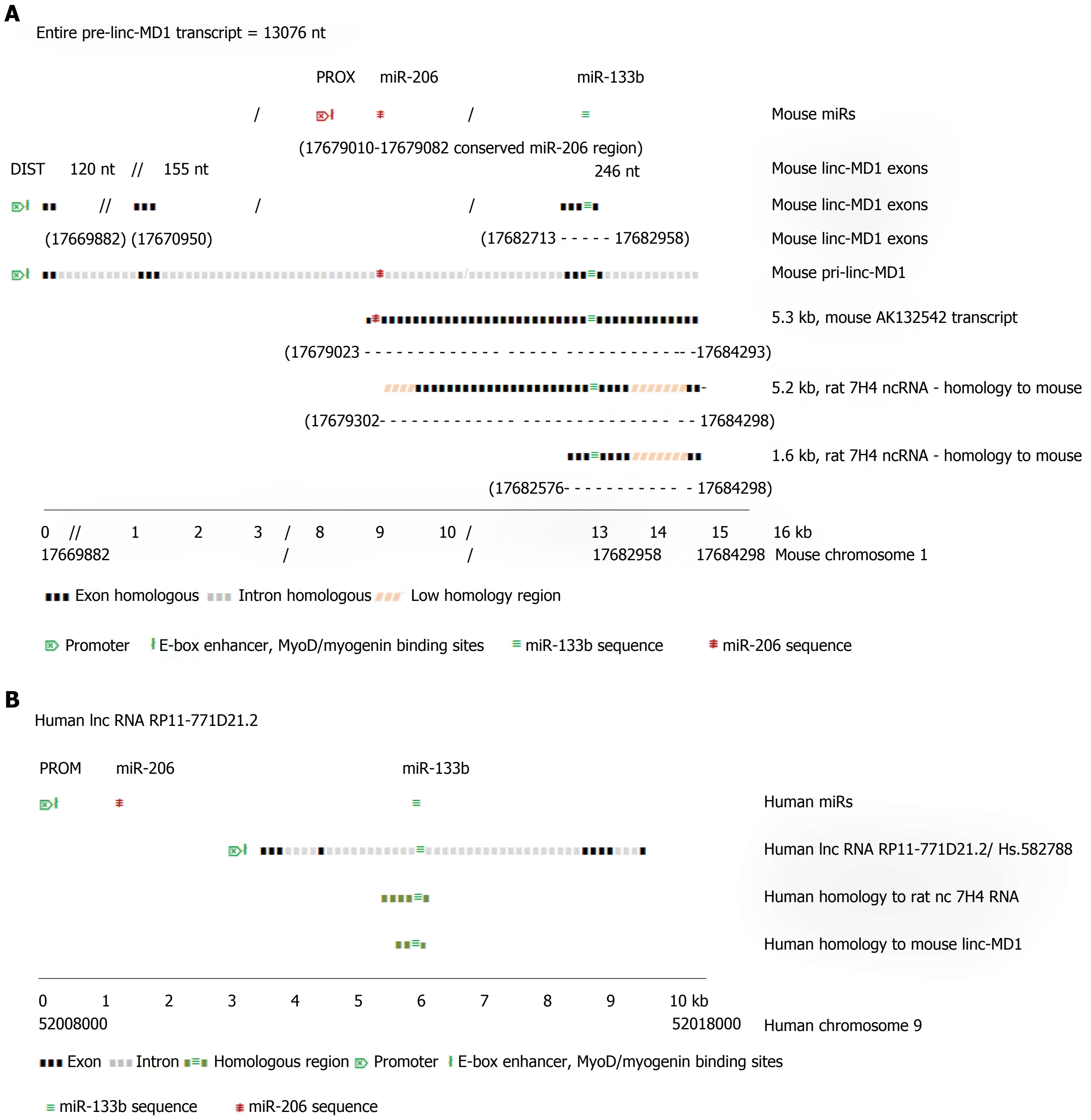

Figure 2 Alignment of the principal transcripts of the miR-206/miR-133b locus of (A) mouse chromosome 1 and (B) human chromosome 9, compiled from several sources. A: The primary long intergenic non-coding polyadenylated RNA (linc-MD1) of 15 kb is initiated at the upstream distal promoter (DIST) and encompasses both *microRNA-206* and *-133b* genes, however maturation of the pri-linc-MD1 results only in the release of pre-miR-133b which maturates into mir-133b which accumulates in the cell nucleus, as well as the mature 521 bp spliced linc-MD1 RNA which accumulates in the cytoplasm of skeletal muscle cells[38]. The mature linc-MD1 RNA sequence contains binding sites for miR-135 and miR-133 and acts as a complementary "sponge" to regulate their abundance and regulate expression of their target genes including key muscle transcription factors. Accumulation of linc-MD1 RNA and miR-133b are mutually exclusive. The DIST promoter contains E-box sequences recognized by MyoD and is active in differentiating muscle cells when increasing levels of MyoD induce the expression of linc-MD1 or miR-133b. In contrast, the primary transcript of miR-206 initiates at an independent proximal promoter (PROX) which is located intronic to linc-MD1 gene and is already active in undifferentiated proliferating cells. The PROX promoter binds both MyoD and myogenin (ChiP data)[38] and is functional in the presence of myogenin alone, although increased expression activity is also associated with differentiation of muscle cells[11]. The primary expressed transcript for miR-206 is likely coincident with the 5.3 kb random cloned mouse transcript cDNA, GenBank sequence AK132542[40], although the first 13 nt of the pre-mir-206 sequence is absent from that sequence. A second polyadenylated non coding RNA 7H4 was previously identified in rat muscle cells which are specifically associated with nerve synapses[39] and is expressed at rat development stages coincident with the strong expression of MyoD and myogenin[11]. The 5.2 kb long 7H4 ncRNA clone is slightly truncated at the 5' terminus compared to the AK132542 sequence, and may represent a processed product from which pre-miR-206 has been cleaved[8]. A second 1.6 kb short 7H4 ncRNA transcript, exactly coincident with the 3' terminal region of the longer transcript, is also abundant in rat muscle[39] and may represent a second processing product; B: The lnc RNA RP11-771D21.2 (Hs.582788) has been identified in RNA seq libraries and aligned with known genomic loci. Information about the regulation of its expression is not available.

(2011) and Rosenberg *et al*[40] (2006) to illustrate the aligned transcript regions of the mouse pri-linc-MD-1, the 5.3 kb random cloned mouse transcript cDNA (GenBank sequence) AK132542 and the 5.2 kb rat 7H4 ncRNA transcript. The independent pre-miR-206 transcript overlaps almost completely with the AK132542 transcript which is likely the mouse homolog of the expressed rat ncRNA 7H4. The *7H4 RNA* gene is almost fully conserved in the mouse genome, with the 7H4 RNA overlapping the 3' exon of *linc-MD1* gene (containing *miR-133b* gene) almost to the 3' terminus of the *miR-206* gene. Velleca *et al*[39] (1994) found two major transcripts of 7H4 RNA, a long 5.2 kb molecule, and a short 1.6 kb molecule coincident with the 3'-terminal region of the 5.2 kb transcript. The 1.6 kb fragment is much more abundant than the full length molecule, suggesting it is a product from the excision of miR-133b from the full length primary transcript. Notably, both long and short ncRNA 7H4 transcripts contain the entire *miR-133b* gene locus, suggesting they may function in rat similar to mature linc-MD1 in mouse, to bind complementary miRNAs, including miR-133. Similarly in man, ncRNA RP11-771D21.2 may represent the functional human homologue of mouse linc-MD1 RNA (Figure 2B).

Recently Legnini *et al*[41] (2014) reported that the mutually alternative synthesis of linc-MD1 and miR-133b is controlled by the pleiotropic mRNA regulator protein, HuR. In developing skeletal muscle, HuR favors accumulation of mature linc-MD1 by binding to it and repressing cleavage that would release pre-miR-133b. The level of HuR protein expression is also under the repressive negative control by miR-133 targetting, yet the sponging-up of miR-133 by the linc-MD1 helps consolidate HuR expression by forward positive control. Muscle developmental progression to later differentiation stages may involve overcoming this HuR-linMD1 repression of miR-133b expression by the independent miR-133a1/2 isomers which could downregulate HuR expression, allowing miR-133b excision, permitting developing muscle to exit from the control circuit. The level of linc-MD1 correlates inversely with the level of miR-135/-133b, which in turn control the expression of transcription factors MAML1 and MEF2C which are necessary for specific muscle gene expression. Thus, linc-MD1 activity provides another mechanism for pleiotropic regulation, slowing or activating muscle differentiation. Other evidence suggests the influence of HuR on many gene mRNA transcripts depends on the interplay of HuR with particular regulatory miRs that target and control the expression of the self-same mRNAs.

In sum, because the myomiRs target components of key signalling pathways and processes that control muscle cell development and maintenance, expression of the myomiRs is tightly regulated, often *via* feedback and feedforward circuits that provide both tight regulatory control and the ability to amplify myomiR expression. In muscle the myomiRs display high interconnectedness in terms of the regulation of their expression and the complementary processes that their regulatory functions influence. *MyomiR* genes are apparently cistronically encoded, yet expression of each of *myomiR* genes can be individually controlled by various transcription regulatory factors and other interactions such as RNA-RNA binding, such that expression of particular *myomiR* genes can be selectively enhanced under cellular conditions in which particular transcriptional regulatory factors are available.

ESTABLISHMENT OF NEUROMUSCULAR JUNCTIONS

MicroRNA miR-206 is expressed (virtually) exclusively in (developing) skeletal muscle[8], contributing to muscle differentiation programs through repression of Idl-3 protein expression, a downregulator of MyoD activity, as well as repressing the p180 subunit of DNA polymerase alpha, essential for DNA synthesis which occurs during differentiation[42]. MyoD itself promotes the expression of the miR-133 cistrons[11]. Further, in fast twitch muscle of mouse[12] and rat[43] miR-206 has been found to promote formation of new neuromuscular junctions following peripheral nerve denervation (scission). The expression of miR-206 and miR-133b are both upregulated strongly in muscle after denervation (as is 7H4 ncRNA), whereas miR-1 and miR-133a are downregulated. Four months after nerve scission, the re-innervated muscle was predominantly type II glycolytic fibres, suggesting that miR-206 may aid the determination of fibre type *via* down-regulation of MEF2 transcription factor activity[43]. Valdez *et al*[44] (2014) also examined the role of miR-133b and miR-206 on neuromuscular junction repair in injured mice. In miR-206 null mice, re-innervation was impaired following nerve injury, and in mice null for *-133b* and *-206* genes the same impaired neuromuscular repair was seen as in single gene *miR-206* null mice, whilst in single gene *miR-133b* null mice development and re-innervation proceeds normally following nerve injury. Together, these findings imply that miR-206 is the major regulator of nerve repair and reconnection to muscle following injury. In support, in miR-133b null mice Pitx3 levels were normal and impairment of locomotion was not detectable, controversially implying that miR-133b has no significant roles in neuron development, neuron maintenance and function *in vivo*[45]. In contrast, other studies with miR-206 null mice show no obvious phenotypic effects, muscles develop normally and mouse physiology appears normal, suggesting that other factors (including miR-133b) can replace miR-206 during development[46]. However, if the miR-206 null mice are then denervated, about 90% of both wt and miR-206 null mice recover and re-innervate after about

8 wk. This strongly suggests that other factors (including miR-133b) can provide redundant functions for the absent miR-206, including promoting compensatory peripheral nerve regeneration. Furthermore, miR-133b directly stimulates neurite outgrowth following nerve damage in rat brain after treatment with multipotent MSC cells[47], suggesting that elevation of levels of muscle miR-133b after muscle denervation is related to nerve regeneration, and that miR-133b may suffice in miR-206 null mice to replace absent functions. These various observations imply the likelihood that both miR-206 and -133b have functions in the recovery and maintenance of nerve-muscle signalling.

RETROGRADE SIGNALLING BETWEEN MUSCLE AND NERVE

Additionally, miR-206 targets BDNF which promotes efficient skeletal muscle regeneration following damage[48]. BDNF also controls the initiation and maintenance of the differentiated state of muscle cells, potentially *via* the regulation of retrograde signalling at the neuromuscular junction. The loss of neural input to muscle also causes HDAC4 to accumulate, reducing MEF2-regulated gene expression. Importantly, miR-206 targets HDAC4 and fibroblast growth factor signalling pathways in muscle. HDAC4 regulates neuromuscular-related gene expression and acts in the regulation of muscle remodelling, influencing the formation of appropriate nerve types which connect to the muscle[49]. Significantly, it has been shown that expression of miR-1/miR-133a is also regulated by an intragenic MEF2-enhancer[9], and miR-1 also regulates a MEF-2 dependent retrograde signal at the neuromuscular junction, suggesting that members of both myomiR cistons act to maintain neuromuscular homeostasis[34].

In mouse, members of the MyoD muscle transcription factor family, myf-4 and myogenin, are progressively downregulated during maturation from embryonic day 15 to the first postnatal weeks (weeks 1-3), coinciding with induction of muscle innervation[50,51]. In contrast, muscle denervation results in strong expression of MyoD and myogenin, preceding the accumulation of nAChR, α-subunit[39]. Additionally during myogenic differentiation, acetylcholinesterase transcript levels increase dramatically (5 ×), principally due to its stabilization by binding with HuR protein[52], consistent with a regulatory role of HuR in neuron excitability. Normally the expression of MyoD and myogenin is suppressed by activated nerve signal pathways, including by electrical conduction *per se*, and sets of muscle genes regulated by the MyoD family and myogenin are downregulated by increasing electrical activity and other nerve-derived signals. Thus again, a pronounced neuromuscular maintenance function for miR-206/-133b can be implied from interplay of signalling control between skeletal muscle and nerve. Both myogenin and MyoD induce the expression of miR-133b and -206, while repression of these factors inhibits their expression. On balance it appears that cistronic miR-206 and -133b and linc-MD1 homologues may contribute to programs of regulatory developmental gene expression in growing muscle and peripheral nerve, facilitating programs to interregulate the developing nerve connections with muscle, and speculatively aid in coordinating appropriate nerve and muscle gene expression programs, establishing interactions between skeletal muscles and their appropriate innervating nerves to maintain muscle fibre type and their correct neuromuscular junction associations.

MUSCLE MITOCHONDRIAL FUNCTION

Zhang *et al*[53] (2014) reported that miR-1 enters skeletal muscle mitochondria efficiently during muscle development whereby it stimulates the translation of specific mitochondrial genome-encoded transcripts, contributing positive regulation to muscle development. This stimulation of translation requires specific base-pairing between miR and its target mtRNA as well as interactions with mt-located Ago2 protein. These observations contrast earlier findings of Das *et al*[54] (2012) who showed that the mature miR-181c translocates into rat cardiac muscle mitochondria, reducing mitochondrial cytochome oxygenase 1 (mt-COX1) compared to mt-COX2 and mt-COX3 proteins. The reduced mt-COX1 causes mitochondrial complex IV remodelling, resulting in increased mt respiration and increased ROS generation. Recently, Das *et al*[55] (2014) used cationic nanoparticles to deliver miR-181c into rat cardiac mitochondria *in vivo,* causing cardiac dysfunction and a tendency to develop heart failure. Taken together, these studies reveal important new miR-mediated regulatory pathways in muscle mitochondria involving direct manipulation of mitochondrial gene expression by cytosolic miRNAs, including by a myomiR.

Importantly in both cardiac and skeletal muscle, mitochondrial UPC2/UCP3 uncoupling proteins regulate energy homeostasis and the rate of development and differentiation, with UPC2 repressing differentiation and promoting cell proliferation. However, MyoD activates miR-133a expression which in turn directly downregulates UCP2 mRNA to alleviate the developmental repression, suggesting a feedback network involving MyoD-miR-133a-UCP2[56]. Additionally, over-expression of myogenin and MyoD in mouse C2C12 myoblasts[57] increase expression strongly from the UCP3 promoter, but act weakly at the UCP2 promoter. Together these observations suggest UCPs helps maintain balance between muscle differentiation and proliferation during myogenesis, regulated by a MyoD-miR-133a-UCP2 feedback network and by differential responsiveness of UCP2 and UCP3 promoters to activation by myogenin and MyoD.

Furthermore, a downregulation of mitochondrial function is associated with skeletal muscle injury, including increased ROS and reduced cellular ATP generation. However, the recovery and regeneration of post-injury skeletal muscle involves the activation and proliferation of resident stem cells, including satellite cells and endothelial precursor cells followed by their differentiation into myocytes. Jash *et al*[58] (2014) showed during recovery from muscle injury that the AMPK-CRTC2-CREB and Raptor-mTORC-4EBP1 pathways are activated in satellite cells. mTORC1 positively regulated Ccnd1 translation, yet destabilized Ccnd1 mRNA. These opposing effects of mTORC1 were mediated by two miRs which target the 3'-UTR of Ccnd1 mRNA: one being miR-1 which in mTORC-knockdown muscle was downregulated, allowing Ccnd1 mRNA to accumulate. The authors suggest that mTORC may act to coordinate satellite cell proliferation during the activation of myogenesis.

MUSCLE DEGENERATION AND INFLAMMATION

During conditions of skeletal muscle atrophy and wasting, the cytokine TWEAK and its binding receptor Fn14 are elevated, activating catabolic and pro-inflammatory processes[59]. TWEAK inhibits expression of myoD, MEF2C and myogenin which in turn inhibits expression of miR-1, -133, and -206, suppressing differentiation of progenitor cells into myocytes. HMOX1, another factor associated with inflammation[60], also inhibits myoblast differentiation and myotube formation, by inhibition of expression of each of the myomiRs, again by limiting their transcription factors, MyoD and myogenin. Thus, both HMOX1 and TWEAK may be potentially involved in the regulation of broadly common inflammation associated pathways in skeletal muscle.

Interestingly, TWEAK[61] has a role in stimulating the proliferation of normal neonatal rat cardiomyocytes, increasing cell numbers accompanied by expression of cell proliferation markers Cyclin D2 and Ki67, and other cell cycle factors. In contrast, adult rat cardiomyocytes cannot be stimulated by TWEAK because of the developmental downregulation of its receptor Fn14 in adult cells, coincident with the loss of proliferation capacity in mammalian cardiomycetes several weeks after birth. Fn14 is present in neonatal cardiomyocytes, interacting with TWEAK to activate downstream signalling *via* ERK and PI3K signalling pathways, as well as *via* inhibiting glycogen synthase kinase-3β.

FAPs are quiescent progenitor cells resident in normal muscle that can facilitate myofibre regeneration after muscle damage by providing factors which stimulate proliferating myogenic progenitor cells. In dystrophic muscle disease, FAPs typically proliferate and give rise to their differentiated progeny, fibroblasts and adipocytes which replace muscle tissue. However, Saccone *et al*[62] (2014) found in early-stage disease dystrophic (mdx) mouse muscles that HDAC inhibitors can activate and commit FAPs themselves towards regeneration of muscle tissue, by derepressing a "latent" myogenic program. The inhibition of HDAC induces two core components of the myogenic transcriptional machinery, MyoD and BAF60C, which upregulate expression of miR-1-2, miR-133, and miR-206. The structural subunits of the BAF chromatin remodelling complex (BAF60a, BAF60b and BAF60c) bind to Brg1 (the core complex ATPase) and provide functional specificity[63]. BAF60c is a specific member of the complex during myogenesis, and is essential for the myogenesis process. Interestingly, BAF60a and BAF60b are targets for downregulation by miR-133 and miR-1/206, suggesting that such negative regulation increases the availability of (non-target) BAF60c to join the muscle remodelling complex. Furthermore, a recent study of inflammatory myopathies[64] including dermatomyositis, polymyositis, and inclusion body myositis found increased expression of the inflammatory cytokine TNFα was associated with decreased expression of miR-1, miR-133a, and miR-133b in all subtypes, plus the decreased expression of miR-206 in dermatomyositis. TNFα inhibited the expression of myogenic miRNAs in cells in an NF-κB-dependent manner, while the overexpression of miR-1, miR-206, or miR-133a/b could relieve the TNFα blockage of myogenic cell differentiation. Overall, the dysregulation of myomiR expression in muscle degenerative diseases was demonstrated to be intrinsic to the disease progression.

In diseased cardiac tissues, pre-inflammatory reactions involve upregulation of *CNN* genes, and *in vitro* the downregulation of CNN2 blocks multiple proinflammatory and profibrotic pathways in mouse activated primary cardiac fibroblasts (PCFBs)[65]. Immune cell chemotaxis towards CCN2-depleted PCFBs is also reduced strongly. CCN2 is a direct regulation target of miR-133b, and silencing of CCN2 expression by siRNA strongly decreases the expression of stretch-induced chemokines, matrix metalloproteinases, extracellular matrix and a cell-to-cell contact protein, indicating that CCN2 is involved in control of multiple signal pathways for muscle regeneration. Exogenous factors also influence muscle recovery after injury. PRP plasma is an enriched source of autologous platelet α-granule-derived growth factors and cytokines which can stimulate tissue healing[66]. When PRP is applied to injured rat soleus muscle, the recruitment, proliferation and differentiation of cells for muscle recovery is stimulated. Molecular analysis showed that 5 d after PRP treatment the expression of proinflammatory cytokines IL-1β, and TGF-β1 was increased strongly, which in turn induced expression of myogenic factors MyoD1, Myf5 and Pax7, and muscle IGF-1Eb isoform, and muscle recovery was strongly accelerated. Concomitantly miR-133a and miR-1 were downregulated (miR-133a markedly), while SRF was

upregulated, phosphoryled αB-cristallin was increased, as were apoptotic factors (NF-κB-p65 and caspase 3) which together indicate enhanced cell survival. Overall, PRP contributes to repair of injured skeletal muscle by *via* the control of secondary pathways (regulated by myomiRs and heat shock proteins) that modulate both inflammatory and myogenic pathways, with each contributing to the regulated tissue regeneration.

ROLES OF THE MYOMIRS IN OTHER TISSUES

Limb regeneration in lower vertebrates

Whilst miR-133 plays a central role is the repair of damaged muscle and nerves in mammals, in lower vertebrates such as amphibians and teleost fish which retain the capacity for regeneration of entire limbs after damage or loss, here the downregulation of miR-133 plays a central role in organizing the reactivation of cells for the repair of complex tissues. Yin and Poss[67] (2008) found that miR-133 controls complex biological processes involving formation of the regeneration blastema, a proliferative mesenchymal cell mass which is the progenitor for regeneration of the lost structures, ultimately developing into organized organs, including connective tissues, muscle, blood vessels and nerve tissues[67]. When zebrafish fins are excised, the depletion of miR-133 is controlled by increased Fgf signalling (Tables 1 and 2). In normal developed fins, high levels of miR-133 are maintained, accompanied by a cessation of Fgf signalling, indicating that high miR-133 levels normally suppresses tissue proliferation factors and signalling pathways, maintaining developed tissue homeostasis[68]. Increased miR-133b also influences spinal cord regeneration in adult zebrafish, reducing the level of RhoA protein, an inhibitor of axonal growth, and stimulating spinal cord regeneration of axons from neurons in particular brain structures[69].

MAMMALS

Corneal repair

In mouse cornea after laser ablation injury[70], miR-133b is the most strongly reduced miR (amongst others) during wound recovery, allowing increased expression of its targets which include CTGF growth factor, SMA, and COL1A1. Transforming growth factor β1-treated rabbit corneal fibroblasts also produced significant decrease in miR-133b, associated with significantly increased expression of CTGF, SMA, and COL1A1, and helped to minimise scar development during corneal recovery. See Table 2 for other tissues.

NERVE CELL DIFFERENTIATION

The miR-133b has roles in early stem cell differentiation leading to nerve development. ADSC stem cells can be induced to differentiate into neuron-like cells by IGF-Ⅰ signalling, which increases miR-133b expression *via* the downregulation of beta-Ⅲ-tubulin, Pitx3 and IGF-IR by translational repression of their proteins[71]. Neural differentiation from ADSC involves a feedback control mechanism in which IGF-I upregulates miR-133b, while miR-133b in turn downregulates the signal receptor activity, IGF-IR. Xin *et al*[47,72] found multipotent MSC cells regulate the growth of neurites *via* direct exosomal transfer of miR-133b to neural cells. Middle cerebral artery occluded rat brains elevate miR-133b in MSC exosomes, which stimulates neural regeneration. Exosomes transfer to adjacent astrocytes and neurons, reducing the expression of selected miR-133b targets, including CTGF and RhoA[72]. The first identified molecular role for miR-133b was in neural tissue[73] where it regulated the maturation of mammalian midbrain dopaminergic neurons (DNs), along with the paired-like homeodomain transcription factor Pitx3, which itself then regulated the transcription of miR-133b in a feedback control loop.

ADIPOCYTE DIFFERENTIATION

Several studies found that miR-133 a/b isomers play key roles in the differentiation of brown fat tissues from precursor cells after cold exposure[74-76]. Strong reduction of the transcription regulator MEF2 caused reduction of miR-133a, allowing an increase in the adipocyte progenitor specific Prdm16 (a miR-133 target), which promotes the differentiation of both myogenic precursor cells and white fat precursor cells into brown adipocytes. Adult mouse skeletal muscle satellite cells can differentiate into brown adipose *via* miRNA-133 targeting of Prdm16, leading researchers to suggest that the presence of these miRs may indicate energy dissipating cell lineages (muscle, nerve), compared to energy storing cells, such as white adipose tissue[76]. Mice with knockdown of *miR-133a1/a2* genes respond to cold exposure more strongly than wild-type animals and have increased insulin sensitivity and glucose tolerance associated with activation of the brown fat and thermogenic gene programs in subcutaneous white adipose tissue.

CHONDROCYTE DIFFERENTIATION

MiR-1 is highly expressed in the hypertrophic zone of growth plate cartilage, some 8-fold higher than in the proliferation zone[77]. MiR-1 strongly promotes chondrocyte proliferation and differentiation, including induction of the expression of chondrocyte markers Indian hedgehog and Col X, and acts by targetting HDAC4. Additionally HDAC4 negatively regulates chondrocyte hypertrophy by inhibiting Runx2, a critical transcription factor for chondrocyte hypertrophy. In contrast, miR-1 is repressed strongly during hypertrophic

Table 1 Roles and targets of the myomiRs, miR-1, -206, -133a, -133b

Factor(s)	Regulation	Regulator	Tissue/cell	Ref.
Fish and lower vertebrates: Development and regeneration				
Ttk protein kinase (mps1)	Upregulated mps1: a target of miR-133	Downregulation of miR-133 by Fgf	Regeneration of Zebrafish caudal fin (appendage)	[68]
RhoA	Downregulation of RhoA mRNA	Upregulation of miR-133b expression	Regenerating adult zebrafish spinal cord, axon outgrowth	[69]
RhoA	Downregulation of RhoA protein	Upregulation of miR-1 and miR-133 expression	Zebrafish muscle gene expression and regulation of sarcomeric actin organization	[166]
Cell cycle factors mps1, cdc37 and PA2G4, and cell junction components cx43 and cldn5	Upregulated mps1, cdc37, PA2G4, cx43, cldn5	Downregulated miR-133(a1) stimulates cardiac cell regeneration	Regenerating zebrafish cardiac muscle	[167]
miR-133b	MiR-133b found in developing somites, little in CNS tissues		Whole zebrafish embryos - normal development	[168]
SRF activates muscle specific genes and miRs; HDAC4 represses muscle gene expression	MiR-1 targets HDAC4, promoting myogenesis	In contrast, miR-133a represses SRF, enhancing myoblast proliferation	*X. laevis* embryos: skeletal muscle proliferation and differentiation in cultured myoblasts *in vitro* and in embryos *in vivo*	[7]
nAChR subunits UNC-29, UCR-63; MEF2	Subunits UNC-29, UCR-63, and MEF2 downregulated	miR-1 upregulated	*C. elegans* muscle at the neuromuscular junction	[34]
Mammalian pluripotent cells				
Muscle-specific microRNAs: miR-1 and miR-133a	MiR-1 and miR-133a have opposing functions during differentiation of progenitor cardiac muscles	Muscle-specific microRNAs, miR-1 and miR-133(a) upregulated	Promotion of mesoderm formation from mouse ES cells	[13]
Notch signalling, promotes neural differentiation and inhibits muscle differentiation; opposes miR-1 effects	Dll-1 translationally repressed	miR-1 upregulation, promotes cardiomycete differentiation	Mouse and human ES cell differentiation into muscle	[13]
$SRF^{-/-}$ EBs reflecting the loss of hematopoietic lineages in the absence of SRF	Early endoderm markers, Afp and Hnf4α: strongly down regulated	Increased miR-1 and miR-133a relieve the block on mesodermal differentiation	Mouse endoderm	[13]
Blood cell -specific genes, such as Cd53, CxCl4, and Thbs1, dramatically down regulated	Cd53, CxCl4, and Thbs1 expression was reinitiated by reintroduction of miR-1 or miR-133			
mES(miR-1)- and mES(miR-133a)-EBs compared to in control EBs	Nodal stimulated expression of endoderm markers Afp and Hnf4α in control EBs. Dramatically lower levels in mES(miR-1)- and mES(miR-133a)- EBs	miR-1 or miR-133 can each function as potent repressors of endoderm gene expression	mES cells, that lack either miR-1 or miR-133(a) during differentiation into EBs	[13]
IGF-1 IGF-1R	IGF-1 signalling and miR-133 co-regulate myoblast differentiation *via* a feedback loop	IGF-1 upregulates miR-133; miR-133 downregulates IGF-1R	Myogenic differentiation of C2C12 myoblasts; Mouse during development from embryonic to mature skeletal muscle	[24]
IGF-1	IGF-1 signalling and miR-1 coregulate differentiation of myoblasts *via* a feedback loop	IGF-1 signalling downregulates miR-1 by repression of FoxO3a; miR-1 down-regulates IGF-1	Differentiating C2C12 myoblasts	[25]
Reversine [2-(4-morpholinoanilino)-N6-cyclohexyladenine]	Decrease in active histone modifications; including trimethylation of histone H3K4/H3K36, phosphorylation of H3S10; Stimulates expression of polycomb genes Phc1 and Ezh2	miR-133a expression strongly inhibited by reversine; reduced acetylation of H3K14 at miR-133a promoter Reduced expression of myogenin, MyoD, Myf5 and Aurora A and B kinases	Reversine dedifferentiates murine C2C12 myoblasts back into multipotent progenitor cells, *via* extensive epigenetic modification of histones resulting in chromatin remodelling, and altered gene expression	[20-23]
FZD7 and FRS2	miR-1 promotes cardiac differentiation; miR-1 targets FZD7 and FRS2	Activitation of WNT and signalling cause MCPs differentiation into cardiomyocytes	Mouse and human ES cells	[169]
miR-206/133b cluster	*PAX7* gene expression unchanged; miR-206/133b cluster is not required for development, and survival of skeletal muscle cells	miR-206/133b cistron knock-out mice cells	Muscle satellite cell differentiation *in vitro*	[170]
Differentiating skeletal muscle				
DNA polymerase alpha	Repression of Idl-3 protein expression Repression of p180 subunit of DNA polymerase alpha	miR-206 up-regulated	Mouse skeletal muscle differentiation	[42]
MEF2 transcription factor	MEF2 activates of miR-1-2 and 133a-1 transcription; binds muscle-specific enhancer	Bicistronic primary transcript of miR-1-2 and 133a-1	Development of mammalian skeletal muscle	[9]

MRFs, Myf5, MyoD, Myogenin and MRF4	Myf5 essential for miR-1 and miR-206 expression during skeletal muscle myogenesis	Forced expression of MRFs in neural tube induces miR-1 and miR-206 expression	Chicken and mouse embryonic muscle	[171]
PTB and neuronal homolog nPTB, exon splicing factors	Downregulation of PTB protein by miR-133 (and miR-206)	Concurrent upregulation of miR-133 and induction of splicing of several PTB-repressed exons	During myoblast differentiation, microRNAs control a developmental exon splicing program	[172]
BDNF	BDNF downregulated	miR-206 upregulated	Differentiation of C2C12 myoblasts into myotubes	[48]
Fstl1 and Utrn	Fstl1 and Utrn downregulated	miR-206 upregulated	Skeletal muscle differentiation	[40]
Utrophin A (muscle)	Utrophin A down-regulated by both miRs	Upregulated miR-133b, miR-206	C2C12 mouse myoblasts, mouse soleus muscle	[173]
CNN3 gene	Negative correlation between miR-1 expression and CNN3 mRNA expression	Normal skeletal muscle	Tongcheng (Chinese) and Landrace (Danish) pigs	[174]
FGFR1 and PP2AC, members of ERK1/2 signalling pathway	miR-133 (a and b) activities increase during myogenesis	miR-133 directly downregulates expression of FGFR1 and PP2AC	Mouse C2C12 myoblast cells	[31]
ERK1/2 signalling pathway activity	ERK1/2 signalling activity suppresses miR-133 expression	Downregulation of expression of miR-133	A reciprocal mechanism for regulating myogenesis	
BAF chromatin remodelling complex (BAF60a, BAF60b and BAF60c)	Positive inclusion of BAF60c in the BAF chromatin remodeling complex	Expression of miR-133 and miR-1/206	Progression of developing somites in chick embryos	[63]
BAF chromatin remodelling complex	Negative regulation of BAF60a and BAF60b; exclusion from BAF chromatin remodelling complex	Expression of miR-133	Progression of developing somites in chick embryos	[63]
BAF chromatin remodelling complex	Exogenous upregulation of BAF60a and BAF60b		Delay in developing somites in chick embryos	[63]
Mitochondrial UCP2 and UCP3	MyoD activates miR-133a expression which in turn directly downregulates UCP2 mRNA	Feedback network involving MyoD-miR-133a-UCP2	Mouse skeletal and cardiac muscles; UCP2 imposes developmental repression	[56]
Mitochondrial UCP2 and UCP3	Exogenous overexpression of myogenin and MyoD transcription factors	Strong increase in UCP3 promoter, expression, weak effect at the UCP2 promoter	Mouse C2C12 myoblasts	[57]
Proliferating myogenic skeletal muscle cells				
MiR-206/133b cluster	MiR-206/133b cluster is not required for survival and regeneration of skeletal muscle	Muscle regeneration proceeds in Mdx mice *in vivo*	miR-206/133b cistron knock-out mice	[170]
Enhanced translation of specific mitochondrial genome-encoded transcripts	miR-1 enters muscle mitochondria and binds mtRNA targets along with Ago factor	Increased expression of mtRNA targets	Proliferating myogenic skeletal muscle cells after muscle injury	[53]
mTOR (serine/threonine kinase)	MyoD stability regulated by mTOR	Regulates miR-1 expression *via* MyoD availability	Regenerating mouse skeletal muscle and differentiating myoblast cells	[32]
AMPK-CRTC2-CREB and Raptor-mTORC-4EBP1 pathways	mTORC regulates timing of satellite cell proliferation during myogenesis	Knockdown of mTORC reduces miR-1 expression	Myogenenic satellite SCs proliferating and differentiating into myogenic precursors following rat skeletal muscle injury	[58]
HDAC4 regulates Pax7-dependent muscle regeneration	Pax7 stimulates SCs differentiation toward the muscle lineage, and limits adipogenic differentiation	HDAC4 upregulated in SCs differentiating into muscle cells	Myogenenic satellite SCs	[175]
pcRNA encoded by the H strand of the rat mitochondrial genome	Introduction of mt pcRNAs into injured muscle restoring mitochondrial mRNA levels; Intramuscular ATP levels were elevated after pcRNA treatment of injured muscle	Enhanced organellar translation and respiration; similarly reactive oxygen species were reduced; Resulted in accelerated rate of wound resolution	Injured rat skeletal muscle is associated with general downregulation of mitochondrial function; reduced ATP, and increased ROS	[176]
Cardiac muscle precursor cells				
GATA binding protein 4, Hand2, T-box5, myocardin, and microRNAs miR-1 and miR-133	Reprogrammed human fibroblasts show sarcomere-like structures and calcium transients; Some cells have spontaneous contractility	Forced over-expression of GATA binding protein 4, Hand2, T-box5, myocardin, and microRNAs miR-1 and miR-133	Human embryonic and adult fibroblasts activated to express cardiac markers	[15]
SRF, MyoD and Mef2 transcription factors	miR-1-1 and miR-1-2 During cardiogenesis miR-1 genes titrate critical cardiac regulatory proteins, control ratio of differentiation to proliferation	miR-1 genes upregulated; Elevated miR-1 targets downregulation of Hand2	Cardiac muscle precursor cells	[30]
Histone deacetylase inhibitor, trichostatin A forces differentiation, yet reduced miR-1 and miR-133a	miR-1 and miR-133a reduce cardiac specific Nkx2.5 protein and Cdk9	miR-1 and miR-133a increase during spontaneous differentiation of cardiac myoblasts	Mouse cardiac stem cells (ES cells)	[10]

Specific inhibition of HDAC4 modulates CSCs to facilitate myocardial repair	Positively proliferative myocytes increased in MI hearts receiving HDAC4 downregulated CSCs	CSCs with downregulated HDAC4 expression improved ventricular function, attenuated ventricular remodeling, promoted regeneration and neovascularization in MI hearts	Mouse CSCs transplanted into MI mouse hearts	[177]
Snai1	Overexpression of miR-133a (miR-133), Gata4, Mef2c, and Tbx5 (GMT) or GMT plus Mesp1 and MyocD improved cardiac cell reprogramming from mouse or human fibroblasts	miR-133a directly represses Snai1 expression, which silences fibroblast signatures; a key molecular process during cardiac reprogramming	Mouse/human fibroblasts more efficiently reprogrammed into cardiomycete-like cells	[16]
β1AR signal transduction cascade	Adenylate cyclase Ⅵ and the catalytic subunit of the cAMP-dependent PKA are components of β1AR transduction cascade	miR-133 directly targets β1AR, Adenylate cyclase Ⅵ and PKA	TetON-miR-133 inducible transgenic mice, subjected to transaortic constriction, maintained cardiac performance with attenuated apoptosis and reduced fibrosis *via* elevated miR-133 expression	[17]
ROS, MDA, SOD and GPx	miR-133 produced a reduction of ROS and MDA levels, and an increase in SOD activity and GPx levels	Overexpression of miR-133, a recognized anti-apoptotic miRNA	*In vitro* rat cardiomyocytes	[18]
Caspase-9	miR-133 directly suppresses caspase-9 expression resulting in downregulation of downstream apoptotic pathways	Overexpression of miR-133	*In vitro* rat cardiomyocytes	[18]
Spred1	miR-1 directly targets Spred1	miR-1 is upregulated in hCMPCs during angiogenic differentiation	hCMPCs	[178]
miRNA-1 and miRNA-133a	miRNA-1 and miRNA-133a have antagonistic roles in the regulation of cardiac differentiation	Forced overexpression of miR-1 alone enhanced cardiac differentiation, in contrast overexpression of miR-133a reduced cardiac differentiation, compared to control cells	Pluripotent P19.CL6 stem cells Overexpression of both miRNAs promoted mesodermal commitment and decreased expression of neural differentiation markers	[179]
Cardiac muscle				
Induction of GATA6, Irx4/5, and Hand2	Cardiac myocytes show defective heart development, altered cardiac morphogenesis, channel activity, and cell cycling	miR-1-2$^{-/-}$ gene knockout	Cardiac myocytes with knockout of both miR-1-2 genes	[180]
mt-COX1 mRNA	3′-UTR of mt-COX1 mRNA bound by miR-181c and Ago1 factor	Overexpression of miR-181c significantly decreased mt-COX1 protein, but not mt-COX1 mRNA level	Overexpression of miR-181c increased mitochondrial respiration and reactive oxygen species in neonatal rat ventricular myocytes	[54]
mt-COX1 mRNA	*In vivo* elevation of miR-181c in rat heart, reduces levels of mt-COX1 protein	Results in reduced capacity for strenuous exercise and evidence of heart failure	Rat cardiac muscle	[55]
Carvedilol, a β-adrenergic blocker	Induces upregulation of miR-133	Cytoprotective effects against cardiomyocyte apoptosis	Rat cardiac tissue, *in vivo*	[18]
GLUT4, and SRF	Both miRs downregulate SRF and KLF15	Both miR-133a and miR-133b target KLF15	Mouse cardiac myocytes	[181]
GLUT4 expression	Both basal and insulin-stimulated glucose uptake are increased	KLF15	Mouse muscle cell lines	[182]
MEF2 transcription factor	MEF2 directly activates transcription of miR-1-2 and 133a-1 binding muscle-specific enhancer between the genes	Bicistronic primary transcript of miR-1-2 and 133a-1	Development of mammalian cardiac muscle	[9]
Myocardium tissue	Enriched in miR-1, miR-133b, miR-133a		Heart structures of rat, Beagle dog and cynomolgus monkey	[183]
Gelsolin	One common miR-133a isomiR targets gelsolin gene more efficiently than standard isomer; New second rat miR-1 gene	Many isomiRs were detected by deep sequencing at higher frequency than the canonical sequence in miRBase	miRNA/isomiR expression profiles in the left ventricular wall of rat heart	[184]
CTGF	CTGF downregulated by both miRs	Exogenous upregulation of miR-133b (and miR-30c)	Cultured cardiomyocytes and ventricular fibroblasts	[185]
MT1-MMP	miR-133a upregulated	miR-133a targets MT1-MMP	Human left ventricular fibroblasts	[186]

Injured and regenerating cardiac muscle				
SERCA2a	Akt/FoxO3A-dependent pathway Activated SERC2a reduces phosphorylation of FoxO3a, allowing entry to nucleus and activation of miR-1 expression	Downregulation of miR-1 expression in failing heart muscle	Failing mouse heart muscle	[187]
IGF-1	IGF-1 signalling and miR-1 co-regulate differentiation of myoblasts *via* a feedback loop	IGF-1 signalling down-regulates miR-1 by repression of FoxO3a; miR-1 down-regulates IGF-1	Mouse heart muscle during cardiac failure states	[25]
Bim and Bmf	Only miR-133a expression enhanced under *in vitro* oxidative stress	miR-133a targets proapoptotic genes Bim and Bmf	Rat adult CPCs miR-1 favors differentiation of CPCs, whereas	[188]
Bim and Bmf	CPCs overexpressing miR-133a improved cardiac function by reducing Bim and Bmf	CPCs overexpressing miR-133a improved cardiac function, increasing vascularization and cardiomyocyte proliferation, reduced fibrosis and hypertrophy	CPCs overexpressing miR-133a in rat myocardial infarction model	[188]
MT1-MMP activity increased in both. Ischemia and reperfusion regions	Interstitial miR-133a decreased with ischemia *in vitro* and *in vivo*; reperfusion returned to steady-state	Phosphorylated Smad2 increased within the ischemia-reperfusion region	Ischemia-reperfusion Yorkshire pigs (90 min ischemia/120 min reperfusion)	[186]
Cardiovascular disease				
CNN2	Strong upregulation of CNN2 expression	miR-133b downregulated; miR-133b directly targets CNN2	Pre-inflammatory events in diseased cardiac tissues	[65]
Circulating platelet derived microparticles	Elevated miR-133		Patients with stable and unstable coronary artery disease	[189]
Acute MI causes upregulation of circulating serum miRs	miR-1, -133a, -133b, and -499-5p were about 15- to 140-fold elevated over control		Acute STEMI patients and experimental mouse MI model	[190]
Circulating miRNAs in serum of cardiovascular disease patients	Released miR-1 and miR-133a are localized in exosomes, and are released by Ca(2+) stimulation	Levels of miR-1, miR-133a, reduced in infarcted mouse myocardium model heart	miR release indicates myocardial damage	[191]
LVM after valve replacement in aortic stenosis	microRNA-133a is a significant positive predictor of LVM normalisation	miR-133 is a key element of the reverse remodelling process	Patients following valve replacement	[192]
Circulating levels of miR-133a	Elevated miR-133a (11-fold)		Troponin-positive acute coronary syndrome patients	[193]
Circulating levels of miR-133a	Elevated miR-133a	Improved potential regression of Left Ventricular Hypertrophy after valve replacement	Patients with aortic stenosis surgery	[194]
Apelin treatment reduces elevated circulating miRs	Elevated miR-133a, miR-208 and miR-1 reduced	High-fat diet elevated miRs and increased left ventricular diastolic and systolic diameters, and wall thickness	Obesity-associated cardiac dysfunction in mouse model	[195]
NAC treatment	Expressed miR-1, miR-499, miR-133a, and miR-133b were strongly depressed in the diabetic cardiomyocytes	NAC restored expression of miR-499, miR-1, miR-133a, and miR-133b significantly in the myocardium	Diabetic rat hearts	[196]
Myocardial junctin elevated	miR-1 targets junctin	NAC reduces junction levels	Development of diabetic cardiomyopathy in rat hearts	[196]
CAD associated ischemic heart failure	miR-133 expression decreased with increased severity of heart failure		Patients with CAD	[197]
Runx2	miR-133a targets Runx2		Transition of VSMCs to osteoblast-like cells	[198]
Increased alkaline phosphatase activity, osteocalcin secretion and Runx2 expression	miR-133a was decreased during osteogenic differentiation		Transition of VSMCs to osteoblast-like cells	[198]
Circulating miR-133a and 208a levels	Cardiac muscle-enriched microRNAs (miR-133a, miR-208a) elevated		Patients with coronary artery disease	[199]
Hypertrophic cardiac muscle				
Cx43 increased	miR-1 targets Cx43	Downregulation of miR-1 mediates induction of pathologic cardiac hypertrophy	Hypertrophic rat cardiomyocytes *in vitro* and *in vivo*	[200]
Cx43 downregulated	miR-1 targets Cx43	Cx43 protein downregulated in miR-1 Tg mice compared to WT mice	Cardiac-specific miR-1 transgenic (Tg) mouse model	[201]

Twf1 upregulated	miR-1 targets Twf1	Strong downregulation of miR-1 in pathologic hypertrophic cardiac cells compared to normal, induces Twf1 expression	*In vivo* in hypertrophic mouse left ventricle; and *in vitro* in phenylephrine-induced hypertrophic cardiomyocytes	[202]
RhoA, Cdc42, Nelf-A/WHSC2	Increased levels of RhoA, Cdc42, Nelf-A/WHSC2	Reduction miR-133a	Hypertrophic cardiac muscle	[6]
Calcineurin, agonist of cardiac hypertrophy	Increased Calcineurin activity; Cyclosporin A inhibits calcineurin	Reduced miR-133a; Prevents miR-133 down-regulation	Hypertrophic cardiac muscle; Cardiac hypertrophy reduced	[203]
NFATc4	NFAFc4 targetted by miR-133a	miR-133a	Cardiomyocyte hypertrophic repression	[204]
Interdependent Calcineurin-NFAT and MEK1-ERK1/2 signalling pathways in cardiomyocytes	MEK1-ERK1/2 signalling augments NFAT and NFAF gene expression; Activated calcineurin activates NFAT, inducing cardiac hypertrophy	MEK1 is part of mitogen-activated protein kinase (MAPK) cascade; MEK1 activates ERK directly	Hypertrophic growth response of mouse cardiomyocytes	[205]
Innervating skeletal muscle				
Innervated skeletal muscle	MyoD, Myf5, Mrt4, nAChRα Each is strongly repressed	Myogenin expression	Mouse skeletal muscle	[50,51]
Denervated muscle (unstimulated)		Myogenin expression up-regulated MyoD, Myf5, Mrt4, nAChRα All strongly stimulated	Mouse skeletal muscle	[51]
Electrically stimulated - Denervated muscle	Myogenin, MyoD, Myf5, Mrt4, partly stimulated; nAChRα inhibited		Mouse skeletal muscle	[51]
HDAC4 SRF	miR-1 promotes myogenesis by targetting HDAC4	miR-133 enhances myoblast proliferation by targetting SRF	Skeletal muscle proliferation and differentiation in myoblast cultures	[7]
Neural activity effect on muscle (HDAC4 - MEF2 Axis)	Loss of neural input leads to concomitant nuclear accumulation of HDAC4	HDAC4 inhibits activation of muscle transcription factor MEF2; results in progressive muscle dysfunction	MEF-2 activity strongly inhibited in denervated mouse skeletal muscle and in ALS muscle	[49]
Innervation and formation of airway smooth muscle	Sonic hedgehog (Shh) /miR-206/ BDNF	Shh signalling blocks miR-206 expression, which in turn increases BDNF protein	Shh coordinates innervation and formation of airway smooth muscle	[206]
nAChR subunits (UNC-29 and UNC-63); retrograde signalling	Subunits UNC-29, UCR-63 and MEF2 downregulated	miR-1 upregulated	*C. elegans* muscle at the neuromuscular junction	[34]
MEF2	Hnrpu, Lsamp, MGC108776, MEF2, Npy, and Ppfibp2 downregulated	miR-206 upregulated	Rat skeletal muscle/re-innervating muscle	[43]
HDAC4	HDAC4 (miR-206 target, prospective miR-133b target) downregulated	miR-206/-133b upregulated (and miR-1/-133a downregulated)	Mouse fast twitch skeletal muscle/re-innervating muscle	[12]
Regenerating injured muscle				
Hnrpu and Npy downregulated Ptprd downregulated	miR-1 upregulated miR-133a upregulated	miR-1, -133a, downregulated 1 mo after denervation, then increased 2 × at 4 mo after re-innervation	Rat skeletal soleus muscle after sciatic nerve injury and subsequent re-innervation	[43]
Hnrpu, Lsamp, MGC108776, MEF2, Npy, and Ppfibp2 downregulated	3 × increase in miR-206 1 mo later, after reinnervation; elevated at least 4 mo	Predominant type Ⅱ fiber at 4 mo, after nerve re-innervation	Rat skeletal soleus muscle after sciatic nerve injury and subsequent re-innervation	[43]
PP2A B56a	PP2A B56a downregulated	133a upregulated	Canine heart failure model: myocytes	[207]
CaMKII-dependent hyperphosphorylation of RyR2	VF myocytes had increased reactive oxygen species and increased RyR oxidation	miR-1 upregulated	Canine post-myocardial infarction model	[208]
Collagen upregulated	TGF-b1 and TGFbRII: upregulated	miR-133a or miR-590: downregulated	Canine model of acute nicotine exposure. Atrial fibrosis *in vivo*; cultured canine atrial fibroblasts *in vitro*	[209]
miR-208 upregulated	miR-1 and miR-133a downregulated		Human MI compared to healthy adult hearts	[210]
Myogenic proteins, MyoD1, myogenin and Pax7	Induced expression of MyoD1, myogenin and Pax7 several days after miR injection	Exogenous injection of miR-1, -133 and -206 promotes myotube differentiation	Regenerating injured mouse skeletal muscle	[211]
Cyclin D1/ Sp1	Cyclin D1/ Sp1 downregulated	miR-1/133 upregulated	Regenerating rat skeletal muscle	[212]
PRP, source of pro-inflammatory cytokines	Stong upregulation of the mRNA of pro-inflammatory cytokines IL-1β and TGF-β1; stimulation of both inflammatory and myogenic pathways; elevated heat shock proteins and increased phosphorylation of αB-cristallin	Stimulated tissue recovery *via* increased myogenic regulators MyoD1, Myf5, Pax7, and IGF-1Eb (muscle isoform) together with SRF; acts *via* increased expression of miR-133a with reduced levels of apoptotic factors (NF-κB-p65 and caspase 3)	Regenerating flexor sublimis muscle of rats, 5 d after injury and treated with PRP	[66]

Muscle degeneration				
Pro-inflammatory cytokine TWEAK	TWEAK upregulated	miR-1-1, miR-1-2, miR-133a, miR-133b and miR-206 downregulated	Degenerating/wasting mouse skeletal muscle	[59]
HMOX1 mediated by codependent inhibition of c/EBPδ binding to myoD promoter	HMOX1 inhibits differentiation of myoblasts and modulates miRNA processing HMOX1 effects partially reversed by enforced expression of miR-133b and miR-206	Downregulation of miR-1, miR-133a, miR-133b, and miR-206. Downregulation of MyoD, myogenin and myosin, and disturbed formation of myotubes. Upregulation of SDF-1 and miR-146a	Degenerating/wasting mouse skeletal muscle	[60]
Dystrophic muscular disease				
Circulating serum microRNAs	miR-1, miR-133a, and miR-206 highly abundant in Mdx serum	miR-1, miR-133a, and miR-206 downregulated or modestly upregulated in muscle	Muscle tissue from patients with Duchenne muscular dystrophy (Mdx)	[213]
Laminin α2 chain deficiency	miR-1, miR-133a, and miR-206 are deregulated in laminin α2 chain-deficient muscle	Laminin α2 chain-deficient mouse	Congenital muscular dystrophy type 1A tissue	[214]
Dystrophic process advances from prominent inflammation with necrosis and regeneration to prominent fibrosis	Deficiency in calpain leads initially to accelerated myofiber formation followed by depletion of satellite cells	Pax7-positive SCs highest in the fibrotic patient group; correlated with down-regulation of miR-1, miR-133a, and miR-206	Muscle from Limb-girdle muscular dystrophy 2 type Ⅰ patients	[215]
Transgenic overexpression of miR-133a1 (in dystrophin point mutation Mdx mice)	Extensive overexpression in skeletal muscle, lesser increase in heart	Normal skeletal muscle and heart development	Mdx mice (model for human muscular dystrophy), extensor digitorum longus muscle	[216]
miR-206 located in nuclear in both normal and DM1 tissues by *in situ* hybridization	Only miR-206 showed an over-expression in majority of DM1 patients	No change in expression of profiled miRs, miR-1, miR-133 (miR-133a/-133b), miR-181 (miR-181a/-181b/-181c)	Skeletal muscle (vastus lateralis) of from patients with myotonic dystrophy type 1 (DM1)	[217]
FAPs facilitate myofiber regeneration	HDAC inhibitors can activate FAPs towards muscle regeneration	Inhibition of HDAC induces MyoD and BAF60C expression, which causes up-regulation of miR-1-2, miR-133, and miR-206 expression	Early stage disease dystrophic mouse muscles, regeneration of myofibres	[62]
TDP-43	TDP-43 interacts with miR-1/-206 isomers, but not miR-133 isomers	Depleted miR-1/-206 allow targets IGF-1 and HDAC4 to accumulate in ALS muscle	Mouse ALS model injured motor neurons and muscle	[33]
Inflammation response in muscle				
Inflammatory myopathies	Increased expression of TNFα	Associated with decreased expression of miR-1, miR-133a, and miR-133b	Inflammatory myopathies including dermatomyositis, polymyositis, and inclusion body myositis	[64]
hBSMCs sensitized with IL-13	Increased muscle RhoA	Reduction of muscle miR-133a	Sensitized human bronchial smooth muscle cells (hBSMCs)	[218]

IGF: Insulin-like growth factor; IGF-1R: IGF-1 receptor; MRFs: Muscle regulatory factors; PTB: Polypyrimidine tract-binding protein; Fstl1: Follistatin-like 1; Utrn: Utrophin; mTOR: Mechanistic target of rapamycin; pcRNA: Polycistronic RNAs; SRF: Serum response factor; Snai1: Snail family zinc finger-1; β1AR: β-adrenergic receptor; PKA: Protein kinase A; MDA: Malondialdehyde; Spred1: Sprouty-related EVH1 domain containing protein 1; mt-COX1: Mitochondrial cytochrome c oxidase subunit 1; SERCA2a: Sarcoplasmic reticulum calcium ATPase 2a; LVM: Left ventricular mass; NAC: N-acetylcysteine; CAD: Coronary artery disease; StAR: Steroidogenic acute regulatory protein; mES: Mouse embryonic stem; EBs: Endodermal bodies; SCs: Stem cells; CSCs: Cardiac stem cells; MI: Myocardial infarcted; hCMPCs: Human-derived cardiomyocyte progenitor cells; VSMCs: Vascular smooth muscle cells; CPCs: Cardiac progenitor cells; STEMI: ST-segment elevation MI.

(late-stage) differentiation of chondrocytes in growth cartilage[78]. This differentiation could be reversed by transfection and overexpression of miR-1 which repressed the expression of aggrecan, the major cartilaginous proteoglycan gene in human chondrocytic HCS-2/8 cells and normal chicken chondrocytes. Thus miR-1 is a major effector in early growth and cell proliferation, and its repression at late differentiation stages is important for maintaining cartilage integrity.

MYOMIRS AND IMMUNOLOGICAL RESPONSES

Several reports of myomiR involvement in specialized immunological processes have recently emerged. Stumpova *et al*[79] (2014) found that several miRNAs, including miR-133b, were strongly expressed during *in vitro* maturation of human tolerogenic dendritic cells induced by exogenous IL-10 and TGF-β in comparison to miRs expressed in IL-4-induced and IFN-γ activated dendritic cells. MiR-133b and -206 have been previously reported to be expressed during differentiation of immunocompetent mouse Th17 cells, with miR-133b/-206 cistron transcription occurring along with expression at the nearby *Il17a/f* gene locus[80]. This feature of T cell differentiation towards an IL-17-producing phenotype is shared between αβ and γδ T cells, where the specific co-regulation of miR-133b and miR-206 with the Il17a/f locus extends to human Th17 cells, suggesting presence of miR-133b/-206 in T cells may be biomarkers for Th17-type immuno-reactions.

Table 2 Roles and targets of the myomiRs, miR-1, -206, -133a, -133b in other precursor cells and tissues

Factor(s)	Regulation	Regulator	Tissue/cell	Ref.
Nerve tissues				
Pitx3	Pitx3 downregulated	miR-133b	Mammalian midbrain DNs	[73]
Exosome-mediated transfer of miR-133b from MSC to brain astrocytes	miR-133b transfer from multipotent mesenchymal stromal cells to neural cells	miR-133b upregulated	Mouse MSCs to neural cells	[47]
Ctgf and RhoA	Ctgf and RhoA downregulated	miR-133b upregulated	Multipotent MSCs/Rat brain parenchymal cells	[72]
miR-133b null mice: Striatum dopamine levels unchanged, Pitx3 expression unaffected; motor coordination unaltered	miR-133b has no significant role on mDA neuron development and maintenance *in vivo*	Normal numbers of mDA neurons during development and aging of miR-133b null mice	Mouse mDA neuron development in $^{-/-}$miR-133b mutant mice	[45]
Acute or chronic morphine administration, or morphine withdrawal	miR-133b levels not affected		Rat VTA/ nucleus accumbens shell	[219]
GPM6A, a neuronal glycoprotein	microRNA-133b upregulation	Reduction in gmp6a at mRNA and protein level. Cell filopodium density was reduced	Hippocampus and prefrontal cortex of neonatal male rats stressed when in utero	[220]
Tac1 gene (neurotransmitter substance P)	Tac1 downregulated	miR-206 upregulated	MSCs-derived neural cells	[221]
Ketamine (antidepressive) administration	BDNF, a direct target gene of miR-206, was upregulated	miR-206 was downregulated by ketamine	Rat hippocampus tissue	[222]
Adipogenic tissues				
IGF-1 and IGF-1R	IGF-1 signalling and miR-133b co-regulate ADSC differentiation *via* a feedback loop	miR-133b downregulation of Pitx3; IGF-1 upregulates miR-133b; miR-133b downregulates IGF-1R	Adipose tissue-derived stem cell differentiation into neuron-like cells	[71]
Pdrm16	miR-133a directly targets Prdm16.	Downregulation of miR-133 resultsin differentiation of pre-adipocyte precursors into BAT	Mouse adipocyte differentiation to BAT	[74]
Pdrm16	miR-133 directly targets Prdm16	Downregulation of miR-133 resulted in differentiation of pre-adipocyte precursors into BAT	Mouse primary brown adipocyte (and myogenic) progenitor cells - differentiate into BAT or SAT	[75]
Pdrm16	miR-133 targets Prdm16 controlling brown adipose determination in skeletal muscle satellite cells	miR-133 downregulates Prdm16	Adult mouse skeletal muscle stem cells (satellite cells) differentiate into BAT	[76]
HDAC4 downregulation directs SCs towards adipocyte differentiation	Brown adipose master regulator Prdm16 is upregulated, while its inhibitor miR-133 is also downregulated	HDAC4 downregulated in SCs differentiating into adipocyte progenitor cells	Myogenic satellite SCs	[175]
GLUT4 expression	Both basal and insulin-stimulated glucose uptake are increased	KLF15	Mouse 3T3-L1 preadipocytes differentiating into adipocytes	[182]
Intrinsic insulin resistance	Elevated miR-133b	Undefined role	Adipose tissue of women with PCOS	[223]
Upregulation of LIM homeobox 8 and Zic family member 1 and downregulation of Homeobox C8 and Homeobox C9	Undefined relation of upregulated miR-206, miR-133b	Undefined relation with parallel upregulation of brite/beige markers, TBX1 and TMEM26	Human BAT from the supraclavicular region	[224]
Obesity development	Downregulation of miR-133b, miR-1	Undefined role	Adipose tissue from obese male C57BLJ6 mice	[225]
LXRα regulation of lipogenic genes	miR-1/miR-206 represses LXRα expression at both mRNA and protein levels	miR-1/miR-206-induces a decrease in lipogenic gene levels and lipid droplet accumulation	Mouse hepatocytes	[226]
Osteogenic tissues				
Development of bone on organic or inorganic substrates		miR-133 differentially expressed in osteoblasts grown on different substrates	Osteoblast	[227]
Runx2	miR-133 directly down-regulates Runx2	miR-133 up-regulated	Osteogenic differentiation from C2C12 mesenchymal cells	[228]
HDAC4	HDAC4 downregulates Runx2	miR-1 targets HDAC4, increasing Runx2 activity	Chondrocyte proliferation in cartilage growth plate	[77]
Aggrecan	miR-1 promotes late-stage differentiation of growing cartilage cells	miR-1 targets Aggrecan gene expression	Chicken chondrocytes and human HCS-2/8 cells	[78]
Alveolar cells				
VAMP2/ lung surfactant secretion	miR-206 targets VAMP-2	miR-206 overexpression decreased lung surfactant secretion	Lung alveolar type Ⅱ cells	[229]

Hormonal regulation				
L-thyroxine	miR-206/miR-133b downregulated	L-thyroxine treatment	L-thyroxine treated hypothroidic skeletal muscle from thyroidectomized patients	[230]
	miR-206/miR-133b upregulated	-	Hypothroidic human skeletal muscle	
Thyroid hormone/TEAD1	Thyroid hormone inhibits the slow muscle phenotype by upregulation of miR-133a1 which downregulates TEAD1	miR-133a1 is enriched in fast-twitch muscle and regulates slow-to-fast muscle fiber type conversion	Mouse muscle	[231]
Thyroid hormone/miR-133a1 TEAD1	myosin heavy chain I expression downregulated	TH indirectly downregulates myosin heavy chain I *via* miR-133a/TEAD1	Mouse muscle	[232]
L-thyroxine	pre-miR-206 and pre-mir-133b downregulated	L-thyroxine	L-thyroxine treated hypothyroidic mouse liver;	[232]
	50-500x increase expression of miR-1/-133a and miR-206/-133b	-	Hypothyroidic mouse liver	
Reduced insulin-mediated glucose uptake in cardiomycetes	Downregulation KLF15, which downregulates GLUT4	Forced overexpression of miR-133a and miR-133b	Rat cardiac myocytes	[181]
Cardiac myocyte glucose metabolism	Upregulation KLF15, which upregulates GLUT4	Silencing endogenous miR-133	Rat cardiac myocytes	[181]
Metabolic control of glucose uptake by GLUT4 transporter	Downregulates KLF15, which results in downregulation of GLUT4 levels	Chronic heart failure has depressed miR-133a and -133b levels	Rat cardiac myocytes during chronic heart failure and cardiac hyperthrophy	[181]
Atrial natriuretic factor expression upregulation	Enhanced at LVH and dramatically increased at CHF stage	Both miR-133a and miR-133b downregulated at CHF stage	LVH and CHF in salt-sensitive Dahl rats	[181]
Estrogen	Estrogen replacement strongly decreased IGF-1 protein level in muscles at 1 wk		Ovariectomized rat skeletal muscle	[233]
Multiple targets	miR-133a upregulated in BTBR mice		Pancreatic islets, adipose tissue, and liver from diabetes-resistant (B6) and diabetes-susceptible (BTBR) mice	[234]
Augmentation of adipocyte differentiation by norepinephrine does not alter myomiR levels	miRNAs miR-1, miR-133a and miR-206 specifically expressed both in brown pre- and mature adipocytes	miRNAs miR-1, miR-133a and miR-206 were absent from white adipocytes	Mouse brown adipocytes	[235]
Foxl2	miR-133b targets Foxl2; miR-133b inhibits Foxl2 binding to StAR and CYP19A1 promoter sequences	Foxl2 regulates StAR and CYP19A1 transcriptionally	Estradiol production in ovarian granulosa cells	[236]
Exosome release and cell to cell transfer				
Exosome-mediated transfer of miR-133b from MSCs to brain astrocytes	miR-133b transfer from multipotent mesenchymal stromal cells to neural cells	miR-133b upregulated	Mouse multipotent MSCs to neural cells	[47]
Cell to cell transfer of exosome-enriched extracellular particles	mir-133b promotes neural plasticity and recovery of function after stroke induced damage	miR-133b upregulated	Rat multipotent MSCs *via* transfer of exosome-enriched extracellular particles	[72]
Transplanted stem cells				
MSCs expressing miR-1	Upregulated miR-1	Increased rate of recovery, enhanced survival of transplanted MSCs and cardiomyogenic differentiation	Experimental ligation of the mouse left coronary artery to model myocardial infarction	[237]
Knockdown of Hes-1, member of Notch pathway	Upregulated miR-1 promotes the differentiation of MSCs into cardiac lineage	Role in survival of transplanted MSCs and cardiomyogenic differentiation	Mouse MSCs	[238]
Notch signalling and cardiomyocyte markers, Nkx2.5, GATA-4, cTnT, and Cx43	MSCs expressing exogenous miR-1		Mouse MSCs	[238]
Tissue inflammation				
Selective release of miRs during inflammation into serum	miR-133 selectively released		Review	[239]
Inflammation and cancer	MicroRNA, free radical, cytokine and p53 pathways		Review	[240]
Immunological switch which shapes tissue responses	TWEAK/Fn14 pathway		Review	[241]
Tumor biology	HMOX1		Review	[242]
GM-CSF	Direct supression of GM-CSF expression by miR-133	Elevated expression of miR-133a/-133b during oxidative stress	Mouse alveolar epithelial cells during oxidative stress	[82]

PI3K/Akt and IGF-1 pathways	Activation of PI3K/Akt and IGF-1 pathway activities	Downregulation of miR-133a (and other miRs) by AOM/DSS induced chronic inflammation	Mouse model: AOM/DSS-induced colitis-associated gastro-intestinal cancer	[83]
CTGF, SMA, and COL1A1	Increased expression of CTGF, SMA and COL1A1, which are miR-133b targets	Strong downregulation of miR-133b (and other miRs)	TGF-β treated rabbit corneal fibroblasts; Recovering mouse cornea after laser ablation,	[70]
IL-10 and TGF-β	Exogenous IL-10 and TGF-β induces miR-133b expression	Upregulation of miR-133b	Human tolerogenic dendritic cells during maturation	[79]
IL-17-producing T-cells	Upregulation of Il17a/f gene expression	miR-133b/-206 cistron transcription occurs along with nearby Il17a/f gene expression	Immunocompetent mouse Th17 cells	[80]
NLRP3 inflammasome which processes IL-1β by caspase-1 cleavage	miR-133a-1 suppresses activation of inflammasomes *via* suppression of expression of mitochondrial UCP2	miR-133a-1 overexpression in cells increases caspase-1 p10 and IL-1β p17 cleavage,	Differentiated mouse THP1 cells	[81]
Concanavalin A-induced fulminant hepatitis		miR-133a is the most strongly differentially upregulated miR	Mouse liver following ConA injection	[243]
Infection/immune response to influenza virus (H1N2)	miR-206 expression		Experimental influenza infection in pig lung	[244]
HIF-1α, and its regulator Four-and-a-half LIM (Lin-11, Isl-1 and Mec-3) domain 1 (Fhl-1)	Downregulation of miR-206 and upregulated HIF-1α and Fhl-1 in hypoxic lung tissue and PASMCs	miR-206 targets HIF-1α directly. Hypoxia-induced down-regulation of miR-206 promotes PH in PASMCs	Hypoxia-induced PH in hypoxic rat model in cultured hypoxic PASMCs	[245]
miR-206/NR4A2/NFKB1; Indirectly: inflammatory cytokines (IL6, IL1B, CCL5)	NFKB1 stimulates inflammatory cytokines (IL6, IL1B, CCL5)	Liposaccharides induce miR-206 expression which targets NR4A2 downregulation, which in turn allows upregulation of NFKB1 activity	Astrocyte-associated inflammation during recovery from chronic central nervous system injury	[246]
Cellular factors influencing myomir expression/activity				
miR-1/miR-133a				
Skeletal muscle				
Positive regulator	**Negative regulator**	**Regulated target miR**	**Tissue/cell**	**Ref.**
Myogenin, MyoD		Upregulates miR-1-1 and miR-133a-2 Upregulates miR-1-2 and miR-133a-1	Primary human myoblasts; C2C12 cells	[11]
SRF, MyoD and MEF2		Upregulates miR-1-2	Muscle somites	[30]
MEF2		Upregulates miR-1 and miR-133a	Skeletal muscle	[9]
KSRP (part of Drosha and Dicer complexes)	miR-206 binds 3'-UTR of KSRP and inhibits its expression	KSRP upregulates miR-1 expression	Skeletal muscle	[35,37]
RNA-binding protein LIN28		LIN28 upregulates miR-1 expression; LIN28 promotes pre-miR-1 uridylation by ZCCHC11 (TUT4)	Cardiac muscle of patients with muscular dystrophy	[36]
	MBNL1	MBNL1 downregulates miR-1 expression; MBNL1 binds to UGC motif in the loop of pre-miR-1 and competes for the binding of LIN28; MBNL1 blocks DICER processing of pre-miR-1	Cardiac muscle of patients with muscular dystrophy	[36]
CX43 and CACNA1C calcium channel	CX43 and CACNA1C both increased in both DM1-/DM2-affected hearts, contributing to the cardiac dysfunctions	CX43 and CACNA1C are direct targets of miR-1 repression	Cardiac muscle of patients with muscular dystrophy; CACNA1C and CX43 encode the main calcium- and gap-junction channels in heart	[36]
Utrophin A	miR-206 and KSRP are negative regulators of utrophin A	Overexpression of miR-206 promotes the upregulation of utrophin A, *via* the downregulation of KSRP	Normal and dystrophic muscle cells; miR-206 can switch between (1) direct repression of utrophin A expression, and (2) activation of its expression by decreasing KSRP, allowing close regulation	[37]
	Myostatin	Downregulates miR-1, miR-133a, miR-133b, miR-206	Mouse (35 d) pectoralis skeletal muscle	[29]
	SRF	Downregulates miRs-133a	Skeletal muscle	[1,3]
Prmt5 and Prmt4		Upregulates myomiR expression during differentiation	Mouse skeletal muscle	[247]
Smooth muscle				
Sp-1 transcription factor	pERK1/2	Upregulates miR-133(a)	VSMCs	[248]

Brg1		Upregulates miR-133 (ChIP complex with SRF)	Smooth muscle	[249]
Cardiac muscle				
GATA4, Nkx2.5, Myocardin, SRF		Upregulates miR-1 and miR-133a	Differentiating cardiac muscle	[5]
SRF plus Myocardin		Upregulates miR-1-1 and miR-1-2	Cardiomycetes	[30]
	Calcineurin	Downregulates miR-133a	Hypertrophic cardiac muscle	[203]
miR-206/ miR-133b				
Skeletal muscle				
Mrf5		Upregulates miR-1, miR-206	Skeletal muscle	[171]
Myogenin, MyoD		Upregulates miR-206	Primary human myoblasts; C2C12 cells	[11]
MyoD		Upregulates linc MD1 (encodes miR-133b)	Differentiating myoblasts	[11, 38]
		Binds to (E-box) enhancer of miR-206, miR-133b	skeletal muscle (mouse)	[12,40]
		Upregulates miR-206/miR-133b	Differentiated human foetal skeletal muscle cells	[250]
	FGF2 allows upregulation of Sp1/Cyclin D1	Downregulates p38-mediated miR-1/133 expression	Regenerating rat skeletal muscle	[212]
	Myostatin	Downregulates miR-133a, mir-133b, miR-1, and miR-206	Mouse (35 d) pectoralis skeletal muscle	[29]
	TWEAK downregulates myoD and MEF2c	Downregulates miR-1-1 and miR-133	Degenerating/wasting skeletal muscle	[59]
	HMOX1 downregulates MyoD and myogenin	Downregulates all myomiRs	Inflamed skeletal muscle	[60]
L-Thyroxine treatment		Downregulation of pri-miR-206 and pri-miR-133b No effect on miR-1/miR-133a pairs	Human skeletal muscle	[230]
Smooth muscle				
p-ERK	Activated extracellular signal-regulated kinase p-ERK inversely correlated with VSMC growth	Downregulates miR-133 expression	VSMCs	[248]
Other tissues				
Myogenin		Binds miR-206 enhancer (ChIP)	Fibroblast cell line:	[40]
IGF-I signalling		Upregulates miR-133b	Mouse Adipose derived stem cells	[71]
L-Thyroxine deficiency	Upregulated Col5a3	Strong upregulation of miR-133a and -133b	Hypothyroid mouse liver	[232]
	Downregulated Slc17a8, Gp2, Phlda1, Klk1d3, Klk1 and Dmbt1 Upregulated Vldlr and Akr1c19, and downregulated Upp2, Gdp2, Mup1, Nrp1, and Serpini2	Strong upregulation of miRs -1, -206		
L-Thyroxine treatment	Pre-miR-206 and Pre-miR-133b down-regulated	Upregulation of Gdp2 andMup1	Hypothyroid mouse liver *in vivo*, and in vitro mouse hepatocyte AML12 cells	[232]
PA2G4, mps1, cdc37, cx43, cldn5; cx43 is a miR-133 target	Upregulation of cell cycle factors mps1, cdc37, and PA2G4, and cell junction components cx43 and cldn5	Suppression of miR-133a1 stimulates cardiac cell proliferation	Regeneration of damaged Zebrafish cardiac muscle, associated with reduced miR-133a1	[167]
Fgf	Upregulated Fgf	Downregulates miR-133	Zebrafish regenerating fin blastema	[67]
SHP (nuclear receptor)	Downregulation of miR-206 in nuclear receptor SHP(-/-) mice		SHP(-/-) mice strain, mouse liver	[251]
AP1 transcription factor complex	AP1 induced miR-206 promoter transactivity and expression; this is repressed by YY1	ChIP analysis shows physical association of AP1 (c-Jun) and YY1 with miR-206 promoter	SHP(-/-) nuclear receptor mice strain, mouse liver	[251]
NR3B3	YY1 promoter transactivated by ERRgamma; this inhibited by SHP (NROB2)	Nuclear receptor ERRgamma (NR3B3) binding site on the YY1 promoter	Mouse liver	[251]
Novel cascade "dual inhibitory" mechanism governing miR-206 gene transcription by SHP	(1) SHP inhibition of ERRgamma leads to decreased YY1 expression	(2) Derepression of YY1 on AP1 activity, leads to activation of miR-206	Mouse liver	[251]
Il17a/f locus	miR-133b and miR-206 expression	Coregulated with IL-17 production	αβ and γδ T cells	[80]

IGF: Insulin-like growth factor; MRFs: Muscle regulatory factors; PTB: Polypyrimidine tract-binding protein; Fstl1: Follistatin-like 1; Utrn: Utrophin; mTOR: Mechanistic target of rapamycin; pcRNA: Polycistronic RNAs; SRF: Serum response factor; Snai1: Snail family zinc finger-1; β1AR: β-adrenergic receptor; PKA: Protein kinase A; MDA: Malondialdehyde; Spred1: Sprouty-related EVH1 domain containing protein 1; mt-COX1: Mitochondrial cytochrome C oxidase subunit 1; SERCA2a: Sarcoplasmic reticulum calcium ATPase 2a; LVM: Left ventricular mass; NAC: N-acetylcysteine; CAD: Coronary artery disease; StAR: Steroidogenic acute regulatory protein; VTA: Ventral tegmental area; BAT: Brown adipose tissue; SCs: Stem cells; PCOS: Polycystic ovary syndrome; LVH: Left cardiac ventricular hypertrophy; CHF: Chronic heart failure; DNs: Dopaminergic neurons; mDA: Midbrain dopaminergic; AOM: Azoxymethane; DSS: Dextran sulfate sodium; PH: Pulmonary hypertension; PASMCs: Pulmonary artery smooth muscle cells.

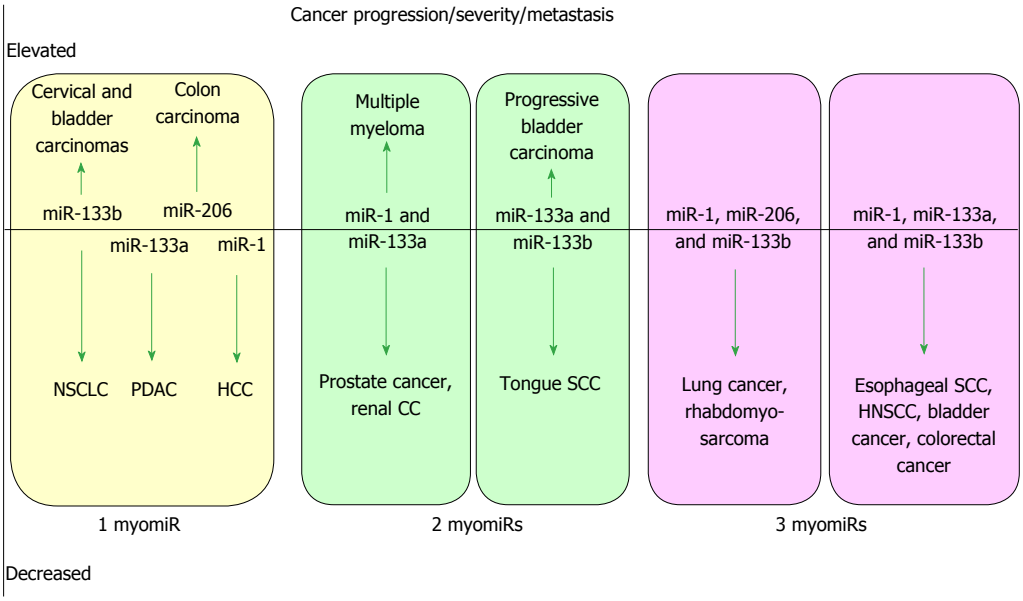

Figure 3 Roles of the myomiRs during cancer progression. Altered expression of myomiRs is associated with cancer progression and metastasis. Note that the changed level of myomiR typically contributes to cancer progression. Reduced levels of a single myomiR are associated with PDAC[103], NSCLC[105] and HCC[98], whilst an elevated single miR is associated with cervical carcinoma[121] and bladder cancer (TCC)[122]. Increased expression of miR-1/-133a is associated with t(14;16) translocation multiple myeloma[152], whilst reduced expression is associated with prostate cancer[102] and RCC[138], respectively. Reduced expression of other myomiR combinations is also associated with TSCC[111], ESCC[132], HNSCC[114,143], GIST[281], bladder cancer (TCC)[93], lung cancer[85,99], colorectal cancer[86,87] and rhabdomyosarcoma[88].

Bandyopadhyay *et al*[81] (2014) examined the effect of overexpression or suppression of miR-133a-1 in differentiated mouse THP1 cells which express the NLRP3 inflammasome, finding that miR-133a-1 overexpression suppresses expression of mitochondrial UCP2, resulting in increased caspase-1 p10 activity which subsequently causes IL-1β p17 cleavage. SiRNA silencing of UCP2 expression enhanced H_2O_2 stimulated inflammasome activity, and conversely, overexpression of UCP2 decreased the inflammasome activation, suggesting that the mechanism by which miR-133a-1 suppresses inflammasome activation involves the direct targetting of UCP2.

Further, the pulmonary cytokine GM-CSF is normally produced in lung alveolar epithelial cells (AECs) during a defense response. GM-CSF expression is suppressed by oxidative stress *via* altered mRNA turnover[82], in which miR-133a and -133b are upregulated in primary AECs. *In vitro* cell experiments confirmed that miR-133a and miR-133b bind the 3'-UTR of GM-CSF and suppress its expression, and that their inhibition can reverse oxygen-induced suppression of GM-CSF expression, suggesting that miR-133 isomers are important regulators of GM-CSF expression in AECs during oxidative stress. Studies of mouse colorectal epithelial cells involving the azoxymethane/dextran sulfate-induced mouse model of colitis-associated cancer found that the induced chronic colorectal epithelial cell inflammation downregulates miR-133a and other miRs associated with the modulation of PI3K/Akt and IGF-1 associated pathways, particularly during the earlier inflammatory stages[83].

Overall, whilst myomiRs miR-1-2, miR-133 and miR-206 have central roles muscle regeneration and (neuromuscular) repair, and in the regulation of aspects of inflammation and immunological responses during regeneration of injured and diseased muscles, miR-133a and miR-133b also appear to be involved in other regulatory processes affecting, repair, inflammation and immunological responses a number of other non-muscle cells/tissues, suggesting that these may involve common signalling pathways in a range of tissues in which myomiR play a regulatory role on the levels of signalling pathway components.

MYOMIRS AND CANCER

This review also examines the numerous cancers with prominent dysregulation of one or more of the canonical myomiRs, and the molecular events influenced by them. We focus on the deregulated myomiRs and their key target genes (up- or down-regulated) which have demonstrable effects *in vitro* on cell migration, proliferation or apoptosis, or those which are *in vivo* risk factors for cancer progression or patient survival. Although cancers characteristically have changed expression of large numbers of different protein genes and numerous different miRs which may contribute to the cancer pathology, these other deregulated genes and factors are not discussed except in relation with the myomiRs or their known targets. Table 3 lists the deregulated myomiRs reported in many different cancers. In addition, Tables 4 and 5 list targets and pathways influenced by

Table 3 The deregulated expression of the canonical myomiRs in different cancers

MiR-1	MiR-206	MiR-133a	MiR-133b	Cancer type	Ref.
		+	+	Progressive bladder cancer (TCC)	[122]
-		-		Bladder cancer (TCC)	[93,156]
-		-	-	Bladder cancer (TCC)	[92,144]
-	-	-	-	Bladder cancer	[127][1]
-	-	-	-	Bladder cancer	[128][1]
-		-	-	Muscle-invasive bladder cancer	[92]
	-			Proliferating breast cancer	[108]
	-			ERα-positive breast cancer	[109]
-			-	Breast cancer	[95]
			+	Progressive cervical carcinoma	[117,121]
-	-			Chordoma	[90]
	+			Colon cancer	[116]
-				Colon cancer	[101]
		-		CRC	[104,136]
			-	CRC	[86,87]
			+/-	Liver metastasis compared to primary CRC	[118]
-			-	Colon cancer	[95]
		-	-	Progressive GIST	[281]
		-		HNSCC	[143]
			-	HNSCC	[114]
	-			EEC	[110]
		-		ESCC	[132]
-		-	-	ESCC	[94]
	-			Laryngeal SCC cells	[113]
-		-		MSSCC	[137]
		-		TSCC	[111,112]
-				HCC	[98]
+			+	Liver cancer	[95]
-				Lung cancers: (NSCLC, adenocarcinomas, lung SCC, large cell carcinoma, and bronchoalveolar cell carcinoma)	[100]
	-			High metastasis lung tumors	[107]
		-		Lung SCC tissue; lung-SCC cell lines	[115]
			-	NSCLC	[85,105]
-	-			Lung adenocarcinomas; NSCLC cells	[99]
		-	-	Lung carcinomas	[85,115,131]
-			-	Lung cancer	[95]
-			-	Lymphoma	[95]
		+		AML	[120,151]
		+		Multiple myeloma	[152]
			+	Progressive prostate cancer	[123]
-	(-)	-		Prostate cancer	[102]
-			-	Prostate cancer	[95]
-			-	Recurrent prostate cancer compared to non-recurrent cancer	[96]
		-	-	Hormone-insensitive prostate cancer cells	[102]
-		-	-	Osteosarcoma	[91]
-			-	Ovarian cancer	[95]
		-		PDAC	[103]
		-		RCC	[138]
-	-			Rhabdomyosarcoma	[88,89]
-			-	Testicular cancer	[95]

[1]DS: Deep sequencing; TCC: Transitional cell carcinoma; CRC: Colorectal cancer; GIST: Gastrointestinal stromal tumor; HNSCC: Head and neck squamous cell carcinoma; EEC: ERα-positive endometrioid adenocarcinoma; ESCC: Esophageal squamous cell carcinoma; MSSCC: Maxillary sinus squamous cell carcinoma; TSCC: Tongue squamous cell carcinoma; HCC: Hepatocellular carcinoma; NSCLC: Non-small-cell lung cancer; AML: Acute myeloid leukaemia; PDAC: Pancreatic ductal adenocarcinoma; RCC: Renal cell carcinoma.

downregulated and upregulated myomiRs respectively, and Table 6 lists validated myomiR targets related to enhanced cancer progression.

An excellent review by Nohata *et al*[84] (2012) reported changes in the expression of the miR-1/-133a and miR-206/-133b cistron clusters in numerous cancers, typically finding reduced expression of different combinations of myomiRs, such as in lung cancer[85], colorectal cancer[86,87], rhabdomyosarcoma[88,89], chordoma[90] osteosarcoma[91], muscle-invasive bladder cancer[92], bladder cancer (transitional cell carcinoma) (TCC)[93], ESCC[94], breast cancer[95] and prostate cancer[95-97]. In different cancers (Figure 3) deregulation typically involves downregulation of one or more myomiR isomers, indicating they normally function as tumor suppressors in the tissues, limiting

Table 4 Targets and pathways influenced by the downregulated myomiRs in different cancers

Downregulated miR-1				
miR-1 downregulation influences multiple cancer-related pathway processes, and promotes cell proliferation and motility	Epigenetic promoter hypermethylation reduces miR-1/-133a expression in (a subset of) human prostate tumors	Reduced miR-1, miR-133a (and miR-206)	Human prostate tumors	[102]
Actin filament network-associated genes: FN1, LASP1, XPO6, CLCN3 and G6PD; Cell cycle and DNA damage control genes: BRCA1, CHK1, MCM7; Histone acetylation: HDAC4; Oncogenes: NOTCH3 and PTMA	miR-1 downregulation associated with upregulation of multiple cancer-related pathway processes	Reduced miR-1; Exogenous introduction of miR-1 or miR-206 caused similar inhibition of various cancer-related pathway genes	Human prostate cell lines, LNCaP, 22Rv1, PC-3 and RWPE-1	[102]
HSPB1	HSPB1 restores oncogenic pathways in prostate cancer cells	Downregulates miR-1 expression	Progressive prostate cancer PCa cells	[252]
XPO6 and TWF1 (PTK9)	Inverse expression between miR-1, XPO6 and TWF1 proteins in prostate cancer cell lines	Downregulated miR-1 expression	Prostate cancer cell cultures	[253]
CCND2, CXCR4, and SDF-1α	Inverse expression between miR-1 and CXCR4 and SDF-1α protein levels in thyroid carcinomas	Strongly downregulated miR-1 expression in thyroid adenomas and carcinomas	Thyroid adenomas and carcinomas	[254]
MET	MET upregulated	Reduced miR-1	Colon cancer	[101]
		Reduced miR-1, -133b	Colon cancer	[87]
MET, Pim-1 (Ser/Thr kinase), FoxP1 and HDAC4	miR-1 downregulated, miR-1 targets MET, Pim-1, and may regulate FoxP1 and HDAC4	MET, Pim-1, FoxP1 and HDAC4 are often upregulated in lung cancer	NSCLC tissue and A549 cell line	[100]
Fibronectin1	Fibronectin1 upregulated	miR-1 downregulated	Laryngeal SCC Hep2 cells	[255]
Met, Twf1 and Ets1 and Bag4	Met, Twf1 and Ets1 and Bag4 activities upregulated	miR-1 downregulated	Mouse cutaneous squamous cell carcinomas	[256]
Mediator complex subunit 1 (Med1) and 31 (Med31)	Med1 and Med31 activation result in increased Met activity	Reduced miR-1; miR-1 targets Med 1 and Med 31	Osteosarcoma	[257]
NOTCH3 upregulates Asef expression, activating the Asef promoter, enhancing cell migration	NOTCH3 upregulated	Reduced miR-1; miR-1 targets NOTCH3	Colorectal tumor cells	[258]
Overexpression of PIK3CA correlates with low miR-1 expression in NSCLC tissues	71% of NSCLC samples had high PIK3CA expression	69% of NSCLC samples had low miR-1 expression	Predictors of lymph node metastasis in NSCLC tissues	[259]
SLUG expression downregulated by miR-1	Transcriptional repressor of E-cadherin, or an inducer of epithelial-to-mesenchymal transition	Overexpression of miR-1 induces morphological change from a mesenchymal to an epithelial character	NSCLC A549 cell line	[260]
SLUG expression high in chordoma tissue	miR-1 inhibited cell proliferation both time- and dose-dependently in chordoma	Transfection of MiR-1 inhibited Slug expression	mR-1 transfected chordoma cells Slug overexpressed in advanced chordoma tissues and chordoma cells	[261]
MET expression high in chordoma tissue	miR-1 downregulated 97% of chordoma samples	MiR-1 directly targets MET	Decreasing miR-1 expression levels correlated with severity of clinical prognosis	[262]
SRSF9/SRp30c	Exogenous upregulation of miR-1 expression	Novel apoptosis pathway involving SRSF9/SRp30c mediates tumor suppression	Bladder cancer (TCC) cells	[263]
ANXA2 is essential for glioblastoma growth and invasion	ANXA2 is highly abundant protein in glioblastoma-derived extracellular vesicles	miR-1 directly targets ANXA2; Reduced miR-1 in glioblastoma	Human Glioblastoma cells; miR-1 orchestrates glioblastoma extracellular vesicle function	[264]
EDN1	miR-1 downregulated in gastric cancer	miR-1 causes ET-1 silencing in gastric cancer cell lines	Gastric cancer tissue compared with adjacent normal tissue	[265]
EDN1	Elevated expression of EDN1 and reduced miR-1 level	miR-1 directly targets EDN1	Human liver cancer tissues	[266, 267]
Overexpressed EDN1	Enhanced *in vitro* cell proliferation and cell migration. Upregulation of several cell cycle/proliferation- and migration-specific genes	Upregulated UPR pathway mediators, spliced XBP1, ATF6, IRE1, and PERK at both RNA and protein levels	293T cells	[267]
AKT inhibitor diminished the unfolded protein response and eliminated EDN1-induced cell migration	EDN1 effects act *via* activation of the AKT pathway	Results to enhance the UPR and subsequently activate the expression of downstream genes	293T cells	[267]

Edn1	Induced steatosis, fibrosis, glycogen accumulation, bile duct dilation, hyperplasia, and HCC	Liver-specific edn1 expression	Transgenic Zebrafish liver	[267]
API5	API5 expression upregulated thus inhibiting apoptosis	miR-1 expression downregulated	Human liver cancer tissues	[268]
	Apoptosis activated, API5 reduced	Overexpression of miR-1	HepG2 liver cancer cells	
Phosphorylation of ERK and AKT; LASP1	Overexpression of miR-1 inhibits phosphorylation of ERK and AKT and reverses EMT process *via* inhibition of MAPK and PI3K/AKT pathways	MAPK and PI3K/AKT pathways	Transgenic miR-1 expressing CRC cell lines	[269]
LASP1 expression upregulated	Upregulated LASP1 stimulates EMT resulting in cell proliferation and migration	miR-1 downregulated	Colorectal tumor tissue	[269]
PIK3CA	Increased expression of PIK3CA	Downregulated miR-1 expression in lung cancer	NSCLC tissue with poor patient prognosis	[259]
PIK3CA indirectly regulating pAKT and survivin proteins	Overexpressed miR-1 downregulated PIK3CA causing reduced pAKT and survivin proteins	Exogenously overexpressed miR-1 targets PIK3CA directly.	NSCLC A549 cell line	[270]
Signalling pathways such as TGF-β, ErbB3, WNT and VEGFA, and cell motility or adhesion	Ectopic expression of miR-1 and miR-145 downregulates VEGFA and AXL, respectively	Highly downregulated expression of miR-1, miR-133, miR-143 and miR-145 in gall bladder cancer	Gall bladder tumor samples and GBC NOZ cell line	[271]
lncRNA UCA1	Lnc RNA UCA1 upregulated in bladder cancer (TCC); Inverse relationship between miR-1 and lnc UCA1	Downregulated miR-1 expression in bladder cancer (TCC); miR-1 targets lnc RNA UCA1 for downregulation	Human bladder cancer (TCC) tissue	[156]
Downregulated miR-133a				
Moesin	Moesin upregulated	Reduced miR-133a	HNSCC	[143]
ARPC5	ARPC5 upregulated	Reduced miR-133a	HNSCC	[272]
ARPC5 and GSTP1	ARPC5 and GSTP1 upregulated	Reduced miR-133a (and miR-206)	Lung carcinoma	[115]
IGF-1R, TGFBR1, and EGFR are downregulated	Restoration of ectopic-expression of miR-133a in NSCLC suppresses metastatic capacity	miR-133a inhibits cell invasiveness and cell growth *via* suppression of IGF-1R, TGFBR1 and EGFR	NSCLCs	[131]
	Low expression of miR-133a is characteristic of pancreas tissue	Reduced miR-133a	PDAC	[103]
CDC42	CDC42 upregulated causing downstream activation of PAKs	miR-133 downregulated	Gastric cancer tissues	[273]
GSTP1	Upregulated GSTP1	Downregulation of miR-133a in cancer	Bladder cancer (TCC) cell lines	[144]
	Enforced downregulation of GSTP1 inhibits cell proliferation and growth;	Enforced upregulation of miR-133a and miR-133b induces cell apoptosis		
GSTP1 in cancer specimens	GSTP1 upregulated	Reduced miR-133a	Bladder cancer (TCC) tissue	[144]
Actin-binding protein, FSCN1	Upregulated FSCN1; Enforced downregulation of FSCN1 inhibits cell proliferation, migration and invasion	Downregulation of miR-133a; Forced UP exp of miR-133a inhibits cell proliferation, migration and invasion	Bladder cancer (TCC) tissue	[274]
EGFR/AKT signalling pathway	Upregulated EGFR; Activated pAkt-1	Downregulated miR-133a; Enforced expression of miR-133a inhibits EGRF translation; causes inhibition of Akt protein phosphorylation and its nuclear translocation	Human MCF-7 and MDA-MB-231 breast cancer cell lines	[275]
Bcl-xL and Mcl-1 expression	Upregulated Bcl-xL and Mcl-1	Downregulated miR-133a correlated with tumor progression and poor patient prognosis;	Primary human osteosarcoma tissues; Osteosarcoma cell lines	[276]
E3 ubiquitin protein ligase	Downregulation of p21 and p53 proteins	Downregulated miR-133a	Primary CRC tissues	[277]
Enhanced sensitivity to doxorubicin and oxaliplatin	Enhancing apoptosis and inhibited cell proliferation	Ectopic upregulation of miR-133a	CRC cell lines	[277]
LASP1 upregulated	miR-133a expression downregulated	miR-133a targets LASP1	CRC tissues and cell lines	[278]
FTL protein upregulated	miR-133a expression downregulated	miR-133a targets downregulation of FTL protein	Patient breast cancer tissue	[279]

Increased sensitivity to chemotherapeutic drugs doxorubicin and cisplatin	Exogenous upregulation of miR-133a expression	Downregulation of FTL protein	Human MCF-7 breast cancer cells	[279]
Poor survival during breast cancer; upregulated FSCN1	Loss of miR-133a expression	FSCN1 is a direct target gene of miR-133a	Breast cancer tissue	[280]
FSCN1 downregulated	Restoration of miR-133a expression	Inhibited breast cancer cell growth and invasion	Breast cancer cell line	[280]
lncRNA Malat1/Srf/miR-133 regulatory loop	Malat1 transcript has a functional miR-133 target site, miR-133 acts as a competing endogenous RNA, regulating Malat1 levels	*In vitro* depletion of Malat1 in C2C12 cells reduces Srf activity, Srf is an enhancer of miR-133 expression; feed-back regulation loop involving miR-133	Mouse myoblast C2C12 cells	[164]
lncRNA MALAT1	MALAT1 is overexpressed in 46% of ESCC tissues, primarily in high-stage tumors, high expression correlates with lymph node metastasis	*In vitro* depletion of MALAT1 suppresses tumor cell proliferation, cell migration and invasion; G2/M phase arrest was induced and the ratio of apoptotic cells increased	Human ESCC	[162]
WIF1/lncRNA MALAT1	WIF1 (strong tumor suppressor) is systematically downregulated in glioblastoma	WIF1 down regulation correlates with strong upregulation of MALAT1. *In vitro* depletion of MALAT1 suppresses tumor cell proliferation	Glioblastoma	[163]
Downregulated miR-133b				
Fascin-1 mRNA	FSCN1 upregulated	Reduced miR-133b	High-grade GIST tissue	[281]
BCL-2 family (MCL-1 and BCL2L2)	MCL-1 and BCL2L2 upregulated	Reduced miR-133b	Lung cancer	[85]
FAIM antiapoptotic protein and GSTP1	miR-133b directly targets FAIM and GSTP1	Downregulated miR-133b	miR-133b expression significantly downregulated in 75% of prostate cancer tumor specimens	[282]
Gli1	Gli1 upregulated	Gli1 inversely correlated with downregulated expression of miR-133b	Gastric cancer	[283]
Bcl-w and Akt1	Bcl-w and Akt1 proteins overexpressed significantly	miR-133b significantly downregulated	Bladder cancer tissues	[284]
		miR-133b downregulated in tumors compared to surrounding tissue	Gastric and esophageal adenocarcinomas	[285]
			Endometrial sarcoma, leiomyosarcoma, and mixed epithelial-mesenchymal tumors	[286]
Downregulated miR-206				
Notch3/ miR-206	Downregulated Notch3, blocking of the anti-apoptotic activity of Notch3	Forced expression of miR-206 strongly induced apoptotic cell death *via*; also inhibited cell migration and focus formation	HeLa cells	[287]
Met	Upregulated Met	miR-206 downregulated	Human rhabdomyosarcoma	[288]
HGFR	Upregulated HGFR	miR-206 downregulated	Human breast cancer cells	[289]
KLF4	Upregulated KLF4	miR-206 downregulated	RK3E breast epithelium cells	[108]
KLF4; RAS-ERK signalling	Upregulated KLF4 promotes RAS-ERK signalling Endogenous KLF4 binds the promoter regions stimulates expression of miR-206	miR-206 downregulated	TNBC cells	[290]
RASA1 and SPRED1		miR-206 inhibits translation of the RAS pathway suppressors RASA1 and SPRED1	Suppression of RASA1 or SPRED1 increased levels of GTP-bound, wild-type RAS and activated ERK 1/2	
VEGF	VEGF upregulated in Laryngeal SCC tissues	MiR-206 strongly downregulated in LSCC tissues	Laryngeal SCC cancer tissue and cells	[113]
VEGF	VEGF upregulated in ccRCC tissues	MiR-206 strongly downregulated in ccRCC tissues	ccRCC tissues assayed by Deep Sequencing	[291]
Cdc42, MMP-2 and MMP-9	Upregulated Cdc42, MMP-2 and MMP-9	miR-206 downregulated	Human breast cancer tissues	[292]
ERα	miR-206 directly targets ERα 3'-untranslated region	MiR-206 inhibited by ERα agonists, indicating a mutually (double) inhibitory feedback loop;		[293]
		miR-206 downregulated		[109]
	Upregulated ERα		MCF-7 breast cancer cells	[294]
ERα	Upregulated ERα	miR-206 downregulated	EEC tissue	[110]

K-Ras	K-Ras is direct target of miR-206; MiR-206 expression significantly downregulated and k-Ras upregulated on OSCC tissues	Low miR-206 potentiates metastases, and shorter overall survival	OSCC tissue samples and cell lines	[295]
MiR-206	Enforced upregulated of miR-206 attenuated cell proliferation, increased apoptosis and inhibited cell migration and invasion	MiR-206 strongly downregulated in lung cancer tissues	Lung cancer - tissues and cell lines	[107]
EGFR/MAPK signalling switches MCF-7 breast cancer cells from ERα-positive, Luminal-A phenotype to ERα-negative, basal-like phenotype	EGFR signalling represses estrogenic responses in MCF-7 cells by enhancing miR-206 activity Elevated miR-206 reduces cell proliferation, enhances apoptosis, and reduces numerous estrogen-responsive genes	miR-206 downregulates steroid receptor co-activators SRC-1 and SRC-3 and GATA-3 transcription factor, directly	MCF-7 breast cancer cells	[296]
Greater lymph node metastasis, venous invasion, and at a more advanced stage	miR-206 expression strongly downregulated	Correlates with tumor progression	Human gastric cancer tissue	[297]
CCND2	miR-206 expression strongly downregulated	Correlates with upregulation of CCND2 and cancer progression	Human breast cancer Human gastric cancer	[298] [299]
MET	miR-206 expression strongly downregulated	Upregulation of MET	Papillary thyroid carcinoma	[300]
Prognostic signature of metastatic colorectal cancer	miR-206 expression strongly downregulated	Prognostic signature of metastases: miRs 21, 135a, 335, 206 and let-7a	Metastatic CRC	[301]
Notch3, Hes1, Bcl-2 and MMP-9;	Exogenous upregulation of miR-206 expression;	Notch3, Hes1, Bcl-2 and MMP-9 downregulated at both mRNA and protein level;	Human HHC Hep2 cells.	[302]
p57, Bax and caspase-3	miR-206 is a potent tumor supressor	p57 and Bax upregulated, and cleaved caspase-3 protein upregulated	Reduced apoptosis, and cell migration in HepG2 cells overexpressing miR-206	
STC2, HDAC4, KLF4, IGF1R, FRS2, SFRP1, BCL2, BDNF and K-ras	Exogenous upregulation of miR-206 expression; miR-206 is a potent tumor supressor	STC2, HDAC4, KLF4, IGF1R, FRS2, SFRP1, BCL2, BDNF, and K-ras downregulated strongly in SCG-7901 cells overexpressing miR-206	Gastric carcinoma SCG-7901 cells Reduced apoptosis, and cell migration in SCG-7901 cells overexpressing miR-206	[303]
Cyclin C, CCND1 and CDK4	Cyclin C, CCND1 and CDK4 upregulated in melanoma tissue; Exogenous upregulation of miR-206 expression reduced growth and migration/invasion of several melanoma cell lines; G1 arrest in melanoma cells	hsa-miR-206 downregulated in melanoma tissue Overexpression of miR-206 in melanoma cells strongly downregulated cyclin C, CCND1 and CDK4	Human melanoma cancer tissue, and cell lines	[304]
Coronin, actin-binding protein	Silencing of coronin expression reduced tumor cell migration and altered the cellular actin skeleton and cell morphology, but did not effect cell proliferation	Downregulated miR-206 allowed upregulation of coronin, a direct target; Upregulated miR-206 reduced TNBC cell migration and cell proliferation	TNBC cell lines	[305]
RNA binding protein DEAD-END (DND1), DNA cytosine deaminase (AICDA), and APOBEC3	DND1 blocks miRNA interaction with 3'-UTR of specific mRNAs, restores protein expression; APOBEC3G binds DND1 counteracts repression and restores miRNA activity	APOBEC3G blocks DND1 to restore miR-206 inhibition of CX43 translation	Mouse cells	[306]
Advanced clinical stage, T classification, metastasis and poor histological differentiation		Significant association with decreased miR-206 expression	Paired human osteosarcoma and normal adjacent tissues	[307]
Ellagic acid inhibits E2-induced mammary tumorigenesis	Reverses the downregulation of miR-206		ACI model rat mammary tissue	[308]
Actin-like 6A (BAF53a), a subunit of the SWI/SNF chromatin remodeling complex	Elevated BAF53a	Downregulation of miR-206	Primary rhabdomyosarcoma tumors	[309]
Actin-like 6A (BAF53a)	BAF53a transcript is significantly higher in primary rhabdomyosarcomas than in normal muscle	Restoration of miR-206 expression downregulated BAF53a, which inhibits proliferation and anchorage independent growth; BAF53a and is a direct target of miR-206	Primary rhabdomyosarcoma tumors	[309]

Wnt and transcription factors Tbx3 and Lef1	Exogenous upregulation of miR-206 expression	Inhibition of Wnt, Tbx3 and Lef1 activities	Estrogen receptor alpha (ER-α)-positive human breast cancer; developing mammary buds	[310]
ANXA2 and KRAS	Stimulation of KRAS activity then induces NFKB1 expression;	Downregulated miR-206 in PDAC	PDAC tissues and cell lines	[311]
Induces NFKB1	Increased KRAS results in stimulation of cytokines CXCR2, CXCL1, CCL2, as well as CSF2 (GM-CSF) and VEGFC	Increased cell cycle progression, cell proliferation, migration and invasion		
Downregulated miR-1 and miR-133a				
PNP	PNP upregulated	Reduced miR-1, -133a	Prostate cancer	[97]
TAGLN2	TAGLN2 upregulated	Reduced miR-1, -133a	RCC	[136]
TAGLN2 and PNP	TAGLN2 and PNP upregulated	Reduced miR-1, -133a	MSSCC	[137]
PTMA and PNP	PTMA and PNP upregulated	Reduced miR-1, -133a	Bladder cancer (TCC)	[312]
LASP1	LASP1 upregulated Forced expression of each miR decreased LASP1 in cell lines	Reduced miR-1, 133a, (and miR-218)	Bladder cancer (TCC)	[313]
DNA methylation regulates miR-1-1 and miR-133a-2 cistron expression	Inverse correlation with TAGLN2 levels	CpG islands upstream of miR-1-133a hypermethylated	Colorectal carcinoma tissue and liver cancer tissue	[314]
Downregulated miR-1 and miR-133b				
	miR-1 and mir-133b have sufficient power to distinguish recurrent specimens from non-recurrent prostate cancer	miR-1 and mir-133b are significantly downregulated in recurrent prostate cancer tissue specimens	Recurrent prostate cancer tissue	[96]
Downregulated miR-1 and miR-206				
NRF2 upregulated	Downregulated miR-1 and miR-206 expression	Upregulated expression of NRF2 induces increased expression HDAC4	Primary lung adenocarcinoma; DU145 human prostate cancer cell line	[99]
Loss of NRF2	Decreased expression histone deacetylase (HDAC4)	Results in increased expression of miR-1 and miR-206; which inhibits PPP expression; Reduced PPP acts as a regulatory feedback loop stimulates HDAC4 expression	A549 human NSCLC cell line	[99]
c-Met	c-Met upregulated	miR-1 and -206 downregulated	Human rhabdomyosarcoma	[89]
ARPC5 and GSTP1	ARPC5 and GSTP1 upregulated	Reduced miR-133a (and miR-206)	Lung SCC cell lines	[115]
Downregulated miR-133a and miR-133b				
PKM2	PKM2 upregulated	Downregulated miR-133a, -133b	TSCC	[111]
FSCN1	FSCN1 upregulated	Downregulated miR-133a, -133b, (miR-145)	ESCC	[132]
		miR-133a, miR-133b downregulated	ESCC	[94]
KRT7	KRT7 upregulated	Downregulated (miR-133a and miR-133b)	Bladder cancer (TCC) and *in vitro* in BC KK47 cells	[315]
Downregulated miR-1, miR-206 and miR-133				
myomiRs	Patient to patient variation in the up or down regulation of miR expression in both tumor and matched normal tissues	In tumors strong down regulation of highly expressed miR-1/133a; (downregulation of weakly expressed miR-206/-133b)	Bladder cancer assayed by deep sequencing	[315]
Candidate tumor suppressor miRNAs in RCC	Each of miR-206, miR-1, miR-133b strongly downregulated	Restored expression strongly inhibited cancer cell proliferation,	RCC	[316]
Shorter overall survival and disease-free survival	Correlated with increased downregulated of miR-133b and/or miR-206	Both miR-133b and miR-206 significantly downregulated	Osteosarcoma tissues	[317]
Cell invasion and metastasis	miR-1, miR-133a, miR-133b downregulated	miR-133a, miR-133b involved in invasion and metastasis	ESCC	[94]

UPR: Unfolded protein response; PAKs: P21-activated kinases; EDN1: Endothelin 1; AKT1: V-akt murine thymoma viral oncogene homolog 1; HCC: Hepatocellular carcinoma; API5: Apoptosis inhibitor 5; LASP1: LIM and SH3 domain protein 1; XPO6: Exportin-6; CLCN3: Chloride channel, voltage-sensitive 3; G6PD: Glucose-6-phosphate dehydrogenase; BRCA1: Breast cancer 1, early onset; MCM7: Minichromosome maintenance complex component 7; PTMA: Prothymosin alpha; TWF1: Twinfilin actin-binding protein 1; CXCR4: Chemokine (C-X-C motif) receptor 4; HDAC4: Histone deacetylase 4; ANXA2: Annexin A2; SRSF9/SRp30c: Splicing factor serine/arginine-rich 9; ARPC5: Actin-related protein 2/3 complex subunit 5; GSTP1: Glutathione S-transferase pi 1; FSCN1: Fascin homolog 1; FTL: Ferritin light chain; BCL2L2: B-cell CLL/lymphoma 2-like 2; EGFR: Epidermal growth factor receptor; PNP: Purine nucleoside phosphorylase; PKM2: Pyruvate kinase, muscle type M2; KRT7: Keratin 7.

Table 5 Targets and pathways influenced by the upregulated myomiRs in different cancers

Factor(s)	Regulation	Regulator	Tissue/cell	Ref.
Upregulated miR-133b				
Activated p-ERK, pAKT1 cause in vitro proliferation of cervical cancer cell lines, and promote *in vivo* tumorigenesis and metastasis	Downregulation of MST2, CDC42, RHOA	Upregulated miR-133b	Human cervical carcinoma tissue compared to surrounding normal cervical tissue	[121]
Decreased patient survival		Upregulated miR-133b	Progression bladder cancer	[122]
Androgen receptor	miR-133b directly represses CDC2L5, PTPRK, RB1CC1, CPNE3	miR-133b directly upregulated by AR	Hormone-sensitive human prostate cancer (LNCaP) cells stimulated by androgen	[123]
Activatived neuroendocrine neoplasia proliferation	Mutation in von Hippel-Lindau tumor suppressor, E3 ubiquitin protein ligase gene (VHL)	Upregulated miR-133b expression in VHL- deficient pheochromocytoma	Human pheochromocytoma (PCCs) and paraganglioma (PGLs) neuroendocrine neoplasias	[318]
Upregulated miR-206				
Cell reprogramming factor KLF4	KLF4 downregulated in colon cancer tissue, associated with increased miR-206	miR-206 strongly upregulated in colon cancer tissues	Human colon cancer tissue	[116]
Upregulated miR-1 and miR-133				
Decreased survival of R172 IDH2-mutated subset of CN-AML patients, increases resistance to chemotherapy	Distinctive gene and microRNA expression profiles accurately predicted R172 IDH2 mutations	Upregulated expression of miR-1 and miR-133	*De novo* CN-AML patient bone marrow and blood samples	[151]
EVI1 increases aggressive cancer growth	EVI1 expression upregulated in established patient samples ChIP assays show EVI1 binds to miR-1-2 gene promoter directly	Upregulated expression of miR-1-2 and miR-133-a-1	EVI1 expressing AML subset of patients	[120]
CCND2	miR-1 and miR-133a were specifically overexpressed in the cases with t(14;16) translocation, correlates with down-regulated CCND2 expression	Upregulated miR-1 and miR-133-a	Multiple myeloma	[152]
Secreted myomiRs				
miRs selectively released into serum (within exosome microparticles)	miR-1, miR-133a, and miR-133b selectively released		Human breast cancer	[319]
Circulating microRNA	Tumor-derived exosomes		Human non-small-cell lung cancer	[320]

AKT1: V-akt murine thymoma viral oncogene homolog 1; CN-AML: Cytogenetically normal acute myeloid leukemia.

the abundance of factors involved in aspects of cell proliferation[84].

Some cancers however show that elevation of myomiR levels promotes cancer progression (Figure 3), indicating that in such cell environments the deregulated myomiR is oncogenic and their targets here are normal tumor-suppressor cell factors. These are both regulatory roles that myomiRs normally exert, either by influencing particular cell signalling pathways that maintain a differentiated non-proliferating state in mature cell development stages, or by influencing other signalling pathways involved in cell proliferation and tissue genesis stages. Notably, the reports of deregulated myomiRs in cancers often reveal significant relation between the myomiR concentration and tumor severity, with greatest disregulation of expression statistically associated with metastasis, or with tumors of high metastatic potential, or with decreasing prospects of patient survival[88,98-102]. Yet, double knockout mice lacking both *miR-133a1/2* gene alleles[14] do not display an elevated incidence of tumors in any organs or tissues *in vivo*, similarly animals with knockout of *miR-206* expression[46], or knockdown of *miR-133b* or double knockdown of *-133b/-206*[44] are not reported to be associated with tumors, indicating that the singular lack of myomiR(s) alone is not (usually) sufficient to initiate tumorigenesis. Hence the oncogenic role of the deregulated myomiRs is a significant potentiating one, dysregulating cell signalling pathways in concert with the multiplicity of other molecular and cell environmental changes occurring in the developing tumor.

It is also notable that expression of cistronic myomiR isomers is not co-ordinated in different carcinomas, emphasizing individual deregulation of control of expression of each *myomiR* gene. For example, at least one miR of either cistronic pair is expressed in 16/20 cancers having altered miR-133 expression, showing also that each miRs has independent expression in non-muscle cells and tissues. Since the myomiRs influence numerous developmental pathways in normal muscle and other tissues, the differential expression of the myomiR isomers may potentially influence the pathology of cancers differently.

Cancer and downregulated myomiRs

Reduced expression of myomiRs was associated with numerous cancers, such as with PDAC[103] colorectal cancer[86,104], NSCLC[105], HCC[98], prostate

Table 6 Validated myomiR targets related to cancer progression

Up regulated cell factor	Down regulated cell factor	Cancer type	Ref.
Downregulated myomiRs			
Downregulated miR-1			
Mediator complex subunit 1 (Med1) and 31 (Med31) upregulated	miR-1 downregulated	Osteosarcoma	[257]
Slug expression upregulated; enhanced cell migratory and invasive activities	miR-1 downregulated	Chordoma	[261]
Slug expression upregulated; stimulation of EMT process	miR-1 reduced increasingly with cancer progression	Prostate adenocarcinoma	[321]
Downregulated miR-133a			
ARPC5 upregulated;	Downregulated miR-133a (> miR-206)	Lung SCC	[115]
		HNSCC	[272]
CAV1 upregulated;	miR-133a downregulated	HNSCC	[322]
Moesin upregulated;	miR-133a downregulated	HNSCC	[143]
FSCN1 upregulated;	miR-133a/ miR-133b downregulated	ESCC	[132]
		Bladder cancer (TCC)	[274]
GSTP1 upregulated;	miR-133a downregulated	HNSCC	[323]
		Bladder cancer (TCC)	[144]
		Lung SCC	[115]
LASP1 upregulated;	miR-133a downregulated in 83% of colorectal tumors	Colorectal cancer	[136]
CAV1 downregulated with miR-133a levels, and is lowest in metastatic cancers;	Contrastingly, higher levels of miR-133a correlate with poor prognosis and increased metastasis		
FSCN1 upregulated in non-metastatic tumors			
LASP1 upregulated;	miR-133a downregulated	Bladder cancer (TCC)	[313]
PKM2 upregulated;	miR-133a downregulated	TSCC	[111]
Moesin upregulated;	miR-133a downregulated	HNSCC	[143]
EGFR upregulated;	miR-133 downregulated	Hormone-sensitive prostate cancer cell lines	[324]
Human TERT telomerase catalytic subunit upregulated;	miR-133a downregulated		[325]
TCF7 transcription factor upregulated;	miR-133a downregulated		[325]
FSCN1 and MMP14 upregulated;	miR-133a downregulated	ESCC	[326]
Reduced miR-133a expression correlated significantly with advanced clinical stages, poor histological differentiation and lymph node metastasis	Marked downregulation of miR-133a in primary EOC tumors and OVCAR-3 cell line	Epithelial ovarian cancer (EOC), and in OVCAR-3 cell line	[327]
Downregulated miR-133b			
FSCN1 upregulated;	miR-133a/-133b downregulated	ESCC	[132]
FSCN1 mRNA upregulated;	miR-133b downregulated	Progressive GIST	[281]
BCL2L2 upregulated;	miR-133b downregulated	Lung cancer	[85]
MCL1 upregulated;	miR-133b downregulated	Lung cancer	[85]
MET upregulated;	miR-133b downregulated	Colorectal cancer	[87]
MET protein upregulated;	miR-133b downregulated	high grade osteosarcoma tumor samples and cell lines	[328]
EGFR upregulated;	miR-133b downregulated	NSCLC	[105]
Multiple cell factors elevated;	miR-133b downregulated	Prostate cancer	[282]
FGFR1 downregulated;	miR-133b downregulated	Gastric cancer	[329]
Gli1 protein downregulated by miR133b, Gli1 target genes, OPN and Zeb2, are indirectly regulated	miR-133b downregulated	Gastric cancer	[283]
TAp63 supresses metastasis; downregulation target of miR-133b	miR-133b is a transcription target of TAp63, downregulated	Colon cancer cells	[330]
Chemokine (C-X-C motif) receptor 4 protein downregulated by miR133b; upregulated in advanced cancer	miR-133b downregulated	CRC	[331]
TBP-like 1 mRNA and protein are upregulated in CRC	miR-133b downregulated in CRC	CRC	[332]
Strong additional down regulation of miR-133b aids liver metastatic niche for CRC cells	miR-133b downregulated 3 × (significant) in liver metastasis compared to primary CRC Interestingly, miR-133b is not downregulated significantly in lung metastasis compared to primary CRC	miR-133b downregulated in primary CRC compared to surrounding tissue	Metastatic cancer arising from primary hCRC	[333]
SP1 targeted directly by miR-133, causing reduced expression of MMP-9 and Cyclin D1	miR-133a and -133b downregulated	Gastric cancer	[334]
miR-133b target MMP-9 is upregulated	miR-133b downregulated	RCC	[335]

Downregulated miR-206				
	ERα	ERα downregulates miR-206	ERα-positive breast cancer;	[294]
		miR-206 downregulated	Double feedback loop	[109]
		miR-206 downregulated		[293,336]
	ERα	miR-206 downregulated	EEC tissue	[110]
	SRC-1, SRC-3 and GATA-3 proteins contribute to estrogenic signalling	miR-206 downregulated	ERα-positive breast cancer Signalling contributes to Luminal-A phenotype	[296]
	KLF4 over expressed in proliferating cells and cancers.	miR-206 levels are KLF4 dependent. KLF4 and miR-206 feedback pathway oppositely affect KLF4 protein translation	Breast cancer cells and normal cells	[108]
	FGBP1	miR-206 gene double knockdown	miR-206$^{-/-}$ mouse skeletal muscle.	[12]
	VEGF upregulated	miR-206 downregulated	Laryngeal SCC cells	[113]
	VEGF upregulated	miR-206 downregulated	CRC tumors compared to matched normal tissue; (^{1}DS assay)	[337]
	miR-206 correlates with negative ER status, negative PR status, and negative HER-2 status	Downregulated miR-206	Breast cancer tumor tissue	[338]
	miR-206 was downregulated in clinical TNBC tumor samples, one of its targets, actin-binding protein coronin was upregulated	Downregulated miR-206 associates with increased metastasis potential in breast cancers	High metastatic capacity TNBC tumors	[305]
Downregulated miR-1 and miR-133a				
	PNP upregulated	miR-1/miR-133a downregulated	MSSCC	[137]
			Prostate cancer	[97]
			Bladder cancer (TCC)	[312]
	TAGLN2 upregulated;	miR-1/miR-133a downregulated	MSSCC;	[137]
			RCC	[138]
			HNSCC	[339]
			Bladder cancer (TCC)	[93]
	PTMA upregulated	miR-1 and miR-133a downregulated	Bladder cancer (TCC)	[312]
Downregulated miR-1 and miR-206				
	MET levels correlated inversely with miR-1/206 expression	miR-1/206 downregulated	Up-regulation of MET in rhabdomyosarcoma	[89,288]
	HGFR upregulated	miR-1/206 downregulated	Breast cancer cells	[289]
	G6PD; PGD; TKT; GPD2 upregulated	miR-1/206 downregulated	Primary lung adenocarcinoma	[99]
Upregulated myomiRs				
Upregulated miR-133b				
miR-133b	miR-133b strongly upregulated	MST1, CDC42, RHOA, and DUSP1 downregulated	Cervical carcinoma	[121]
miR-133b	miR-133b is directly upregulated by AR	miR-133b represses CDC2L5, PTPRK, RB1CC1, and CPNE3	PCa prostate cancer cell line	[123]
Upregulated miR-206				
miR-206	Strongly upregulated miR-206	KLF4 downregulated	Human colon cancer tissue	[116]
Upregulated miR-1 and miR-133a				
miR-1-2 and miR-133-a-1	Upregulated miR-1-2 and miR-133-a-1	EVI1 (transcriptional activator of miR-1 and miR-133b)	AML	[120,151]
miR-1 and miR-133-a	Upregulated miR-1 and miR-133-a	Downregulated CCND2	Multiple myeloma	[152]
Up-regulation of exogenous myomiR expression in cell lines				
Reduced cell proliferation	Estrogen receptor alpha	Overexpression of miR-206 has an inhibitory effect on cell proliferation	ERα-positive breast cancer cells over expressing mir-206	[289]
miR-133b	GSTP1 downregulated	Transgenic miR-133b overexpression	HeLa cervical cancer cells	[282]
miR-133b	FAIM downregulated	Transgenic miR-133b overexpression	HeLa cervical cancer cells	[282]
Apoptosis increased	TNFα-induced cell death is activated	Transgenic miR-133b overexpression	HeLa cervical cancer cells	[282]
Increased cell proliferation and migration	Downregulation of MST2 Downregulation of CDC42 Downregulation of RHOA	Transgenic miR-133b overexpression	CaSki cervical cancer cells	[121]
Increased cell proliferation and migration	Indirect upregulation of p-AKT1 activity Indirect upregulation of p-ERK activity	Transgenic miR-133b overexpression	CaSki cervical cancer cells	[121]
RB1CC1 downregulated	Exogenous upregulation of miR-133b;	miR-133bm promotes cell apoptosis, but suppressed cell proliferation and cell-cycle progression in aggressive PC-3 cells	PC3 prostate cancer cell line	[106]
	miR-133b directly targets RB1CC1 in LNCaP cells	In contrast in low-aggression LNCaP cells, miR-133b stimulate cell proliferation and cell-cycle progression, but inhibit apoptosis	Hormone sensitive prostate cancer LNCaP cell line	

Cell proliferation decreased and apoptosis increased	Met, Twf1 and Ets1 and Bag4 activities downregulated	miR-1 expression is lower in mouse cSCCs compared to normal skin Transgenic miR-1 overexpression	Mouse cutaneous squamous cell carcinomas (cSCCs); A5 and B9 cSCCcell lines	[256]
Ets1 proto-oncogene	Repression of Ets1 expression inhibited HepG2 cell invasion and migration	Transgenic miR-1 overexpression	HCC HepG2 cells	[340]
lncRNA UCA1	Knockdown of lnc UCA1 expression phenocopied the effects of upregulation of hsa-miR-1	hsa-miR-1 decreased the expression of lnc UCA1 in bladder cancer cells in an Ago2-slicer-dependent manner	Human bladder cancer (TCC) cells	[156]
NOTCH3 signalling	miR-206 had a direct inhibition of NOTCH3 signalling and indirect interaction with other signalling pathways *via* CDH2 and MMP-9	miR-206 upregulation blocks the cell cycle, inhibits cancer cell proliferation and migration and activates cell apoptosis	SW480 (plus its metastatic strain) and SW620 colon cancer cell lines	[341]
FSCN1	miR-133b targets FSCN1 in GC cells; the direct knockdown of FSCN1 can also inhibit GC cell growth and invasion	Up regulation of miR-133b in GC cells inhibits cell proliferation, cell migration and invasion	miR-133b is significantly downregulated in GC tissues compared with adjacent normal tissues, as well as in GC cell lines	[342]
FSCN1	miR-133a targets FSCN1 in CRC cells; Overexpression of FSCN1 can reverse the inhibitory effect of miR-133a upregulation, reactivating CRC cell invasion	Up regulation of miR-133a expression and downregulation of FSCN1 protein expression both suppress colorectal cancer cell invasion	miR-133a is significantly downregulated in some colorectal cancer cell lines, as well as in colorectal cancer tissues compared with the normal adjacent tissues	[343]

[1]DS: Deep sequencing. HNSCC: Head and neck squamous cell carcinoma; ESCC: Esophageal squamous cell carcinoma; ARPC5: Actin-related protein2/3 complex, subunit 5, 16 kDa; CAV1: Caveolin-1; FSCN1: Fascin homolog 1; GSTP1: Glutathione S-transferase pi 1; TSCC: Tongue squamous cell carcinoma; EGFR: Epidermal growth factor receptor; TAp63: Tumor protein p63; CRC: Colorectal cancer; KLF4: Kruppel-like factor 4; SRC-1 and SRC-3: Steroid receptor coactivator proteins; HGFR: Hepatocyte growth factor receptor; G6PD: Glucose-6-phosphate dehydrogenase; PGD: 6-Phosphogluconate dehydrogenase; TKT: Transketolase; GPD2: Glycerol-3-phosphate dehydrogenase; RHOA: Ras homolog family member A; AML: Acute myeloid leukaemia; EVI1: Ecotropic virus integration site 1 transcription factor; MST2: Mammalian sterile 20-like kinase 2; RB1CC1: RB1 inducible coiled-coil 1; UCA1: Urothelial cancer associated 1; GC: Gastric cancer.

cancer[102,106], metastatic lung tumors[107], proliferating breast cancer[108], ERα-positive breast cancer[109], EEC[110], NSCLC[85], TSCC[111,112], laryngeal SCC[113], and HNSCC[114] (Table 3). Many of the reports identify reduction in a single myomiR, but in case studies of particular cancers often the different myomiRs have been identified as downregulated, for example in NSCLC tumor samples, miR-1[100], -133a[85,115], -133b[85,115], -206[107] or miR-1/-206[99] have been reported, by implication dysregulation of all of the myomiRs. Similarly, for colorectal cancer, downregulated miR-1[101], -133a[104], or -133b[86], or upregulated miR-206[116], while in prostate cancer downregulated miR-1[101,102] and miR-206[102], miR-133a[97,102] and miR-133b[95,96] have been variously reported (Table 3). Either these studies have examined different subclasses of the particular cancer which have different myomiR profiles, or more likely the method of miR detection or the purpose of the study (*e.g.*, relating a particular miR to a particular deregulated target gene) may have influenced the findings reported, leading to some potentially conflicting and inconsistent reports. Additionally, the mature miR isomers are difficult to distinguish by molecular assay and some reports note cross-identification of miR-133b by Taqman mature miR-133a specific probe[14], which is used in many studies. Others[114,117] also make this point, that the different miR assay platforms generate different profiles which may obscure or confuse the identity of observed molecular changes, and at minimum generate apparently different miR profiles of the same tissues or diseases[118,119].

It is essential to accurately determine the specific expression of particular myomiR isomers and their alleles to understand the control processes of particular pathological states. The expressed alleles of the myomiRs can be assessed accurately by employing pri- or pre-miR RT-PCR assays. For example, only cistron miR-1-2/-133a1 is found expressed in AML, presumably due to specific activation of that cistron[120] and amongst the myomiRs only pre-miR-133b is elevated in cervical cancer[121], in bladder cancer[122], and in progressive prostate cancer[123]. We suggest that initial microarray profiling be confirmed by pri- or pre-miRNA assay of each miR isomer independently.

Significantly, a deep sequencing profile of miR expression in mouse heart[124] found that miR-133b is expressed at about 1/6 of the level of miR-133a, reflecting that microarray-based studies may underestimate the relative levels of important miR isomers. Importantly, such deep sequencing analyses also question the canonical view that miR-133b is not expressed in cardiac tissue, reinforcing the need to employ sensitive and accurate analysis to extend our understanding of miR involvement in biological processes. Discrepancies in miR profiles detected between deep sequencing analysis of liver cancer[344] and microarray/Taqman expression profiling[95], and in comparison of level 3 expression data from the Cancer Genome Atlas (TCGA) with deep sequence data from ovarian cancer patients[119] which found only 1 out of 12 survival-associated miRs identified by sequencing correlated by the TCGA data, emphasize the need for robust analytical and computational methods for in-depth profiling of tumors. Expression profiling of

prostate tumors from individual patients by deep sequencing revealed that the expression of numerous miRs changed according to tumor stage[125]; however qRT-PCR of individual miRs at each tumor stage could not consistently confirm these alterations. A detailed survey of miRs using qRT-PCR accompanied by *in situ* hybridization to confirm the identity of the changed miR expression in matched prostate tumor tissue found less than 50% identity between major altered species when compared with deep sequencing analysis of pooled tumors by the same authors[126]. Furthermore, a deep sequencing profile of expressed miRs in bladder cancer[127] also showed that individual patient profiles varied greatly, and remarkably found also that the majority of deregulated miRs are upregulated in tumor tissue compared to matched normal tissue, with up to 3-5 × more upregulated than downregulated species in some patient tumor samples. Generally however, the myomiRs expressed in normal tissue are found downregulated in tumors when analysed by both qRT-PCR and by sequencing platforms. Significantly, another deep sequencing profile of expressed miRs in bladder cancer[128] revealed a different myomiR expression profile to the above deep sequencing study[127], yet confirmed the pattern of myomiR expression detected previously by the same group using microarray and qRT-PCR techniques[93] (Table 3). Overall, these various platform comparisons suggest the need to re-evaluate the genome-wide miR expression profiles of different cancers by use of deep sequencing and then to confirm findings using independent molecular methods.

Cell factors deregulated in cancer by myomiRs

Teicher[129] (2012) and Frith *et al*[130] (2013) noted in sarcoma tumors, which arise in diverse tissues of mesenchymal origin, that the upregulation of cMET (MET), HIF-1α, IGFR-1 or EGFR, CDK4, MCL1 or mTOR is observed with some elevated frequency in (particular) sarcomas, related to increased cancer severity and enhanced tumor progression, with the significance of each altered pathway likely due to the differentiated tissue in which the sarcoma arises. Downregulated expression of myomiRs occurs in both some sarcomas and carcinomas, linked specifically to the upregulated expression of some of the above gene targets. The different deregulated myomiRs modulate the levels of numerous mRNA/gene targets, but often particular deregulated gene targets are seen in several different cancers. For example, MET is upregulated due to reduced miR-1 levels in colon cancer[87,101], NSCLC[100] and rhabdomyosarcoma[89]. MET binds specifically with HGF, resulting in activation of pathways causing malignant progression *via* increased cell mobility, tissue invasion, and reduction of apoptosis. Reduced miR-1 targetting is only one of several cell alterations which can contribute to MET activation, yet the downregulation of miR-1 relates significantly to increased cancer severity, indicating the likely importance of miR-1 as a pleiotropic suppressor of several pathways important for tumor development.

Oncogenic membrane receptors, such as IGFR-1 and EGFR are upregulated in association with reduced miR-133 expression in NSCLC[131], and a similar EGFR upregulation occurs in hormone-sensitive prostate cancer and in breast cancer (Tables 4-6). Furthermore, a marked upregulation of cyclin C, cyclin D1 and CDK4 is seen in skin melanoma tissues associated with the reduced expression miR-206; whilst the BCL2 family of pro-survival molecules (Mcl-1 and BCL2L2) are both strongly upregulated due to a marked decrease in miR-133b levels (> 20-fold) in lung carcinoma tissue[85]. In addition, a detailed investigation of the role of myomiRs in prostate cancer[102] found that miR-1, miR-133a (and miR-206) were epigenetically supressed through promotor modification in numerous tumor samples and in prostate cancer cell lines. *In vitro* studies with prostate cancer cells showed that the downregulation of miR-1 allowed overexpression of multiple target genes that regulate key pathways affecting cell proliferation and cell migration, such as the actin filament network (FN1, LASP1, XPO6, CLCN3, G6PD), cell cycle and DNA damage control (BRCA1, CHEK1, MCM7) and histone acetylation (HDAC4); and with further downregulation of miR-1 the activation of oncogenic genes such as NOTCH3 and PTMA. Cell studies also showed that miR-206 has similar effects on prostate cancer cell biology as miR-1, suggesting that the combined downregulation of the myomiRs contributes significantly to prostate cancer progression.

In addition, FSCN1 expression is elevated in progressive metastatic ESCC, in breast cancer and in high-grade GIST, in part due to the loss of miR-133 expression[132]. FSCN1 is an actin-binding protein critical to cell adhesion, cell motility, and cell-cell interactions. In normal prenatal pig skeletal muscle, FSCN1 expression increases during major muscle developmental spurts, but postnatally it is expressed highly only in brain tissues during accelerated neural cell development[133]. The CREB pathway is often activated in different metastatic human cancers, causing the upregulation of FSCN1 expression[134]. In HNSCC patients, expression of RSK2 and FSCN1 proteins correlate closely. RSK2 protein expression potentiates filopodia formation and cell bundling, increasing cell invasiveness. Overexpression of FSCN1 can rescue the invasion phenotypes in RSK2 knockdown cells, linking RSK2-CREB signalling to the upregulation of FSCN1. In the highly metastatic PDAC[135], relative FSCN1 expression correlates with expressed HIF-1α levels, suggesting the hypoxic tumor microenvironment might induce FSCN1 expression, contributing to invasion and metastasis. Taken together, the downregulation of the myomiRs can contribute to the deregulated overexpression of oncogenic cell factors such as FSCN1, TAGLN2,

KLF4, MET (cMET), IGFR and others, each of which can potentiate dysregulation of other cell signalling pathways, enhancing oncogenesis and metastasis (Tables 4-6).

Interestingly, the oncogenic membrane receptors, IGF-1R, TGFBR1 and EGFR are upregulated in NSCLCs due to the downregulation of miR-133a, whilst NSCLC patients with highly expressed levels of miR-133a tend to survive longer[131] presumably because these target oncogenic proteins are less strongly expressed. In contrast, although downregulation of miR-133a occurs generally in colorectal tumors, tumors with higher miR-133a levels are associated with increased metastasis, adverse clinical characteristics and poor prognosis[136], suggesting that other cell factors contribute to these differences in outcome. Expression of other targets of miR-133a: LASP1, CAV1, and FSCN1 are also deregulated in a complex pattern. While LASP1 showed negative correlation with miR-133a levels, CAV1 instead had significant positive correlation, which increased in patients with distant metastases, while negative correlation of FSCN1 was only seen in non-metastatic patients. Again the relationship between the deregulated myomiR and its deregulated target(s) display a complexity which suggests the involvement of other factors in early developing and metastatic cancer stages.

The upregulation of yet other cell factors were seen with reduced myomiR expression, such as TAGLN2 with the downregulation of miR-1 and -133a in MSSCC[137], in RCC[138], and in CRC, liver cancer and in bladder cancer (TCC) (Table 6). Interestingly, TAGLN2 is a known tumor suppressor, yet its upregulated expression is associated with increased metastasis, and worse patient prognosis. This outcome may be related to findings in HCC where phosphorylation of TAGLN2 by PFTK1 (an oncogenic serine/threonine protein kinase) inactivates its actin-binding function, abrogating its suppression of cell motility[139]. Furthermore, in mouse metaphase I oocytes after IGF-1 treatment, miRNA-133b was upregulated more than 30-fold and target TAGLN2 was downregulated, stimulating growth and maturation of the oocytes[140]. These several reports indicate that both the miR-133 isomers may target TAGLN2.

OTHER PLEIOTROPIC PATHWAYS

The (semi-) homologous miRs-1 and -206 are downregulated in many cancers, acting as tumor suppressors (Table 3). The homologues share many of the same oncogenic targets, which may be released from negative regulation in tumors. Recently, Singh *et al*[99] (2013) demonstrated that downregulation of miR-1/-206 in lung adenocarcinomas (and NSCLC) have major effects on carbon flux and the activity of metabolic pathways associated with cell proliferation and growth. The inhibition of miR-1/-206 expression results (indirectly) from elevated NRF2 which in turn increases the activity of redox-sensitive HDAC4, affecting myomiR expression. Importantly, key targets of miR-1-2 and -206 include enzymes of the pentose phosphate pathway (including G6PD, PGD and TKT) and the tricarboxylic acid cycle enzyme GPD2, which increase their activities and potentiate cancer cell proliferation and compromise patient survival. Pleiotropic factors, such as KLF4, HDAC4 and IGFR-1 are also elevated in gastric carcinoma and in breast cancer cells in part due to the loss of miR-206[108], yet in contrast KLF4 is reduced in colon cancer tissue due to strong upregulation of -206[116]. KLF4 is a zinc-finger transcription factor that binds to the TGF-β1 promoter and is important during normal cellular differentiation and proliferation. KLF4 is highly expressed in normal cardiac fibroblasts where it promotes the formation of myofibroblasts[141].

Some common molecular targets of the isoforms of miR-133 are elevated in different cancers (Tables 4 and 5). Moesin, a member of the ezrin-radixin-moesin protein family which links functionally between the plasma membrane and the actin-based cytoskeleton of cells and is found in invadopodia of metastatic cells[142], is deregulated in HNSCC, breast cancer, CRC, and prostate cancer. In HNSCC cells both miR-133a/-133b target moesin specifically, and restoration of miR-133b levels in HNSCC cells, as well as in PC10 and H157 lung SCC cell lines, reduces moesin expression, inhibits cell proliferation, cell migration and invasion[143]. The phenotype is also associated with elevation of other miR-133 targets such as ARPC5 and GSTP1[115]. Both ARPC5 and GSTP1 levels are elevated in lung-SCC and elevated GSTP1 is seen in bladder cancer (TCC) associated with reduced levels of miR-133a[144].

Several large cohort studies have examined the changes in expressed miR networks in a variety of cancers. Navon *et al*[95], Hart *et al*[125], Han *et al*[127], Itesako *et al*[128] and Volinia *et al*[145] noted that the downregulated expression of the *miR-133/-1/-206* genes is associated with a variety of solid tissue cancers, with numerous other miRs also having highly significant oncogenic roles in particular cancer types. In sum, the downregulation of the various myomiRs contributes significantly to the upregulation of oncogenic proteins linked to regulation of cell cycle progression in solid tumors, sarcomas and carcinomas.

UPREGULATED MYOMIRS IN CANCER

In yet other cancers in which the upregulation of a myomiR is associated with worsening metastasis or potentiation of cancer severity, the downregulation of different tumor-suppressor factors appears to be critical. In cervical cancer the upregulation of miR-133b is associated with downregulation of Mst2 protein kinase (STE20), Cdc42 and RhoA, which in turn lead to increased p-ERK and pAKT1 signalling activity,

resulting in tumorigenesis and metastatic cancer proliferation[121]. RhoA, Cdc42 and other small Rho GTPases are components the Rho-kinase pathway which is a key controller of fundamental cellular processes such as cell motility, cell proliferation, cell division, cell differentiation, cell apoptosis, as well as morphological structure development, epithelial and skin morphogenesis, nerve system and limb development[146-148]. The downregulation of these key factors restricts cell apoptosis, favouring tumorigenesis. Interestingly, elevated levels of RhoA, Cdc42, Nelf-A/WHSC2 are also observed in hypertrophic cardiac muscle, associated with reduced levels of miR-133a[6], suggesting that both isomers of miR-133 may normally regulate these factors (in muscle). Similarly, the disruption of the Mst2 pathway is also associated with the disruption of cell apoptosis, of abrogating cell cycle regulation and with increased tumorigenesis in mouse intestinal epithelium[149], specifically by derepressing the accumulation of Yes-associated protein[150] which results in strong activation of β-catenin and Notch signalling. Elevation of Notch has also been seen in colorectal tumors associated with reduced miR-1 levels.

In AML the levels of expression of both miR-133a and miR-1 were elevated significantly[120,151]; similar to multiple myeloma where upregulation of these myomiRs was associated with the downregulation of the cyclin CCND2[152]. Wang *et al*[153] (2007) also found in patients with AML that downregulated CCND2 and CCND3 results in dephosphorylation of phospho-retinoblastoma protein and induction of G(1) cell-cycle arrest. These findings suggest that CCND2 may also be downregulated in AML in association with the upregulation of miR-133a and miR-1 levels, similar to multiple myeloma. During development or regeneration of normal muscle, the downregulation of CCND2 strongly enhances the myogenic terminal differentiation of muscle progenitor cells[154]. Taken together, the upregulation of these myomiRs in particular cancers can contribute to the deregulated repression of cell factors such MST2, RHOA, CDC42, CCND2 and others, which then also contribute to dysregulation of other cell signalling pathways, potentiating oncogenesis and metastasis. In contrast, a study of the miR network associated with altered mRNA profiles in AML[155] found that miRs other than myomiRs had highly significant roles in key deregulated pathways. Overall, the several studies suggest that myomiRs also contribute to development of AML.

LONG NON-CODING RNA

Long non-coding RNAs (lncRNAs) are emerging as important new regulators of oncogenic pathways in cancers, and miRs are emerging as important regulators of lncRNA activities. Recently Wang *et al*[156] (2014) reported that deregulated expression of lncRNA UCA1, an important new oncogene in human bladder cancer (TCC), can be downregulated by miR-1 *in vitro*. These two factors are inversely expressed in bladder cancer tissue *in vivo*. lncRNA UCA1 expression is induced by HIF-1α which stimulates bladder cancer cell proliferation, migration, and invasion under hypoxic growth conditions[157]. It is also induced by the transcription factor CCAAT/enhancer binding protein α[158], and in another route for potentiation of bladder cancer cell growth and reduction of cell apoptosis the transcription factor Ets-2 binds directly at the UCA1 promoter, stimulating UCA1 promoter activity[159]. In bladder cancer cell lines the transgenic alteration of lncRNA UCA1 levels positively influences AKT expression and activity, and cell cycle progression could be reduced by inhibition of the PI3-K pathway, indicating that lncRNA UCA1 affected cell cycle progression through CREB[160]. Taken together, lncRNA UCA1 regulates the cell cycle through CREB and *via* PI3K-AKT-dependent pathways in bladder cancer. Interestingly, several of the cellular factors which are induced by lncRNA UCA1 are also regulated at the expression level by myomiRs. miR-206 targets HIF-1α directly, hence hypoxia-induced downregulation of miR-206 promotes pulmonary hypertension *via* elevated HIF-1α in hypoxic rat model pulmonary artery smooth muscle cells (Table 6). Additionally, during regeneration of injured muscle, the AMPK-CRTC2-CREB and Raptor-mTORC-4EBP1 pathways are activated in satellite cells, which involve regulation by miR-1[58]. The involvement of myomiRs in the regulation of these cellular factors in muscle cells suggests a potential for involvement of lncRNA UCA1 in the regulation of normal cellular processes involving the above protein factors.

Recently, the lncRNA MALAT1 which is upregulated during the differentiation of myoblasts into myotubes in normal muscle biogenesis[161] was also reported to be upregulated in several non-muscle cancers associated with worsening patient outcomes[162,163]. In skeletal muscle MALAT1 expression is downregulated by myostatin[161], whilst the silencing of MALAT1 expression in the mouse myoblast C2C12 cells results in the reduction of SRF transcription factor at both RNA and protein levels as well as reduced myocyte differentiation[164]. The MALAT1 transcript has a functional miR-133 target site, thus miR-133 acts as a competing endogenous RNA, regulating MALAT1 levels, which in turn modulates SRF activity. SRF also regulates the expression of miR-133a in C2C12 cells by its binding to the miR-133a enhancer[22], indicating a complex regulatory loop involving SRF, miR-133 and MALAT1.

MYOMIR TARGETS IN MUSCLE AND TUMOURS

Considering the central role of the myomiRs in the cell biology of myogenesis and muscle cell differentiation,

in muscle metabolism, as well as in muscle remodelling and recovery from injury, it may be expected that they regulate the expression of numerous other target genes, in addition to the well documented pathway genes associated with key processes. In non-muscle-tissue cancers in which myomiRs play critical roles, the myomiRs influence expression of a variety of intermediary regulatory pathway genes, causing the potentiation of tumour development and metastasis. Literature searches (PubMed) show that essentially all myomiR targetted genes detected in different cancers have identified roles in several aspects of muscle cell biology. Thus, the myomiRs likely influence the expression of these gene targets in muscle in a normal regulatory manner, yet in non-muscle cancers the deregulated expression of myomiRs contributes to the dysregulated expression of these various gene targets, to the advancement of cancer development.

CONCLUSION

This review examines the diverse and complex regulatory functions of the cistronic myomiRs miR-133, -1 and -206 in numerous tissues. The myomiRs are intimately involved in the regulation of many processes of muscle development, muscle cell metabolism and homeostasis. Indeed some of the myomiRs are critical cell factors that commit stem cells onto the path of muscle cell differentiation and development, and their removal can elicit de-differentiation of committed muscle cells to an undifferentiated state. This centrality of cell regulatory functions suggests that, by necessity, these miRs would also be involved in redeveloping and repairing tissue after damage or injury, and that dysfunctional expression of myomiRs would play important roles during disease states. Furthermore, individual myomiRs have functional roles in the development of numerous non-muscle cells and tissues, beyond their original classification as muscle-specific factors, and hence the observation that myomiRs have roles in an increasing number of different cancer types should perhaps not be surprising. Whilst the myomiRs can display either tumor suppressor or tumor stimulator roles in different cells and tissues, independent cellular function assays confirm that the altered expression of the myomiRs typically correlates with the potentiation of cancer severity. This apparently contradictory ability of miRs to cause tumor suppression or tumor stimulation actions in different tissues relates to the multiple regulatory pathway genes targeted by each miR and the specific regulatory functions targeted in each tissue type. Interestingly, this ambiguity parallels the alternate roles of key signalling pathway regulatory genes in cancers, for example the increased expression of members of the FOX family of genes can cause either tumor suppression or tumor stimulation in different cancer types[165]. Significantly, the number of validated targets of each of the myomiRs has increased greatly in recent years, yet the extent to which each myomiR, miR-133, miR-1 or miR-206, contributes to specific tumorigenesis or tumor progression must await fuller clarification and integration with complex cellular regulatory pathway processes which are not yet fully defined.

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