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Essay

Muscle-specific microRNAs in skeletal muscle development

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ABSTRACT

Proper muscle function constitutes a precondition for good heath and an active lifestyle during an individual's lifespan and any deviations from normal skeletal muscle development and its functions may lead to numerous health conditions including e.g. myopathies and increased mortality. It is thus not surprising that there is an increasing need for understanding skeletal muscle developmental processes and the associated molecular pathways, especially as such information could find further uses in therapy. The understanding of complex skeletal muscle developmental networks was broadened with the discovery of microRNA (miRNA) molecules. MicroRNAs are evolutionary conserved small non-coding RNAs capable of negatively regulating gene expression on a post-transcriptional level by means of miRNA–mRNA interaction. Several miRNAs expressed exclusively in muscle have been labeled myomiRs. MyomiRs represent an integral part of skeletal muscle development, i.e. playing a significant role during skeletal muscle proliferation, differentiation and regeneration. The purpose of this review is to provide a summary of current knowledge regarding the involvement of myomiRs in the individual phases of myogenesis and other aspects of skeletal muscle biology, along with an up-to-date list of myomiR target genes and their functions in skeletal muscle and miRNA-related therapeutic approaches and future prospects.

1. Introduction

1.1. What are microRNAs?

MicroRNAs (miRNAs or miRs, with individual miRNAs and their genes termed miR-# and *mir-#*, respectively) are an evolutionally conserved class of recently identified repressors of gene expression in Chromalveolata, Mycetozoa, Viruses, Viridiplantae (plants) and Metazoa (animals) which function primarily at the post-transcriptional level (Lagos-Quintana, 2001; Lau, 2001; Lee and Ambros, 2001; Bartel, 2004). They represent approximately 22 nucleotides long RNA sequences capable of silencing target genes by binding to target messenger RNAs (mRNAs) which results in target mRNA degradation or protein translation inhibition (Bartel, 2004). The inhibition of gene expression is mediated by Watson-Crick complementary binding between the 5′ end of the miRNA (known as the seed sequence) and sites located in the 3′ UTR (untranslated region) of the target mRNA, although it has also been reported that some miRNAs are capable of targeting the 5′ UTR or coding sequence (Jopling, 2005; Forman et al., 2008; Ørom et al., 2008). Furthermore, there is evidence of small RNAs directly controlling transcription by interacting with the promoter elements of target genes (Schwartz et al., 2008). To add to the complexity, a single miRNA may interact with plenty of genes, while, conversely, a single gene can be targeted by multiple miRNAs. As mentioned above, miRNAs normally act as negative regulators of gene expression; however, there is compelling evidence that miRNAs can also activate gene expression (Vasudevan et al., 2007; Ørom et al., 2008).

The increasing number of newly identified miRNAs led to the establishment of a registry designed to catalog miRNAs and assign miRNA gene names prior to publication (Griffiths-Jones, 2004). The current version of the miRBase database (www.mirbase.org; v21, June 2014) contains 28,645 miRNA loci from 223 species, processed to produce 35,828 mature miRNA products with 2588 human mature miRNAs. Future research of miRNAs is likely to be clinically relevant since miRNAs regulate over 60% – if

Abbreviations: HDAC4, histone deacetylase 4; MEF2, myocyte enhancer factor 2; miRNA, microRNA; MRFs, myogenic regulatory factors; MYF5, myogenic factor 5; MYF6, myogenic factor 6 (herculin); MYH6, myosin, heavy chain 6, cardiac muscle, alpha; MYH7, myosin, heavy chain 7, cardiac muscle, beta; MYH7B, myosin, heavy chain 7B, cardiac muscle, beta; MYOD1, myogenic differentiation 1; MYOG, myogenin (myogenic factor 4); PAX3, paired box 3; PAX7, paired box 7; pre-miRNA, miRNA precursor; pri-miRNA, primary miRNA; RISC, RNA-induced silencing complex; SCs, satellite cells; SRF, serum response factor; UTR, untranslated region

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not all – of the mammalian genome, which emphasizes their importance as a novel means of manipulating gene expression (Friedman et al., 2009).

1.2. Biogenesis and function of microRNAs

Genetic mapping has shown that miRNA genes are derived from intergenic or intragenic regions, both intronic and exonic, and that they are often found in clusters (Lagos-Quintana, 2001; Rodriguez et al., 2004). MicroRNAs are initially transcribed as long primary transcripts by RNA polymerase II in the nucleus (Lee et al., 2004). These transcripts are termed primary miRNAs (pri-miRNAs) and contain a 5′ m^7G cap structure as well as a 3′ poly(A) tail, which are both unique properties of class II gene transcripts (Cai, 2004). Pri-miRNAs are subsequently processed in the nucleus where they form stem-loop structures recognized by a microprocessor complex composed of two core elements, the dsRNA-binding protein DGCR8 (DGCR8 microprocessor complex subunit; also known as Pasha in flies and nematodes) and the RNase III endonuclease Drosha (Lee et al., 2003; Denli et al., 2004; Gregory et al., 2004). Drosha associated with DGCR8 cleaves both strands of the stem near the base of the primary stem-loop to produce an approximately 70 nt hairpin intermediate called a miRNA precursor (pre-miRNA) (Lee et al., 2002, 2003; Zeng and Cullen, 2003). The processing of pri-miRNA may be further regulated by specific transcription factors which include SMAD (small mothers against decapentaplegic) proteins, the signal transducers of TGFB (transforming growth factor beta)/BMP (bone morphogenetic protein), by facilitating the cleavage reaction performed by Drosha (Davis et al., 2008, 2010). Once the pre-miRNA is generated, it is subsequently transported from the nucleus to the cytoplasm for further processing by XPO5 (exportin 5) in the presence of the Ran-GTP cofactor (Yi, 2003). The next step requires a second RNase III endonuclease, Dicer1 in humans, together with its dsRNA binding protein TARBP2 [TAR (HIV-1) RNA binding protein 2] in humans, which cleaves on the loop side of the pre-miRNA hairpin to produce a $\approx$22 nt double stranded miRNA (Bernstein et al., 2001; Grishok et al., 2001; Hutvagner, 2001; Chendrimada et al., 2005). This miRNA duplex is subsequently unwound by helicases which generate two potentially functional miRNAs. These two single-stranded miRNA sequences, i.e. miRNA (leading/mature strand) and miRNA* (passenger strand), and/or 5p and 3p miRNAs, respectively, depending on which arm of the pre-miRNA hairpin they are derived from, have different fates (Lau, 2001). The mature miRNA strand of the miRNA:miRNA* duplex is preferentially transferred to RISC (RNA-induced silencing complex) containing dsRNA binding proteins together with Dicer and AGO2 (argonaute RISC catalytic component 2), the catalytic engine of RISC, while the miRNA* strand is mostly targeted for degradation (Schwarz et al., 2002, 2003; Khvorova et al., 2003; Liu, 2004; Meister et al., 2004; Chendrimada et al., 2005; Lee et al., 2006). Mature miRNA subsequently guides RISC to mRNA 3′ UTR; RISC binding leads either to mRNA degradation or translation inhibition, depending on whether binding is complete or incomplete (Hammond et al., 2000; Martinez et al., 2002; Pillai, 2005). In addition, Brennecke et al. provided evidence that the miRNA 3′ end might also contribute to binding efficiency between miRNA and its targeted mRNA (Brennecke et al., 2005). Authors concluded that 3′ end compensatory sites are responsible for the determination of target specificity within miRNA families, where miRNAs have similar but not identical sequences.

2. Skeletal muscle function and myogenesis

Approximately 42% and 36% of the body of the average male and female, respectively, consists of skeletal muscle mass which has the ability to contract or stretch, thus producing skeletal movement. In addition to locomotion, skeletal muscles also generate heat, store protein reserves and maintain posture while supporting and protecting soft tissues, i.e. internal tissues and organs. Skeletal muscle development has been intensively studied, especially since any deviation from its normal progress may lead to the development of pathological conditions. Human embryonic skeletal muscle myogenesis is a multi-step process which consists of several major stages: (1) proliferation and differentiation of myogenic progenitor cells located in the dermomyotome and/or myotome into myoblasts, (2) differentiation and fusion of myoblasts into myotubes, and (3) differentiation of myotubes into myofibres. Skeletal muscle development is a complicated process which involves genes responsible for proper muscle growth, morphology and contractility, i.e. cell proliferation, differentiation, interactions, migration and death. These processes are predominantly regulated by MRFs (myogenic regulatory factors) of the bHLH (basic helix-loop-helix) family of transcription factors MYOD1 (myogenic differentiation 1), MYF5 (myogenic factor 5), MYOG [myogenin (myogenic factor 4)] and MYF6 [myogenic factor 6 (herculin)] together with other transcription factors involved in myogenesis such as PAX3 (paired box 3), PAX7 (paired box 7) and the MEF2 (myocyte enhancer factor 2) family (Brand-Saberi, 2005). MYOD1 and MYF5 participate in the first stage of skeletal muscle development by promoting proliferation and differentiation of myogenic progenitor cells into myoblasts while MYOG plays an important role in the differentiation of myoblasts into myotubes and MYF6 participate in differentiation and cell fate determination (Ito et al., 2012).

Recently, miRNAs have emerged as new players in skeletal muscle myogenesis by participating in orchestrated gene regulation processes. Their essential role in skeletal muscle development has been highlighted in experiments using Dicer knock-out mice which resulted in embryonic lethality in experimental animals (O'Rourke et al., 2007). In these animals, Dicer knock-out led to skeletal muscle hypoplasia, resulting in a significant decrease in skeletal muscle mass and a lower number of myofibres and aberrant myofibre morphology, increased apoptosis of myogenic cells and enhanced cell death in myoblasts.

3. Muscle-specific microRNAs (myomiRs)

While knowledge of miRNAs is increasing, it has been noted that not all miRNAs are ubiquitously expressed, i.e. that some are expressed in a tissue specific manner (Lee and Ambros, 2001; Lagos-Quintana et al., 2002). MicroRNAs which are exclusively or preferentially expressed in striated muscle are called myomiRs (myo=muscle+miR=microRNA) (McCarthy, 2008). The group currently includes eight miRNAs: miR-1, miR-133a, miR-133b, miR-206, miR-208a, miR-208b, miR-486 and miR-499 (see Table 1) (Sempere et al., 2004; Rooij et al., 2007, 2009; Small et al., 2010). MyomiRs are expressed in both cardiac and skeletal muscle with the exception of miR-206, which is skeletal muscle-specific, and miR-208a, which is cardiac muscle-specific. Some studies have provided evidence that not all myomiRs are solely expressed in a muscle-specific manner but may be detected in low levels in other tissues; however, their main function is still confined to muscle (Lagos-Quintana et al., 2002; Walden et al., 2009). MiR-486 is sometimes considered "muscle-enriched" rather than "muscle-specific" as it is also expressed in other tissues (Small et al., 2010). Differences in the tissue representation of individual miRNAs have been defined as follows: (1) "tissue-specific" miRNAs are detectable in specific tissues in 20-fold or higher expression levels in comparison with the mean values of other tissues, while (2) "tissue-enriched" miRNAs include miRNAs whose expression levels

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