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Mini review

miRNAs regulate expression and function of extracellular matrix molecules ☆

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ABSTRACT

MicroRNAs (miRNAs) are a family of small non-coding RNA molecules that are made up of 18–25 nucleotides that function in post-transcriptional gene regulation. The expression of miRNAs is highly conserved and essential in regulating many cellular processes including formation, maintenance and the remodelling of the extracellular matrix (ECM). In this review, we examine different ECM molecules and the miRNAs involved in regulating their abundance and how these changes influence cell phenotype. For example, miRNAs and their target messenger RNAs (mRNAs) are involved in cell adhesion, by regulating the synthesis and turnover of key ECM adhesion molecules and their receptors including cadherins, integrins and other non-integrin ECM receptors. Other miRNAs regulate the abundance of cytokines and growth factors which in turn stimulate cells to synthesize and secrete specialized ECMs. For example, miR-125a/b and miR-146a and their downstream target mRNAs influence the production of the epidermal growth factor family which has a significant impact on the nature of the ECM formed. miRNAs affect structural ECM proteins important in the assembly, composition and organization of the ECM. Proteins such as collagen, fibronectin, versican, and nephronectin are targeted by several miRNAs. miRNAs can also control the expression of proteins such as matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs), which are involved in ECM remodelling and are important for tissue development, cell motility and wound healing. It has become clear that many different miRNAs control the balance in ECM composition that determines normal tissue function and alterations in the expression of these miRNAs can lead to pathological consequences.

Contents

Abbreviations: miRNA, microRNA; ECM, extracellular matrix; mRNA, messenger RNA; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases; ncRNA, non-coding RNAs; lncRNA, long non-coding RNA; 3′UTR, 3′-untranslated region; Col-1, collagen type I; HCC, hepatocellular carcinoma; SLRP, small leucine-rich proteoglycans; Sox9, SRY-related high mobility group-Box gene 9; EMT, epithelial–mesenchymal transition; BRMS1, breast cancer metastasis suppressor 1; RA, rheumatoid arthritis; ADAMTS-5, A disintegrin and metalloproteinase with thrombospondin motifs-5.

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1. Introduction

The extracellular matrix (ECM) is a complex network of a number of different structural proteins, matricellular proteins, proteoglycans, hyaluronan and a variety of glycoproteins that interact by entanglement and cross linking to form a bioactive polymer that influences the mechanical properties of tissues and the phenotype of the cells that reside in those tissues. The ultimate composition of the ECM is determined by a combination of factors that influence new synthesis and turnover of individual ECM components. Changes in the individual components of the ECM and their organization have a significant impact on the cellular phenotype. MicroRNAs (miRNAs) provide one mechanism that controls the composition of the ECM and hence the phenotype of the cells that reside in that ECM. miRNAs are non-coding RNAs that are made up of 18–25 nucleotides and are able to modulate gene expression, by either inducing the degradation or blocking translation of the target messenger RNAs (mRNAs) (Bartel, 2009). miRNAs are highly conserved, and can be expressed in a tissue-specific manner and perform essential functions in regulating diverse cellular processes including those involved in development, differentiation, and disease (Johnston and Hobert, 2003; Chendrimada et al., 2005; Hatfield et al., 2005; Iorio et al., 2005; Lim et al., 2005; Dalmay and Edwards, 2006; Gauthier and Wollheim, 2006; Ruvkun, 2006; Chen and Stallings, 2007; Foekens et al., 2008; Huang et al., 2008b; Lowery et al., 2009; Wickramasinghe et al., 2009; Yang et al.). There are over 1000 human miRNAs that have been sequenced and reported, and it is estimated that one third of genes are regulated by miRNAs as one miRNA can regulate the expression of many genes (Lewis et al., 2005).

The biogenesis of miRNAs starts with transcription in the nucleus, similar to protein coding genes. Fig. 1 depicts the general biogenesis pathway of miRNAs. Typically, there is only one miRNA gene code for an individual miRNA; however, frequently some groups of miRNAs are transcribed as a single polycistronic transcript when they are clustered together (Baskerville and Bartel, 2005). miRNAs that are expressed in the same cluster usually do not share sequence similarities or target identical genes; however they do function together when they are co-expressed to control multiple target genes (Baskerville and Bartel, 2005). It is estimated that almost 70% of genes encoding for miRNAs overlap with defined transcriptional units and are transcriptionally linked to other genes, coding either for other non-coding RNAs (ncRNAs) or proteins (Rodriguez et al., 2004). miRNA genes have been reported between other genes, in the introns of protein-coding genes, and exons and introns of long non-coding RNA (lncRNA) transcripts (Rodriguez et al., 2004).

Many miRNA genes are also clustered together in the genome and can be transcribed as one transcript (Saini et al., 2007). In humans, over 247 miRNAs occur in clusters that have an inter-miRNA distance of less than 5000 bp (Griffiths-Jones et al., 2008). Also, the biological effect of these clusters can be strongly mediated by the fact that they have a high degree of conservation (Altuvia et al., 2005). For example the expression of the miR-23a–27a–24-2 cluster is upregulated in many disease conditions; heart failure, ulcerative colitis and cancers of the breast, pancreas, kidneys and bladder (van Rooij et al., 2006; Bloomston et al., 2007; Gottardo et al., 2007; Lee et al., 2007; Mertens-Talcott et al., 2007; Wu et al., 2008; Guttilla and White, 2009; Chow et al., 2010). However these miRNAs can also be independently transcribed as many of them have their own TATA box binding motifs which recruit transcriptional activators (Houbaviy et al., 2005). Furthermore, several transcription factors have been shown to be involved in regulating the expression of miRNAs by recruiting co-activators and other transcriptional elements (Shi et al., 2008). For example, Myc and the E2F family upregulate the transcription of the miR-17–92 cluster which has been shown to stimulate tumor growth (Aguda et al., 2008; Li et al., 2011c). In order to regulate translation, the association of the miRNA to the target 3′untranslated region (3′UTR) is believed to be driven through diffusion (Ameres et al., 2007).

miRNAs bind through base pairing to the 3′UTR of target mRNAs. The binding specificity and efficiency are believed to be determined by the 6–7 nucleotide sequence near the 5′ region of miRNA (Lewis et al., 2005). This sequence is called the “seed sequence” (Latronico et al., 2007), and is the initial binding site of the miRNA to the 3′ UTR of the target mRNA (Lim et al., 2005). This seed sequence also determines whether the mRNA is degraded or translation repression occurs due to the degree of complementarity between the seed sequence of miRNA and the binding site in the target mRNA's 3′UTR (Berezikov et al., 2005; Lim et al., 2005). It is also believed that mRNAs that are bound by miRNAs are targeted for degradation and are transported to the p-bodies leading to the translational repression of mRNAs (Liu et al., 2005). In this review, we give an overview of the current knowledge of the role of miRNAs in maintaining and remodelling the ECM structure.

2. Regulation of ECM composition and organization

Any given tissue has a preferred set of ECM components which are organized in such a way as to contribute to the mechanical properties of that tissue and to the organization and phenotype of the cells that reside in that tissue. The nature of the components and how they are organized determine the mechanical properties of the microenvironment surrounding the cells (i.e., stiff and rigid vs. soft and pliable) and these mechanical cues can have a major impact on regulating the differentiation and behavior of various cell types. Cells sense their surroundings by a set of receptors on their surface and this interaction results in signalling cascades that control the phenotype of the cells. Factors that control the composition of the ECM and the organization and availability of specific components of the ECM are critical for driving cellular events that form the basis of development and disease. miRNAs can regulate the composition of the ECM and impact the availability of certain ECMs in a number of different ways. Such a system that has an inherent redundancy generates complex overlapping pathways that can control cellular phenotypes. Some examples are discussed in the following sections.

2.1. Nephronectin

The composition of the ECM is critical in the organization and preservation of epithelial apical–basolateral polarity. Nephronectin is a secreted ECM protein that is expressed in a variety of tissues in the developing mouse embryo (Brandenberger et al., 2001). Exogenous overexpression of nephronectin promotes osteoblast differentiation and bone nodule formation, which appears to be regulated by miRNA (Kahai et al., 2009). While the exact mechanism responsible for the impact of nephronectin expression on osteoblast differentiation is not known, striking cell shape changes are seen in the nephronectin-