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MicroRNA-214 and polycomb group proteins:

A regulatory circuit controlling differentiation and cell fate decisions

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During vertebrate development, gene expression is tightly controlled by dynamic regulatory circuits which determine and maintain cell lineages. These regulatory mechanisms, including transcription factor-DNA interactions and epigenetic programming, insure proper spatial and temporal gene expression. In addition to the aforementioned mechanisms, microRNAs (miRNAs) have been shown to play a critical role in controlling a wide range of cellular processes. miRNAs are 18–25 nucleotide long non-coding RNAs that repress mRNA translation or modulate mRNA degradation by binding to the 3'-untranslated region of target mRNAs. The primary miRNA transcripts are transcribed by RNA polymerase II and further processed to mature miRNAs by the Drosha/DGCR8 and Dicer complexes. Individual miRNAs can target hundreds of mRNAs and their expression is often associated with specific cell types or developmental stages.[1,2] This suggests that even a single miRNA can have a significant impact on numerous biological processes.

Several studies have shown that microRNA-214 (miR-214) is instrumental in determining cell fate in several cell types.[3,4,6] Yet the modalities by which miR-214 modulates cell lineage specification can be quite diverse. In zebrafish, miR-214 is required for muscle cell fate decision during somitogenesis. Inhibition of miR-214 expression decreases slow-muscle cell types in the developing somites. One miR-214 target in zebrafish is *suppressor of fused* (*su(fu)*), a negative regulator of Hedgehog signaling. By repressing *su(fu)* expression in different somite compartments, miR-214 mediates muscle cell fate transition through the Hedgehog pathway.[3] In mouse skeletal muscle, miR-214 shows robust expression in differentiating myoblasts. Overexpression of miR-214 in muscle cells results in premature expression of muscle genes and acceleration of muscle differentiation while blockage of its expression promotes myoblast proliferation and dampens myogenesis.[4] Genetic ablation of a region containing the murine mir-214 locus leads to several developmental defects, including reduced skeletal muscle mass.[5] Unlike zebrafish, in mouse skeletal muscle, miR-214 targets the Polycomb group protein (PcG) Enhancer of zest homologue 2 (Ezh2) to regulate muscle cell differentiation.[4] Ezh2 trimethylates lysine 27 of histone H3 (H3K27me3) and represses gene transcription. It has been shown that Ezh2 is developmentally regulated during myogenesis and blocks muscle differentiation by

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imposing H3K27me3 on muscle specific genes. It is critical to remove Ezh2 binding and its cognate methylation for appropriate muscle gene activation.[7] Therefore, repression of Ezh2 by miR-214 is essential for initiating muscle differentiation.[4] Interestingly, this miR-214-dependent Ezh2 regulation is also observed in embryonic stem (ES) cells. In ES cells induced to differentiate by retinoic acid, upregulation of miR-214 expression coincides with reduction of Ezh2 protein. Ectopic expression of miR-214 in pluripotent ES cells reduces Ezh2 protein level thus derepressing transcription of developmental regulators leading to loss of ES cell pluripotency.[4] In Xenopus, miR-214 is highly expressed in multipotent retinal progenitors at early embryonic stages. By repressing Xotx2 and Xvsx, two key regulators of late retinal neurons, miR-214 controls the developmental timing of these progenitors and determines their fate.[6]

The importance of miR-214 in cell fate commitment suggests that miR-214 expression also needs to be precisely controlled. The relevance of miRNA dynamic regulation is well illustrated in skeletal muscle where miR-214 transcription is regulated by a double-negative feedback loop in which miR-214 is repressed by Ezh2 and activated by myoD/myogenin.[4] In addition of being regulated at the transcriptional level, the processing of primary-214 transcripts to mature miRNAs is controlled by p72 Dead-box RNA helicase subunits in the mouse Drosha complex.[8] Of note, p72 itself associates with MyoD to promote muscle differentiation.[9] Thus, p72 helicase could promote differentiation by both co-activating MyoD-dependent transcription and favoring miR-214 processing. Figure 1 summarizes a working model of the regulatory network involving miR-214 during muscle differentiation. Muscle cell fate is determined by a series of events including transcription and biogenesis of miR-214 and the feedback loop between miR-214 and its target. The mechanisms discussed here may serve as a potential model for miRNA mediated regulatory networks in other biological systems.

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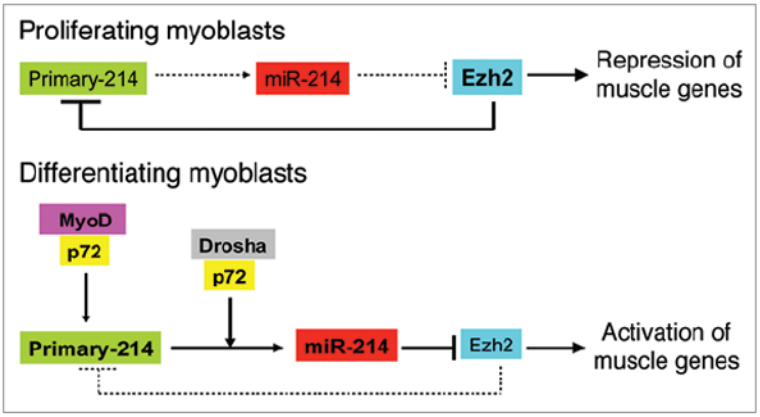

Figure 1.

In proliferating myoblasts, where it is highly expressed, Ezh2 represses primary-miR-214 transcription as well as other muscle specific genes to maintain the myoblasts in undifferented state. Upon differentiation, Ezh2 expression is reduced and miR-214 locus is derepressed. Robust production of miR-214 is achieved by MyoD/p72 mediated transcriptional activation and Drosha/p72 processing. miR-214 then negatively feeds back on Ezh2 by reducing its mRNA translation to further accelerate muscle differentiation.