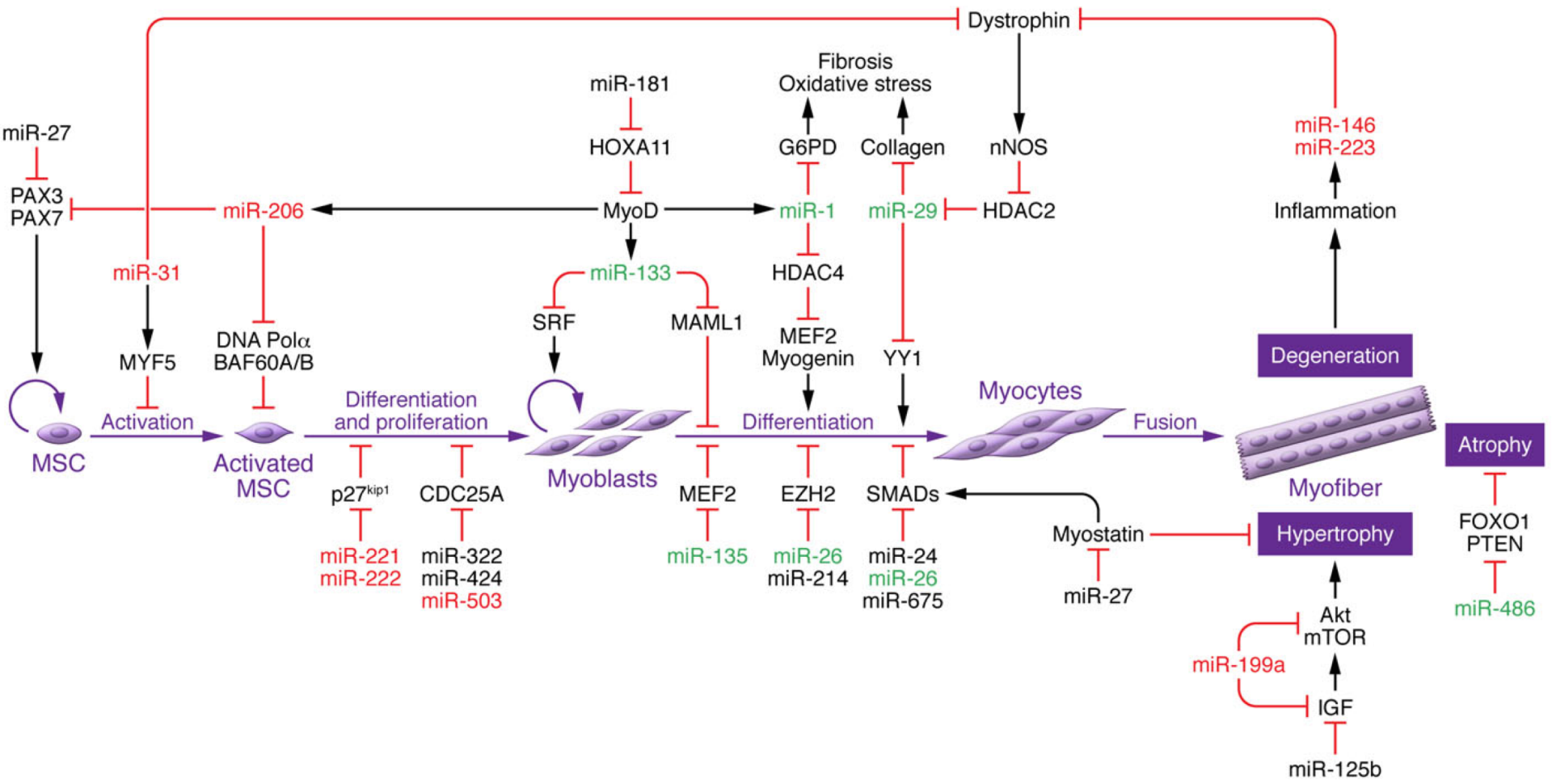
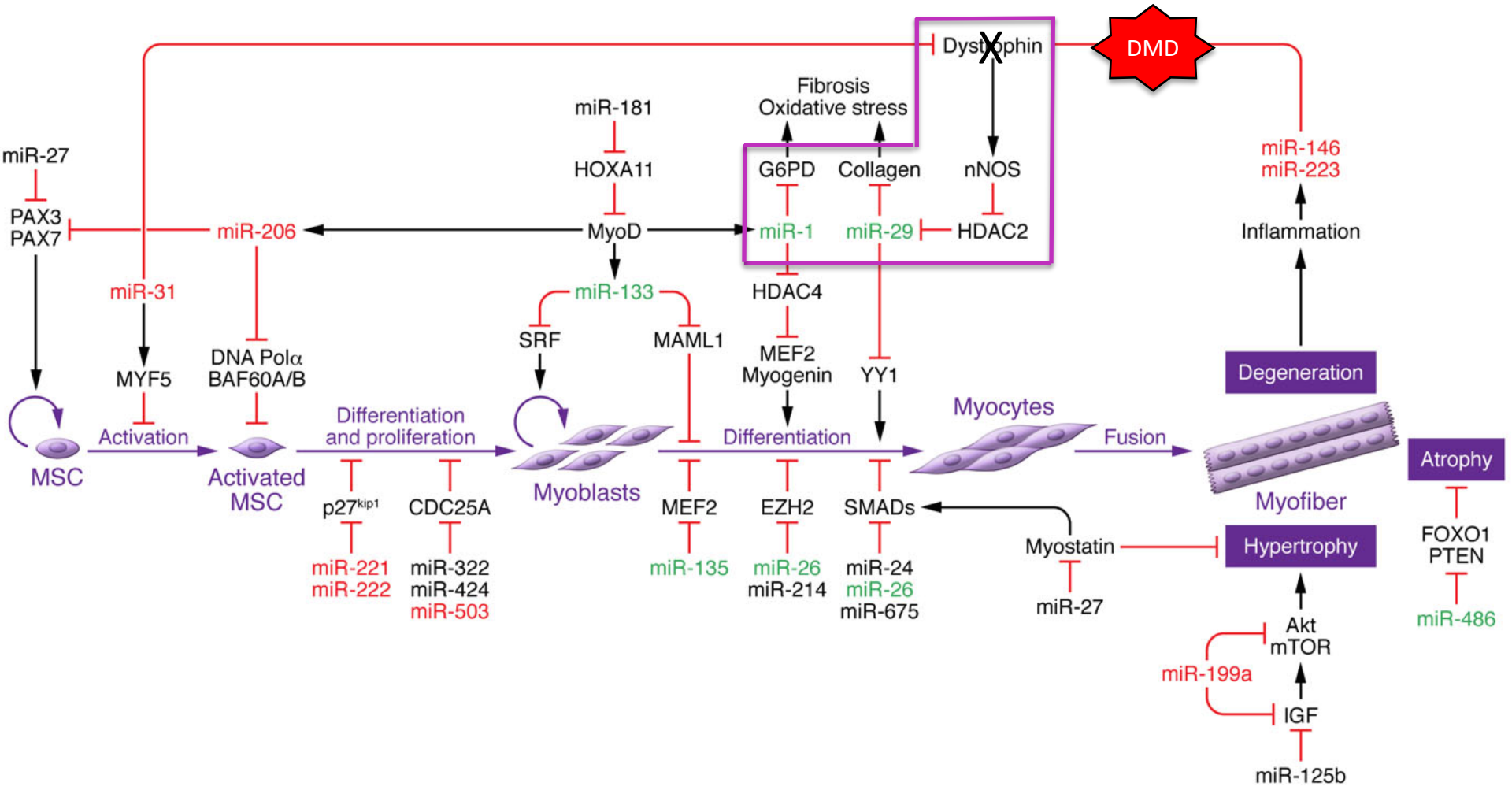
lncRNA and miRNA in muscle differentiation

miRNA in myogenesis



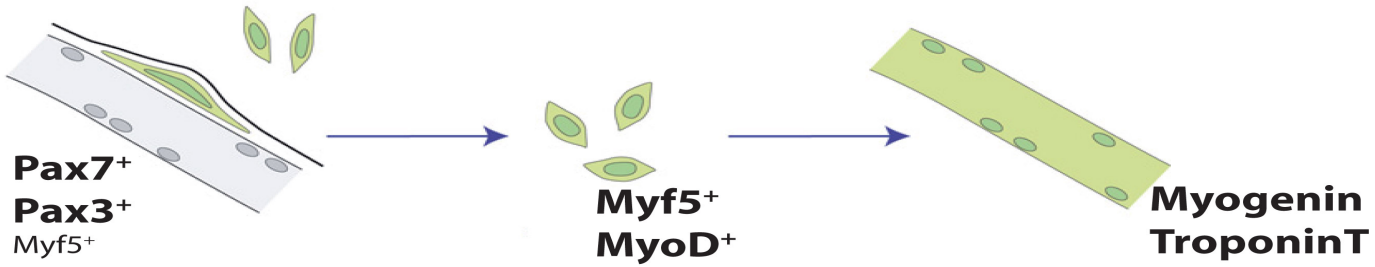
Ballarino M. *et al.* ***J. Clin Invest.,*** 2016

miRNA in myogenesis

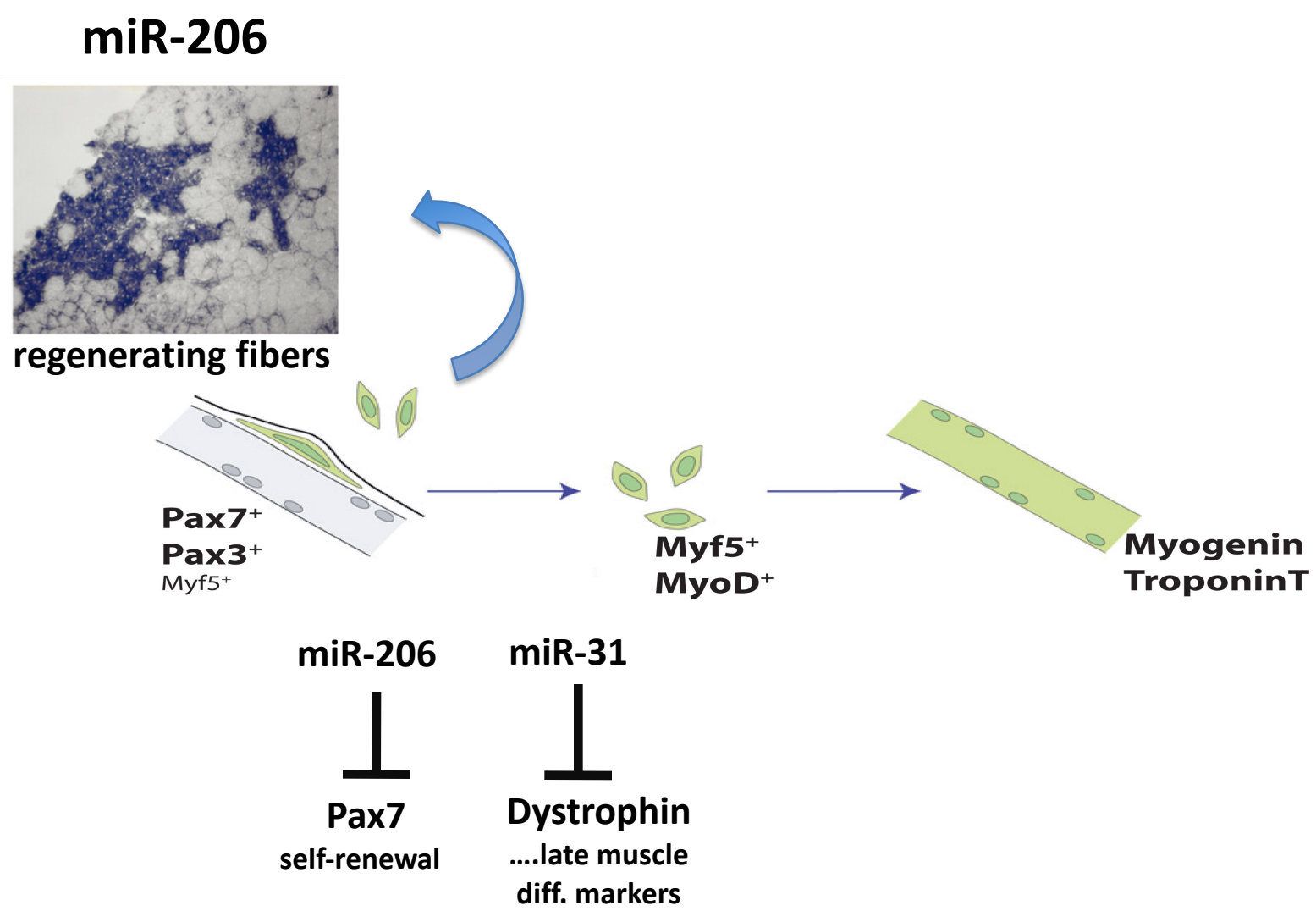


Cacchiarelli et al., ***Cell Metab***. **2010**

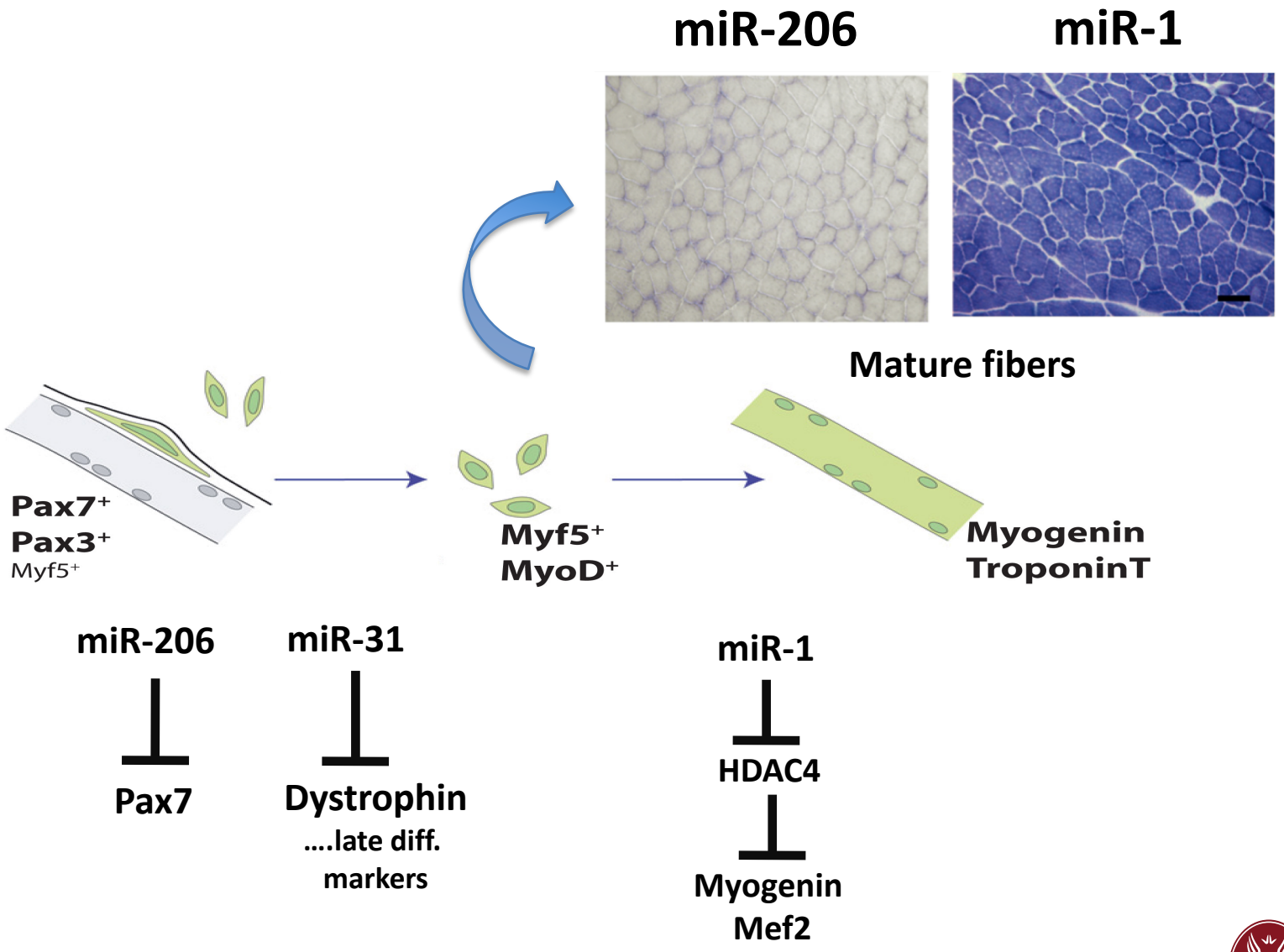
miR-206 and miR-1 are differentially activated during myogenesis



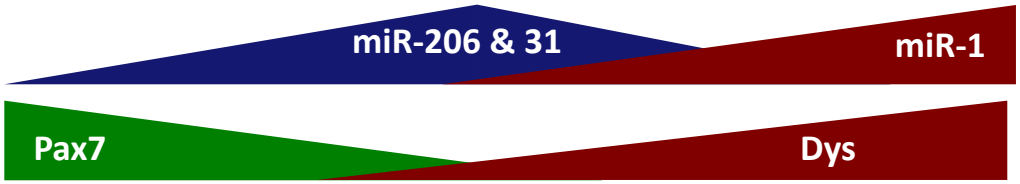
miR-206 and miR-31 are expressed in early phases of myogenesis

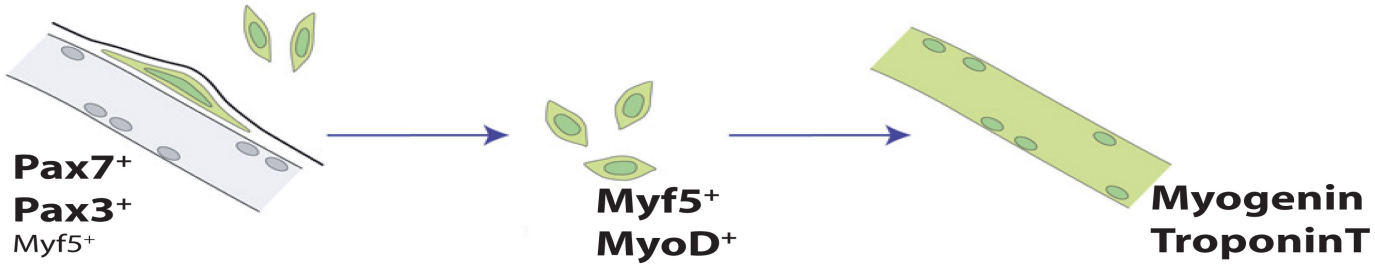


miR-1 is expressed at later stages of myogenesis



miR-206 and miR-1 are differentially activated during myogenesis



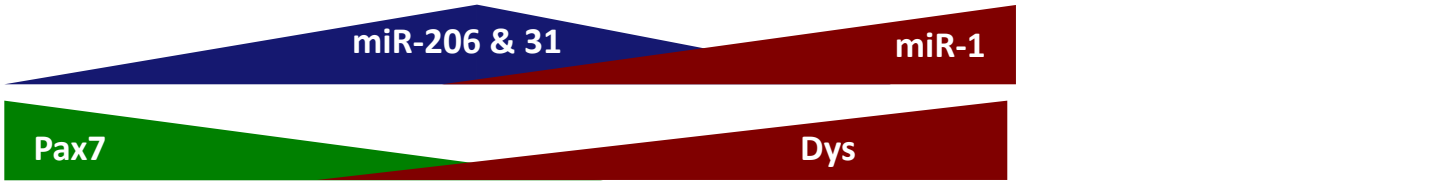


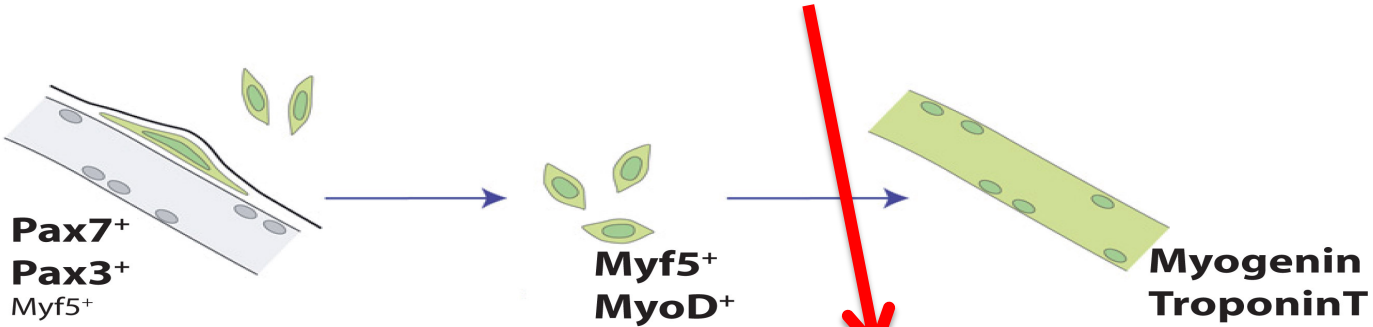
miR-206 ⊣ **Pax7**

miR-31 ⊣ **Dystrophin** ….late diff. markers

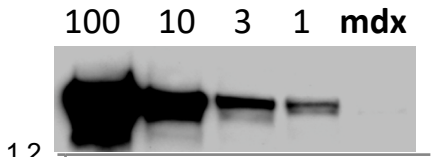
miR-1 ⊣ **HDAC4** ⊣ **Myogenin** **Mef2**

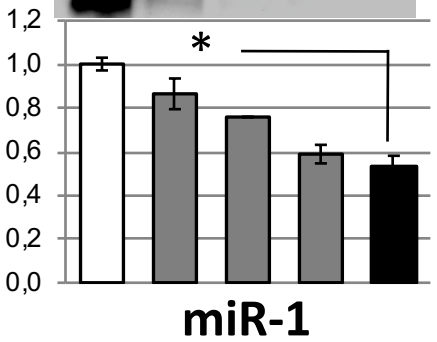
miR-1 levels correlate with dystrophin expression





dys





miR-1

⊥

HDAC4

⊥

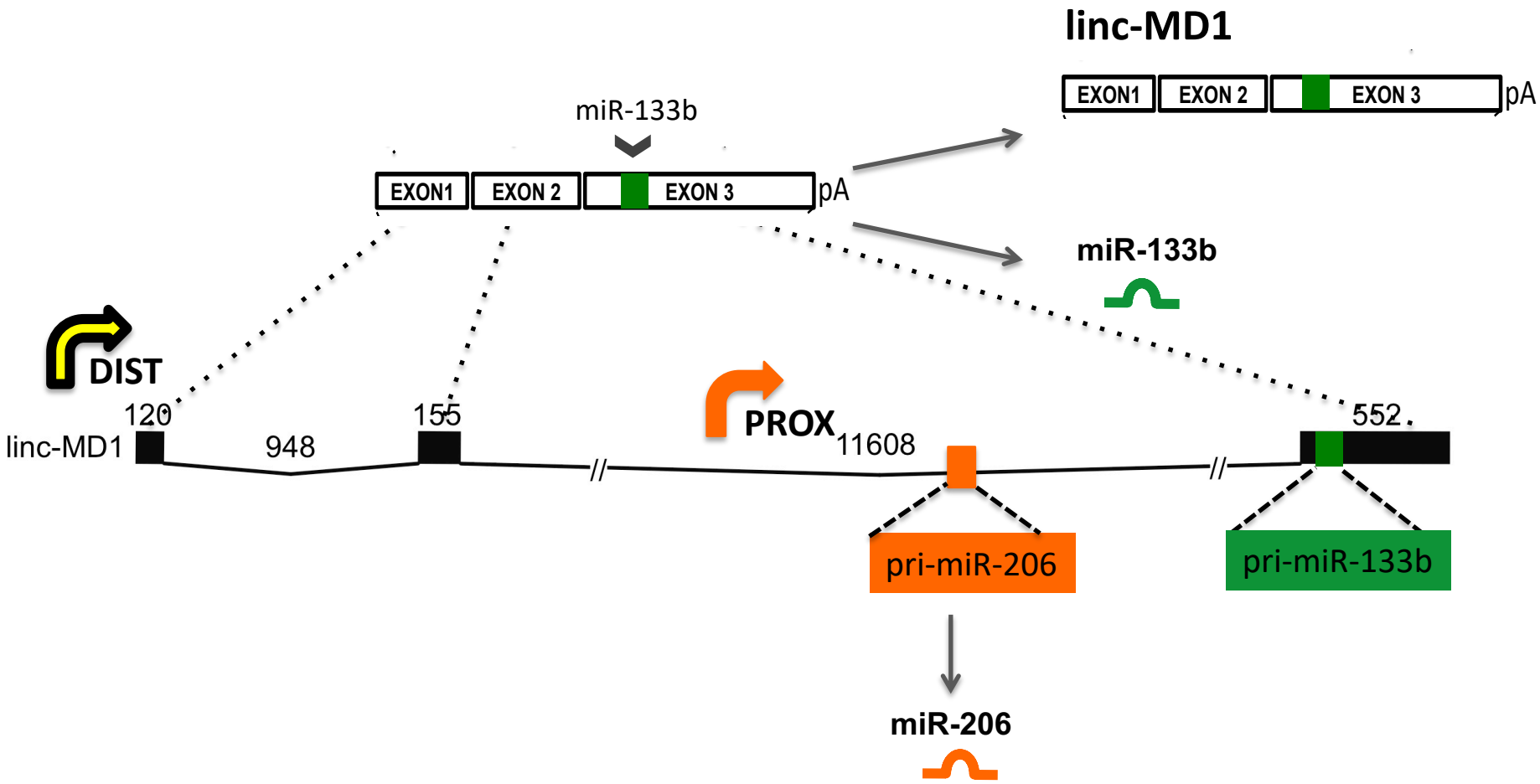
Myogenin
Mef2

miR-206 is *present only in vertebrates*

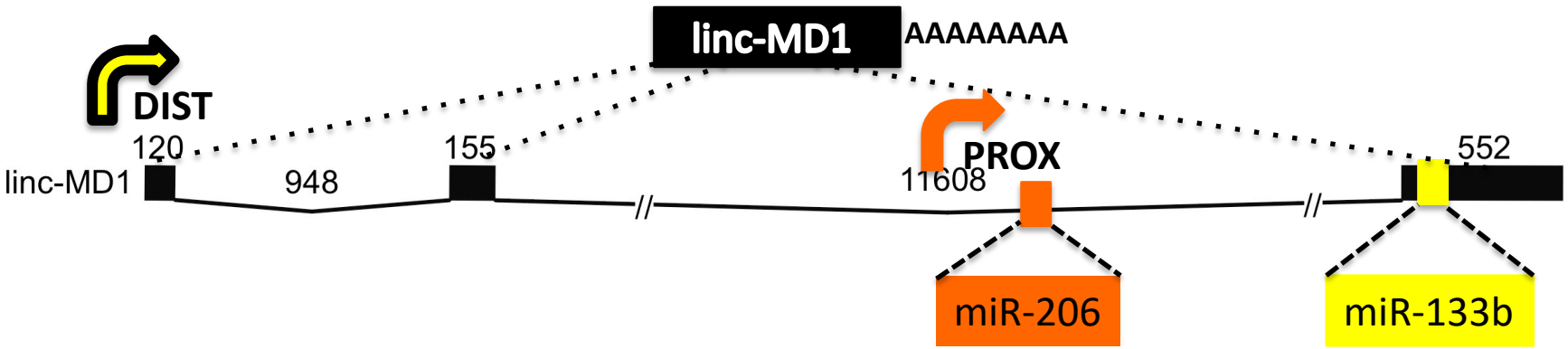
The origin of the miR-206/miR-133b locus correlates, indeed, with the increase in complexity of vertebrate skeletal muscle: in fact, fly and worm do not have satellite cells nor do they possess different fiber types such as slow-twitch and fast twitch fibers as found in vertebrate skeletal muscle

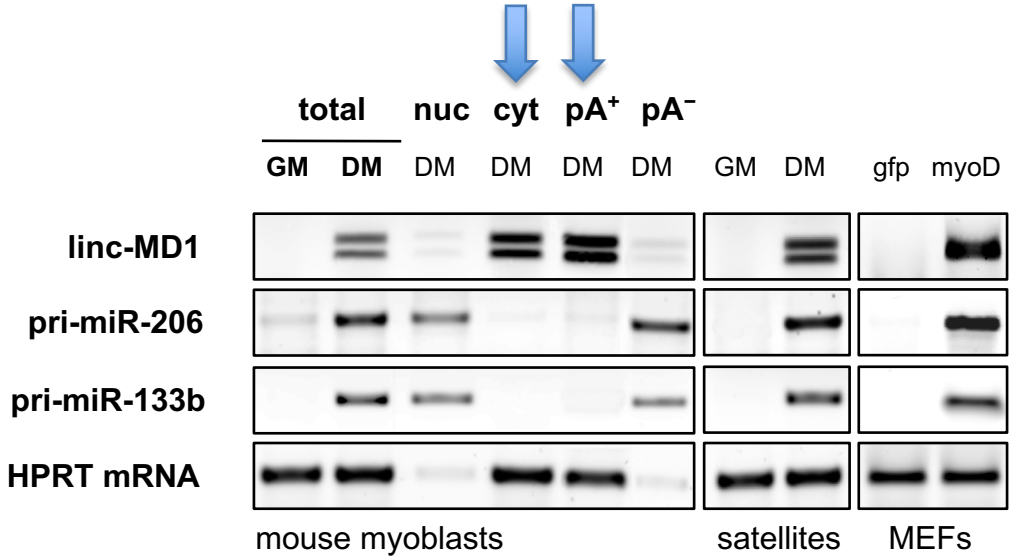
miR-206 – in activated precursor cells
miR1 – in differentiated myoblasts

Different types of transcripts originate from mir-206/mir-133b locus



linc-MD1 is a cytoplasmic polyA+ long non-coding RNA





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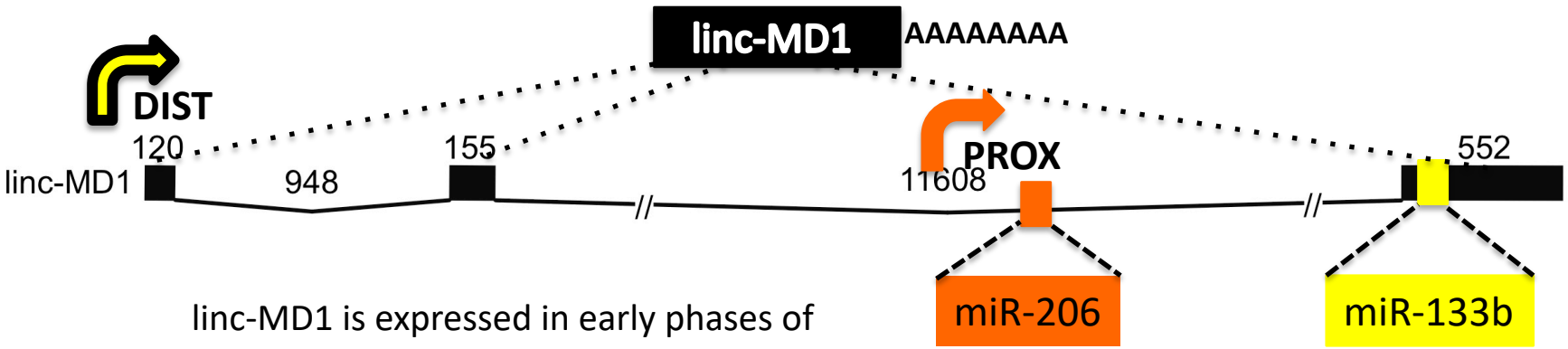
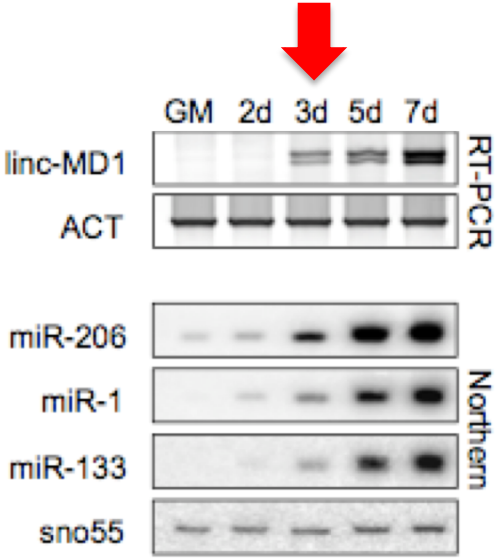
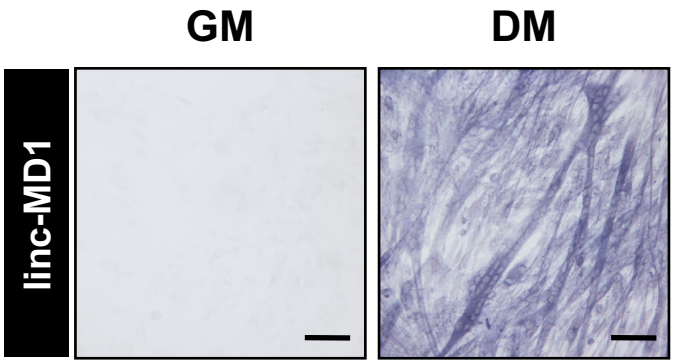


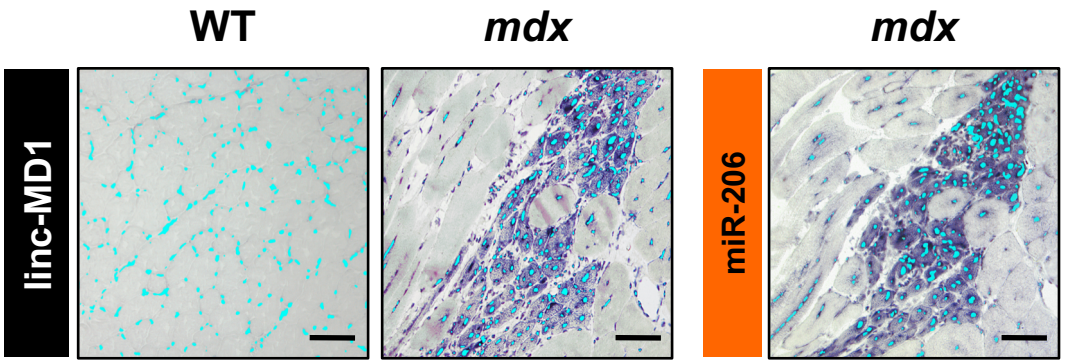
linc-MD1 is expressed in early phases of differentiation from the DIST promoter



linc-MD1 is expressed in differentiating myoblasts and not in mature fibers

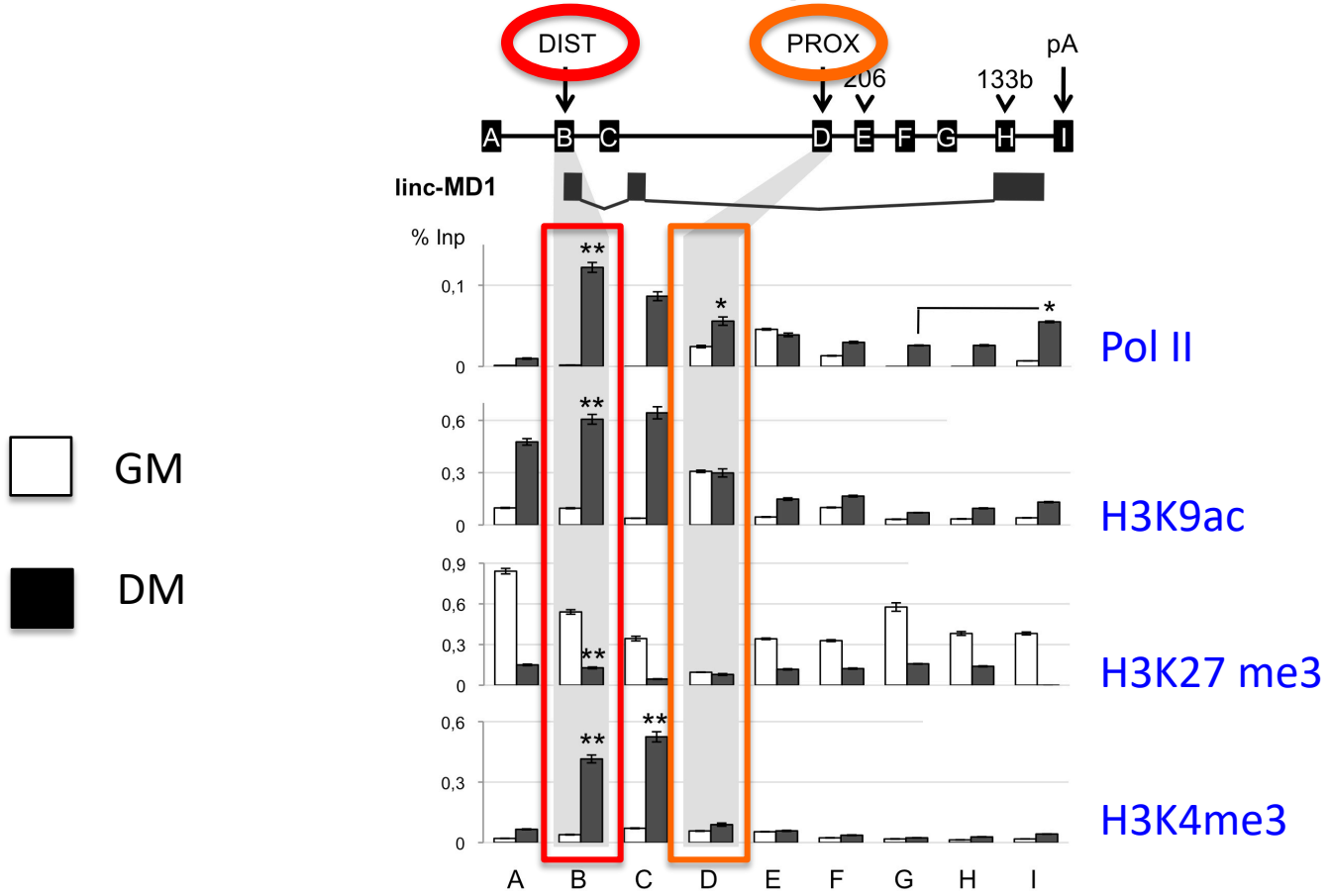


C2 myoblasts



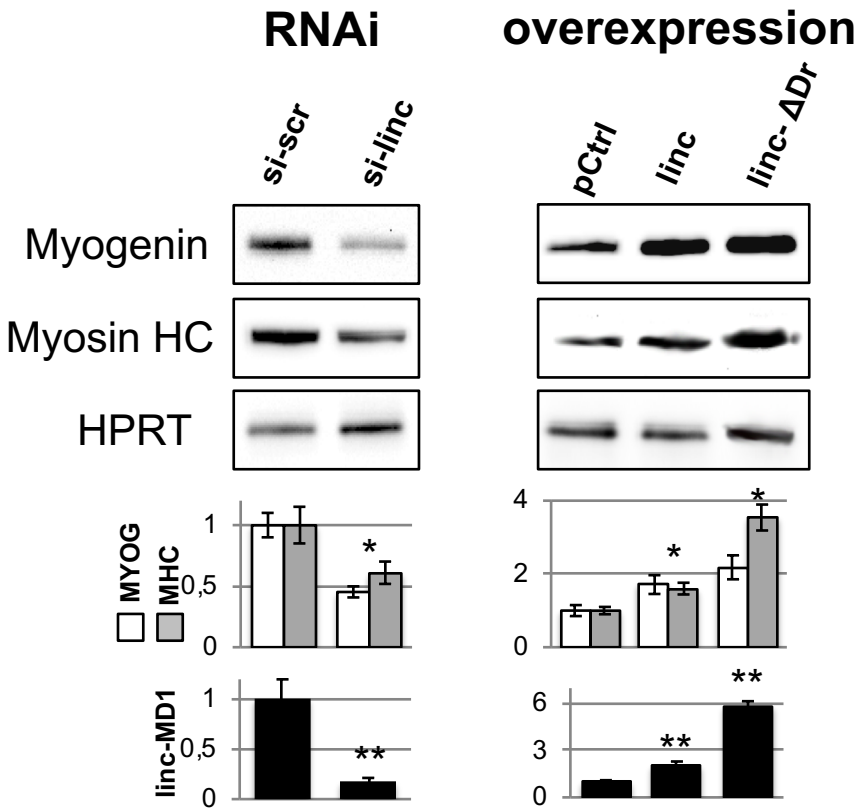
gastrocnemius

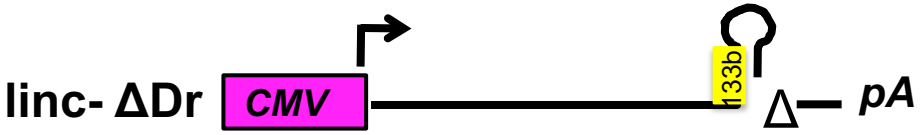
Transcriptional and Epigenetic Regulation of linc-MD1 and miR-206/133b expression



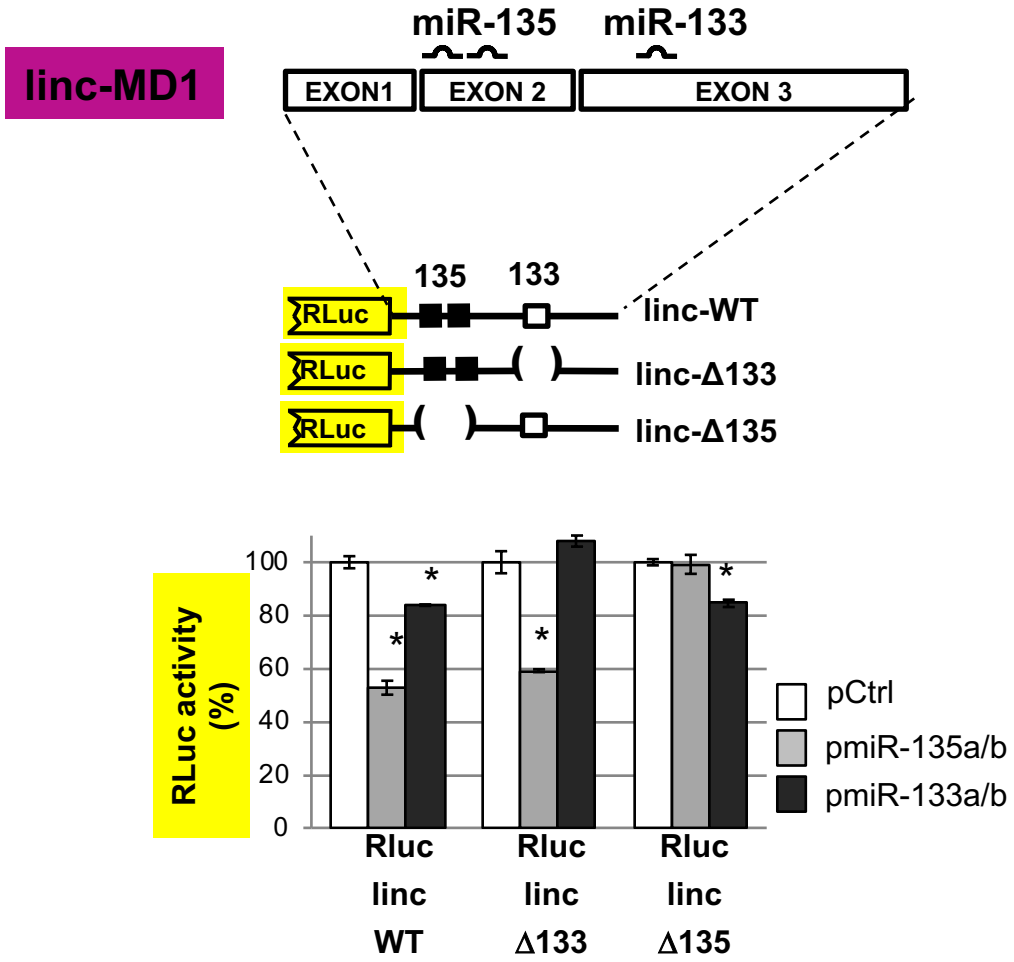
PROX and DIST promoters act at different stages of muscle differentiation, promoting miR-206, miR-133b and linc-MD1 expression

linc-MD1 levels affect expression of early myogenic markers



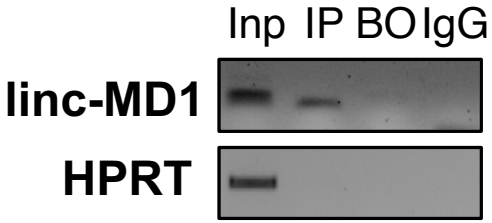


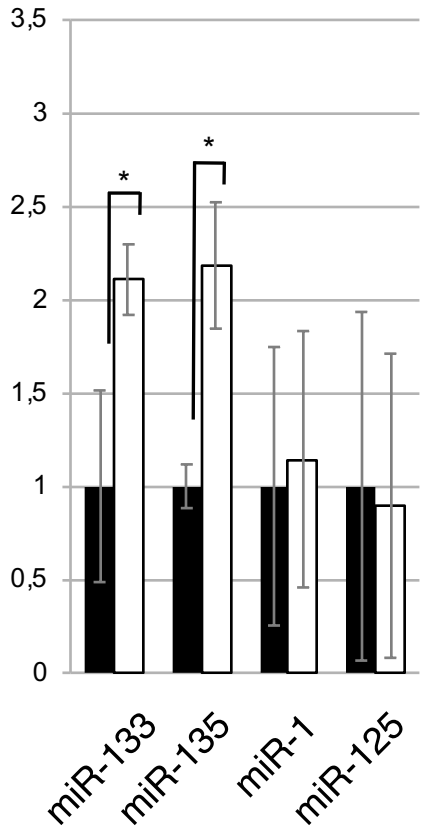
linc-MD1 is target of miR-135 and miR-133



linc-MD1 binds Ago2 and miR-135 and miR-133

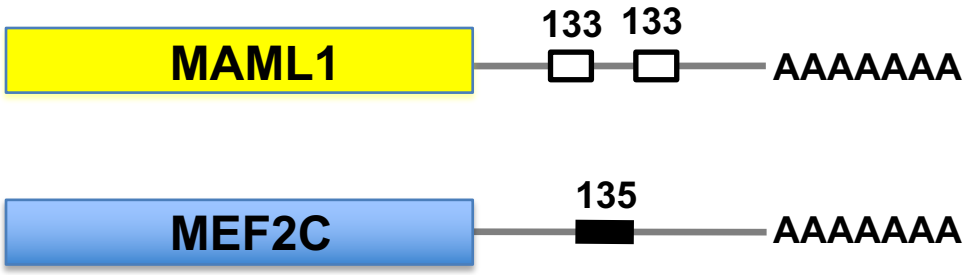
RIP Ago2





RNA pull down

the 3’ UTRs of the myogenic factors MAML1 and MEF2C contain miR-135 and miR-133 binding sites



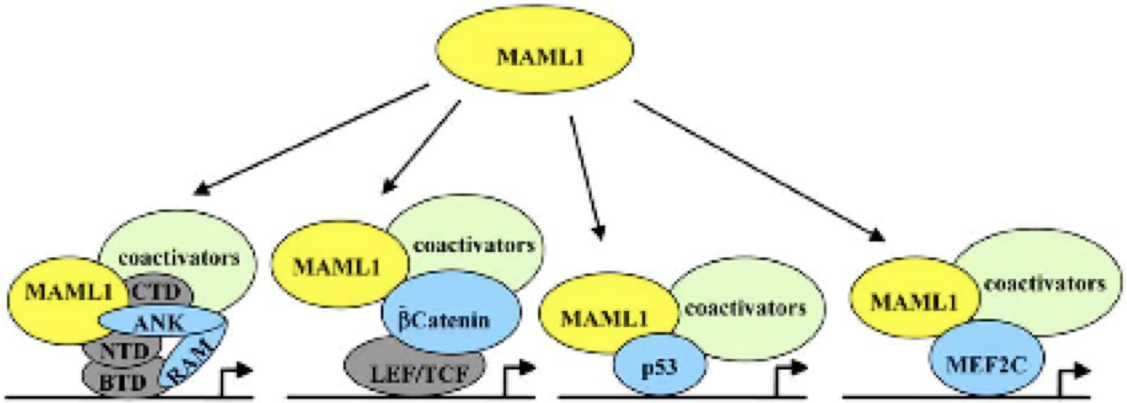
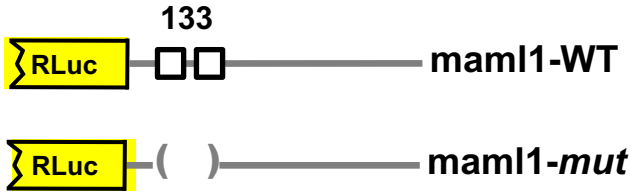
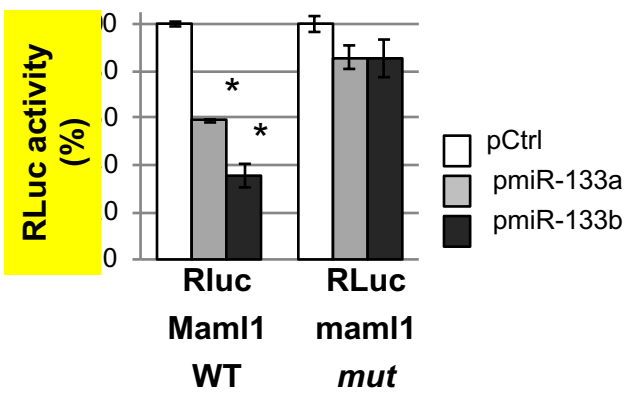
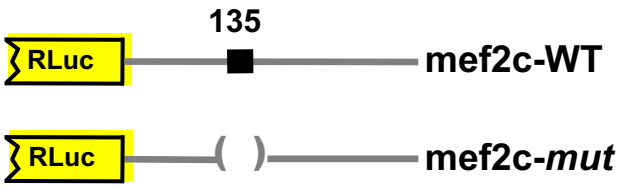


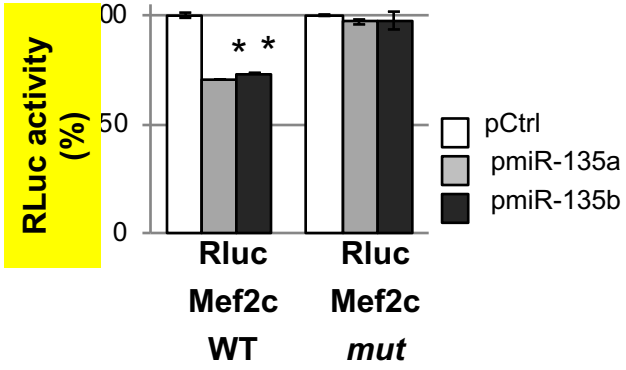
Fig. (1). The MAML1 protein acts as a coactivator for diverse transcription factors. MAML1 is recruited by the ANK (ankyrin repeats) domain of Notch and forms a complex with the DNA-binding protein CSL (composed of NTD (N-terminal domain), CTD (C-terminal domain), and BTD (β-trefoil domain)). The RAM (RBP-Jk associated molecule) domain of Notch interacts with the BTD of CSL. In addition, MAML1 is recruited by β-catenin, p53 and MEF2C to regulate various signalling pathways. Most likely, additional coactivators are working cooperatively with MAML1 in gene regulation.

the myogenic factors MAML1 and MEF2C are target of miR-133 and miR-135

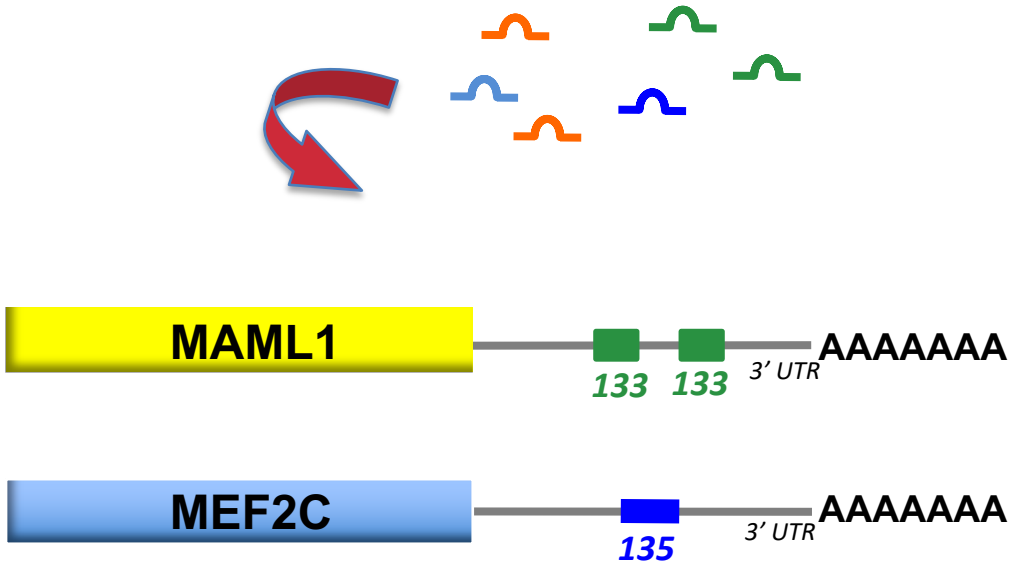






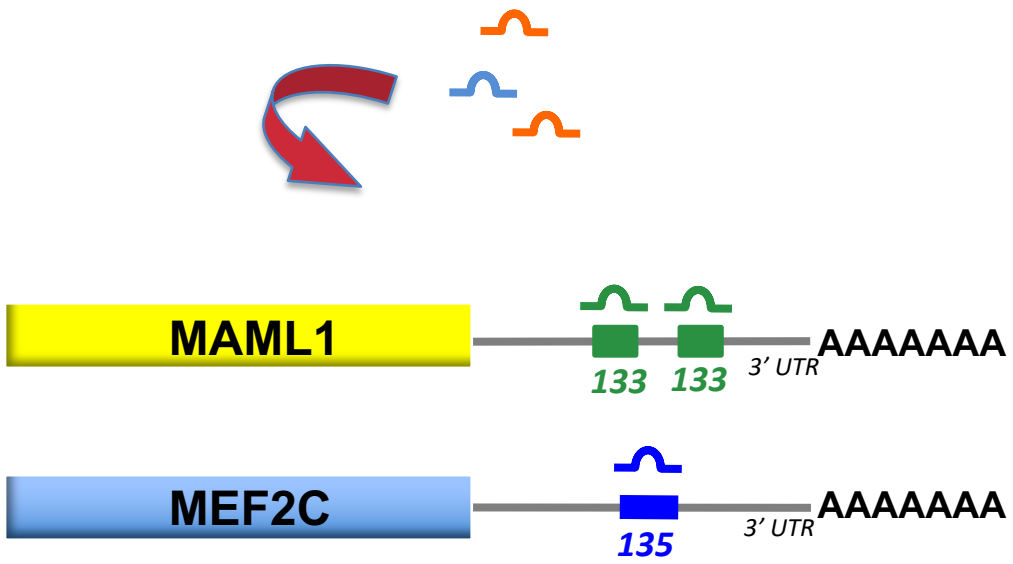


Competition for miRNA binding



MAML1 and MEF2C are myogenic factors controlling muscle differentiation

Competition for miRNA binding



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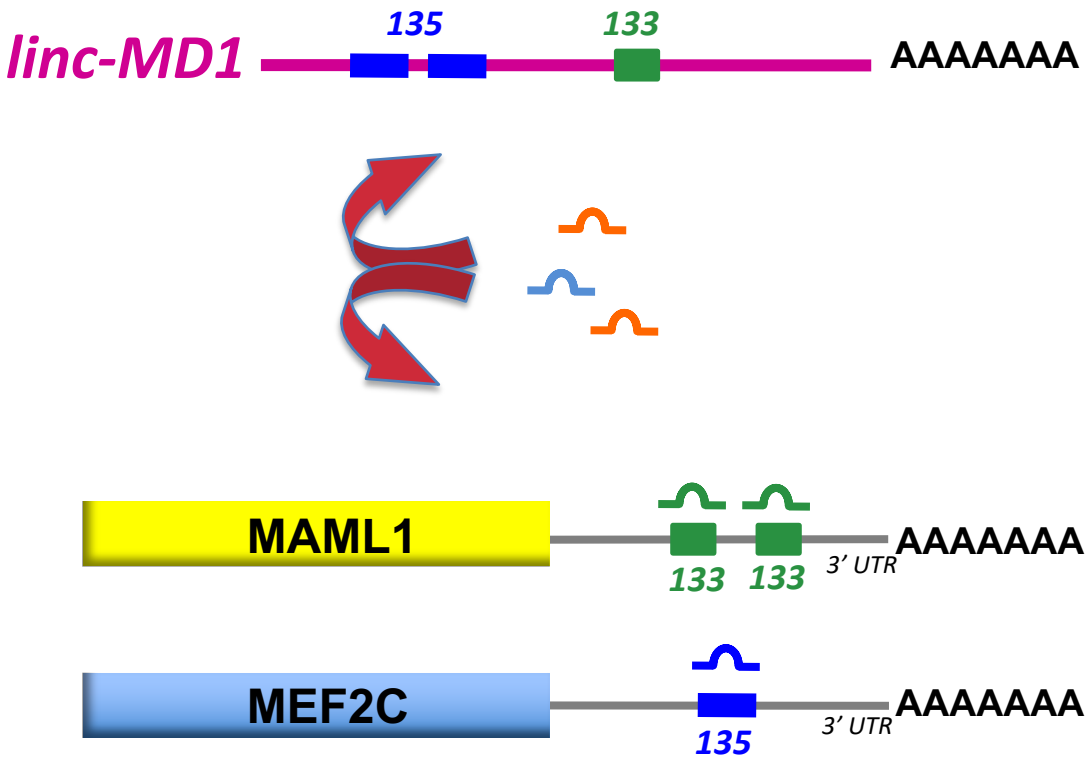

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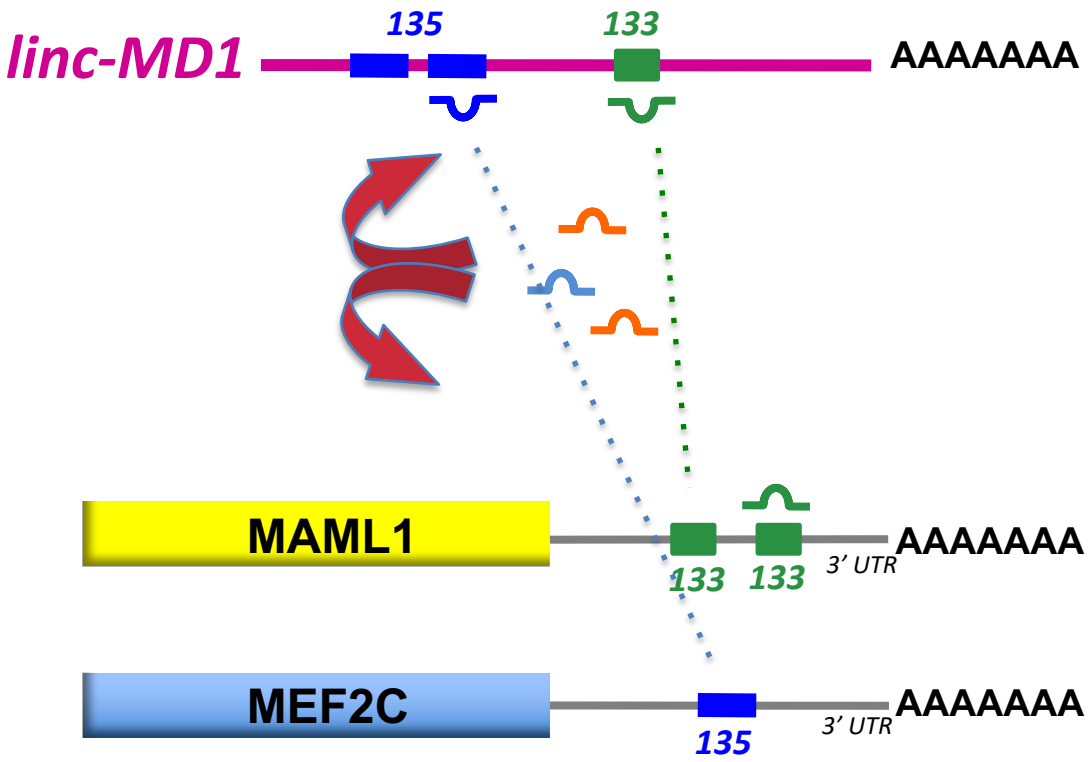
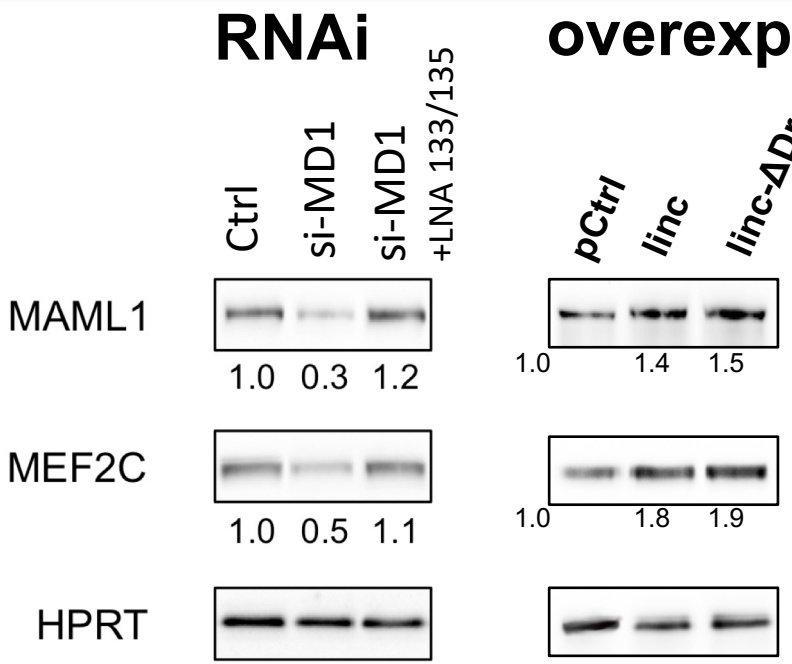
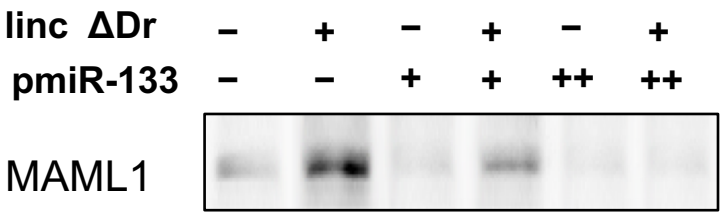
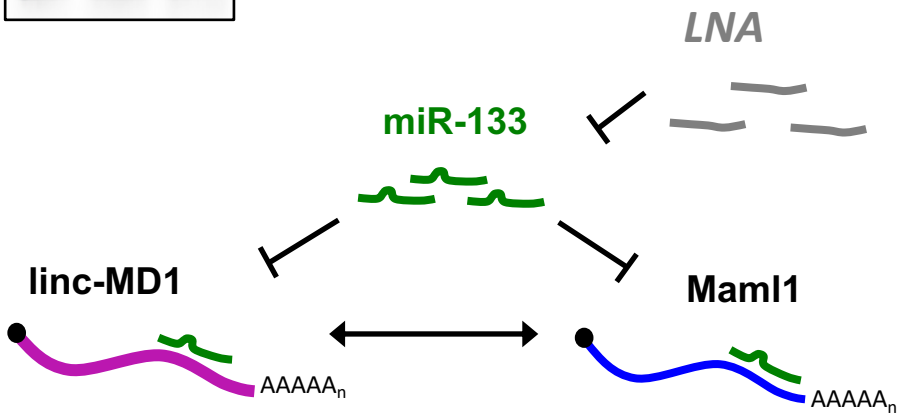


MAML1 and MEF2C are myogenic factors controlling muscle differentiation

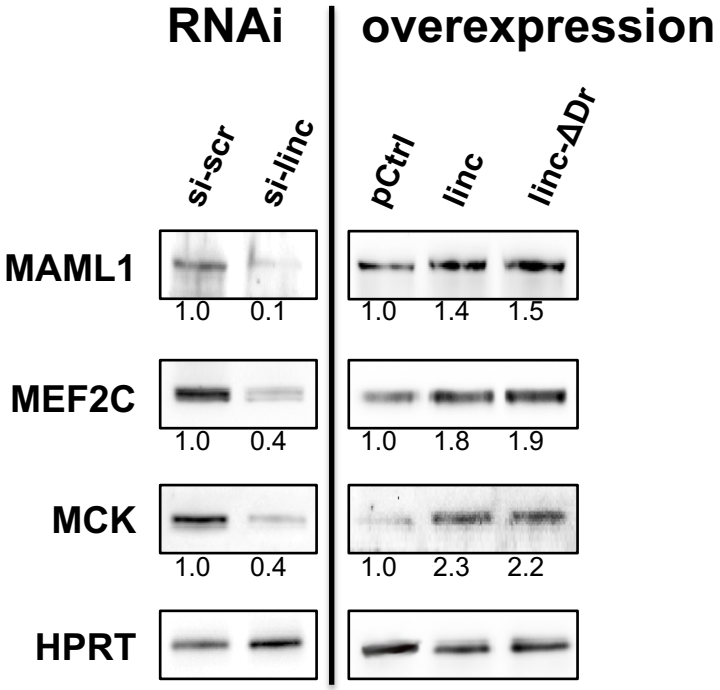
linc-MD1 controls the levels of MAML1 and MEF2C

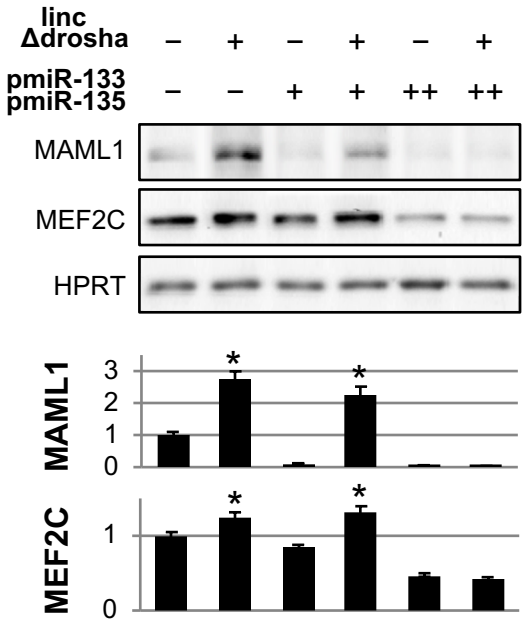




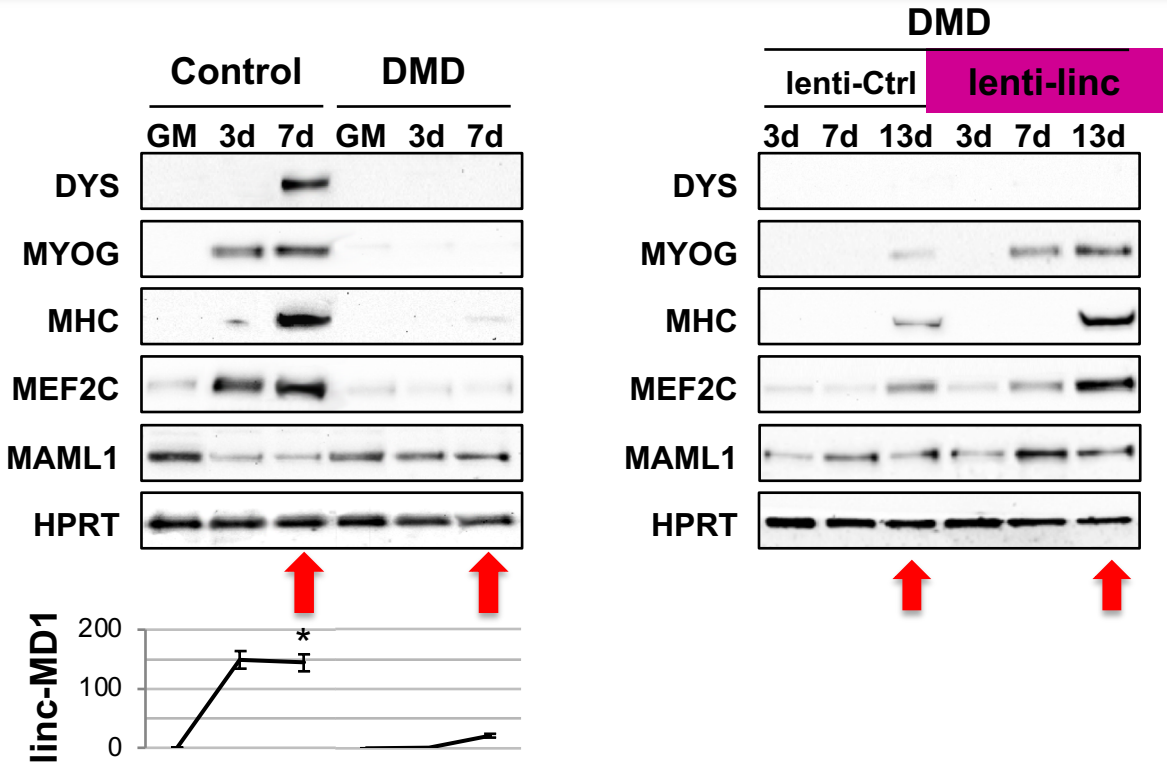


linc-MD1 controls the levels of MAML1 and MEF2C



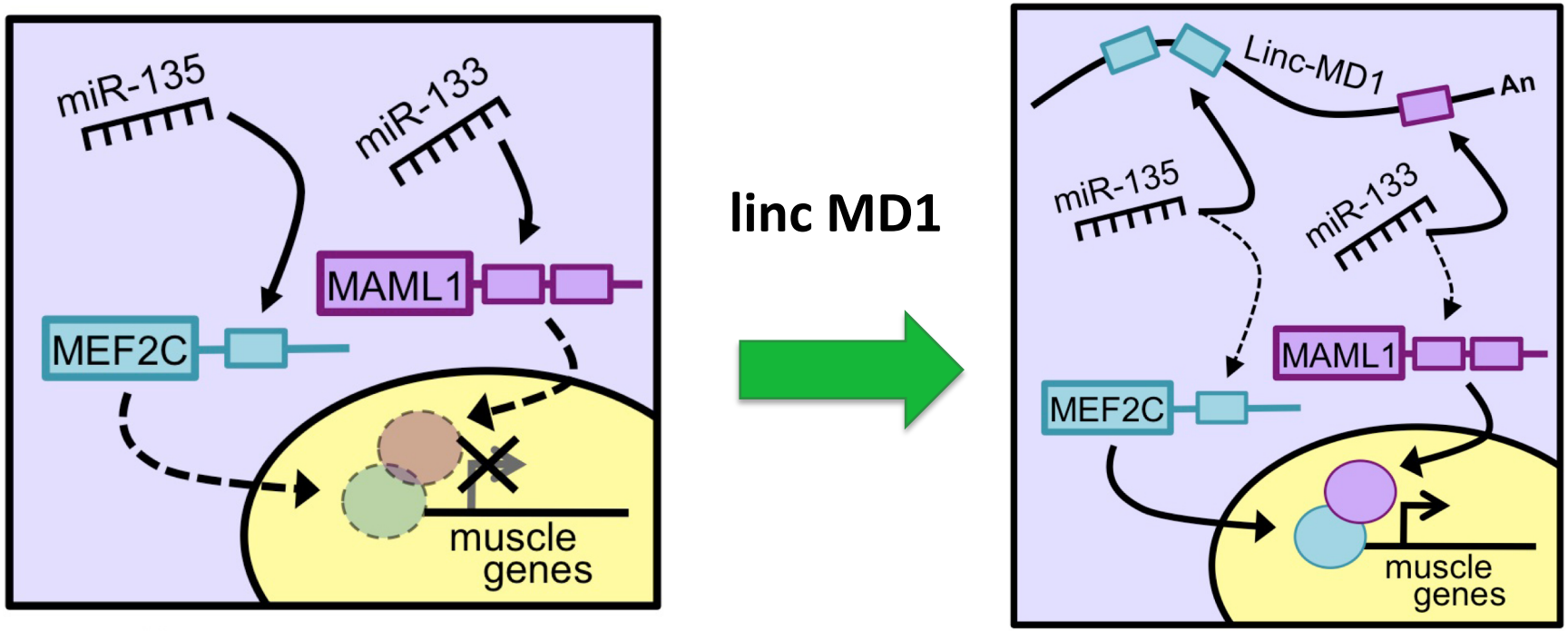


- linc-MD1 controls differentiation in human myoblasts
- it is down-regulated in Duchenne myoblasts



- low levels of linc-MD1 account for the delay in differentiation of DMD myoblasts
- rescue of linc-MD1 restores an almost wt differentiation timing

linc-MD1 acts as a sponge for specific miRNAs



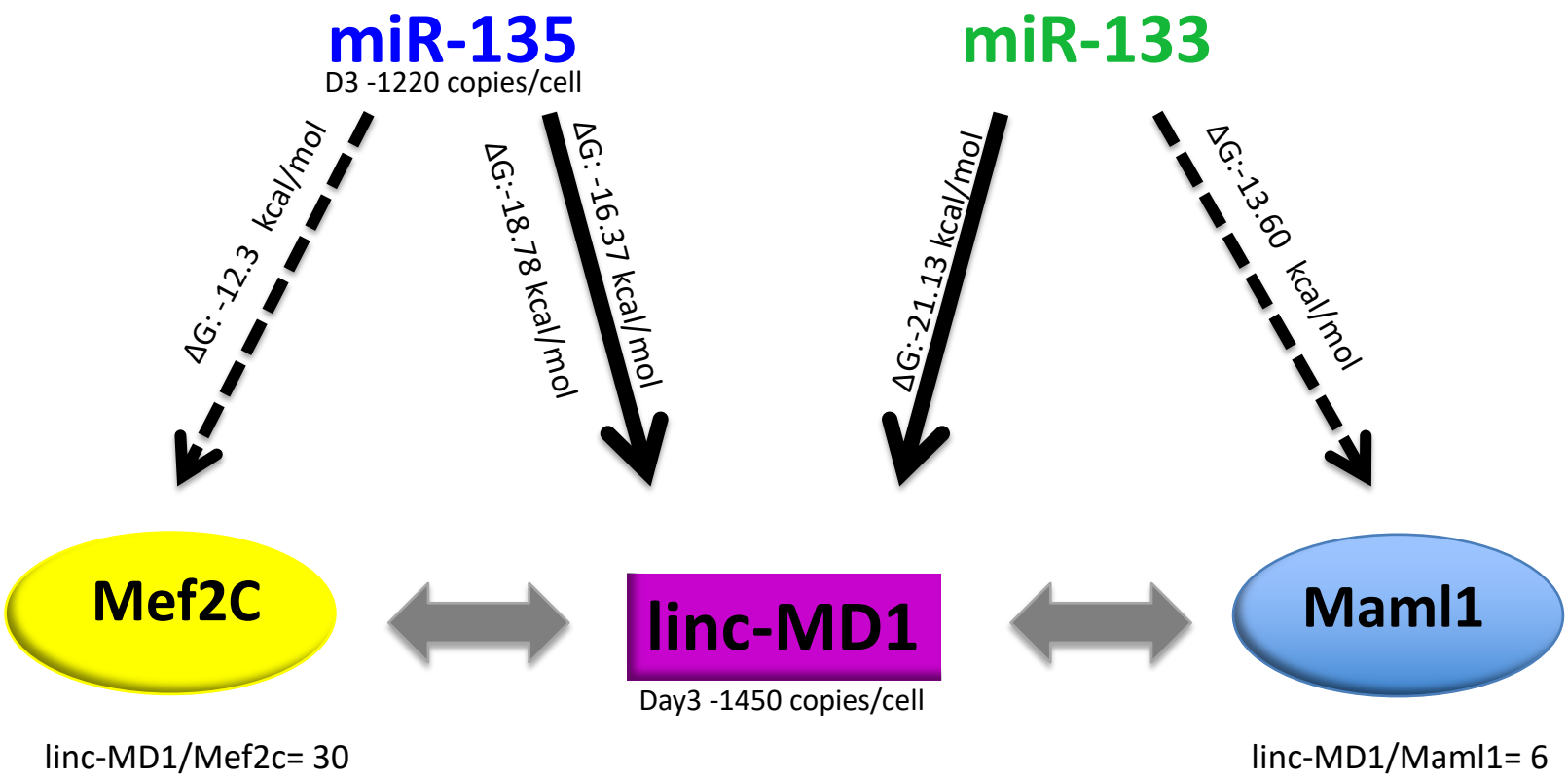
myoblasts

late muscle gene expression

differentiation

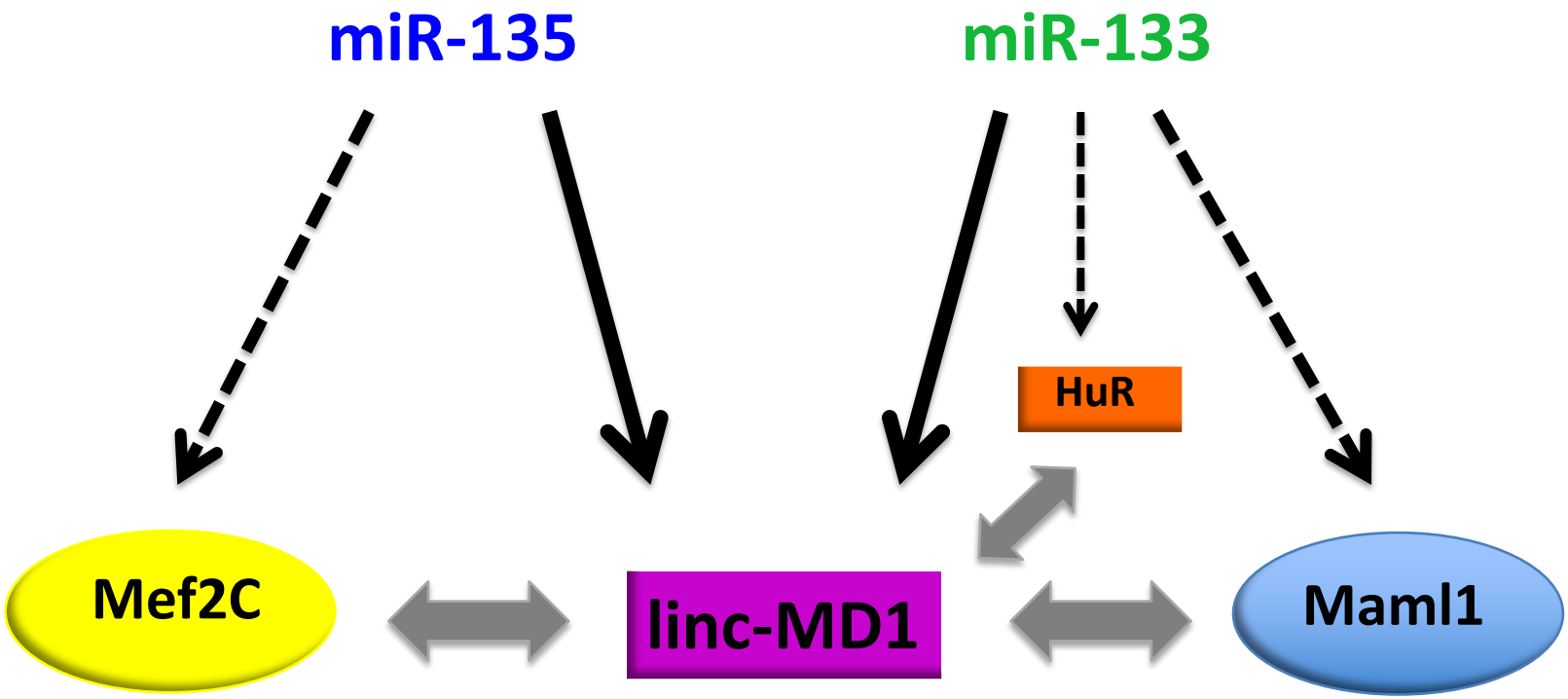
Cesana et al., *Cell* 147, *358-369*, 2011

Crosstalk between coding and non coding RNAs

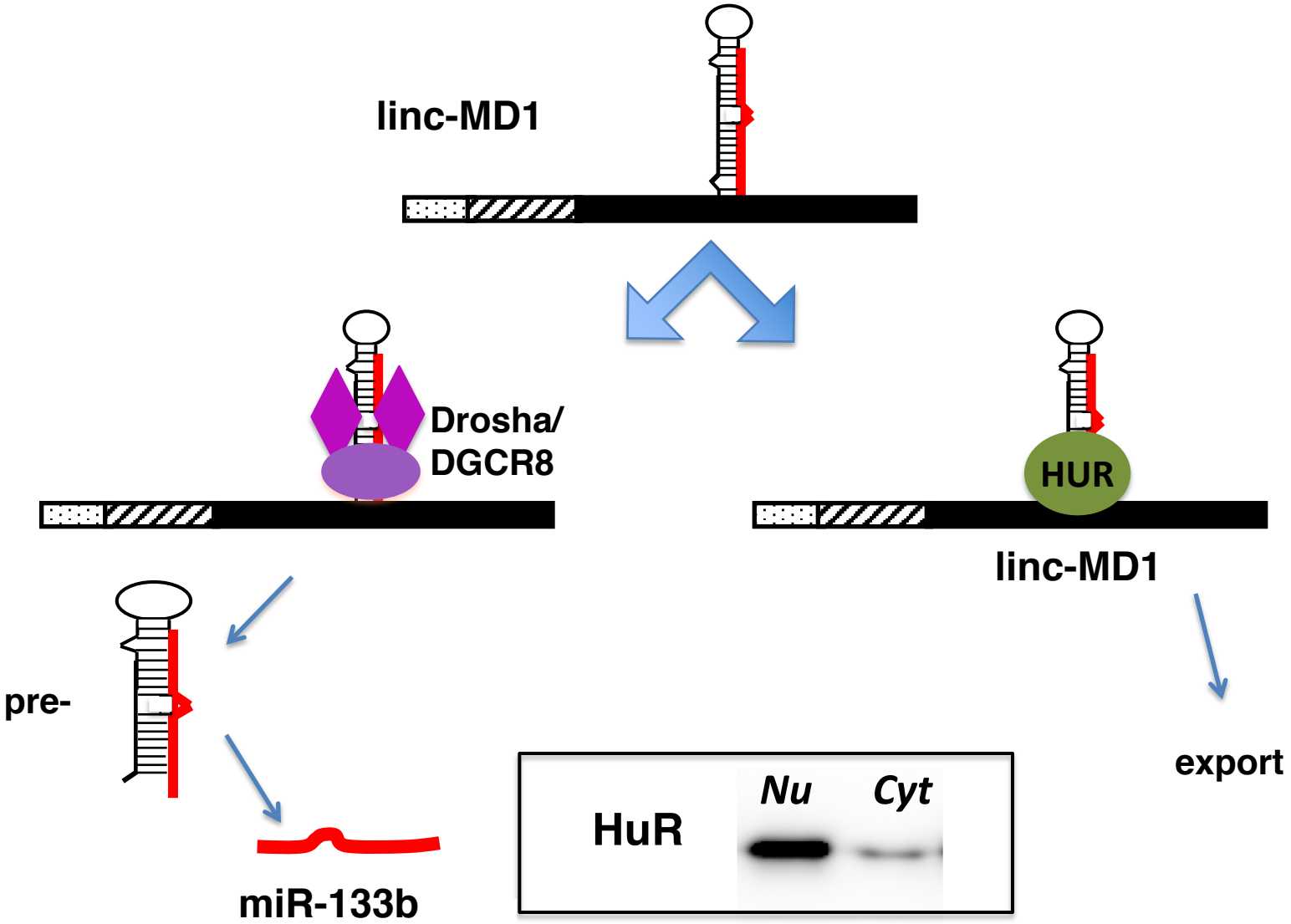


ΔG values were obtained from miRanda (Enright et al., 2003)

Expanding the circuitry……

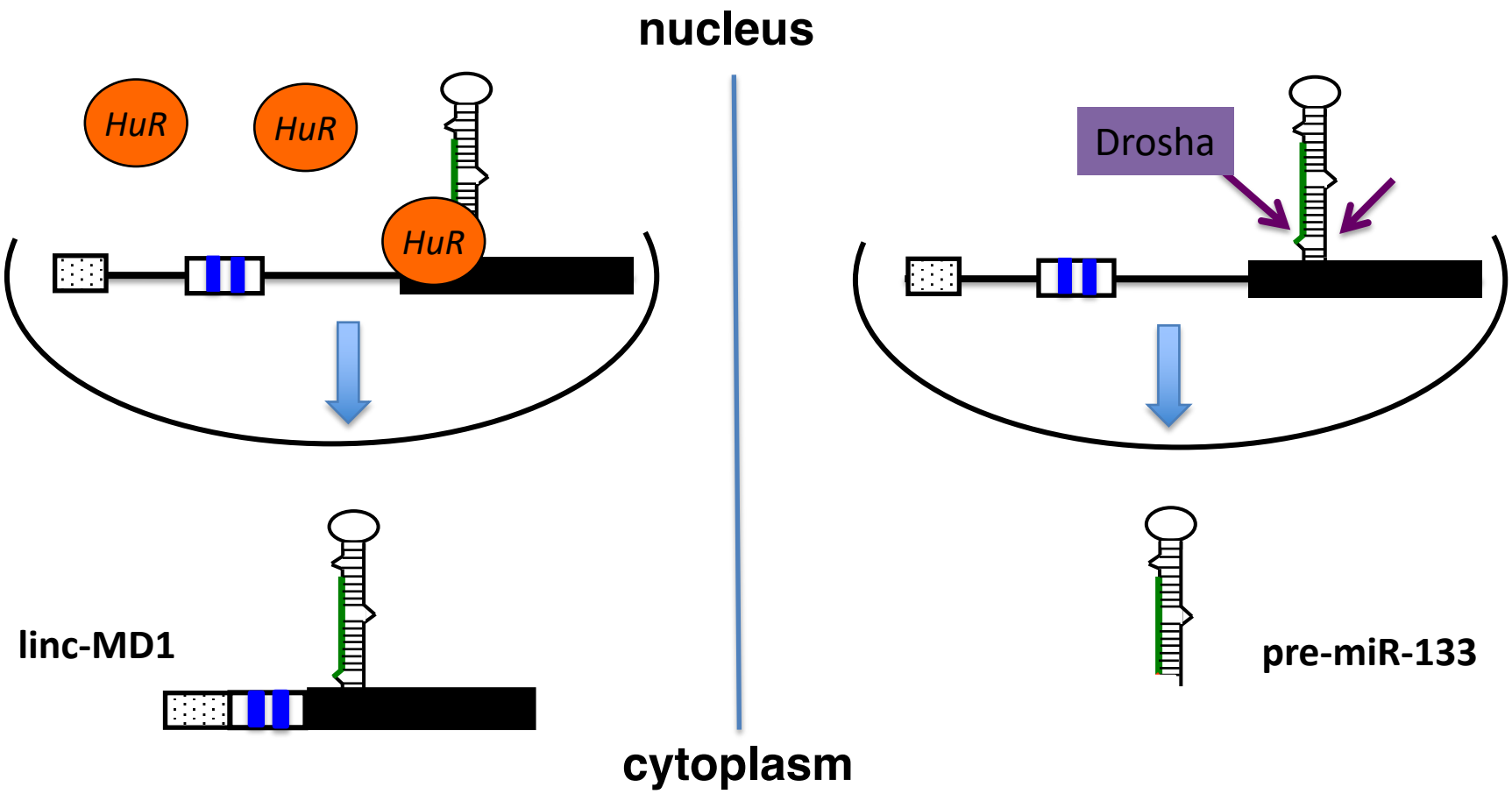


HuR affects the alternative fate of linc-MD1



Legnini et al., Mol *Cell* - 2014

Nuclear HuR controls the relative ratio of linc-MD1 versus miR-133b



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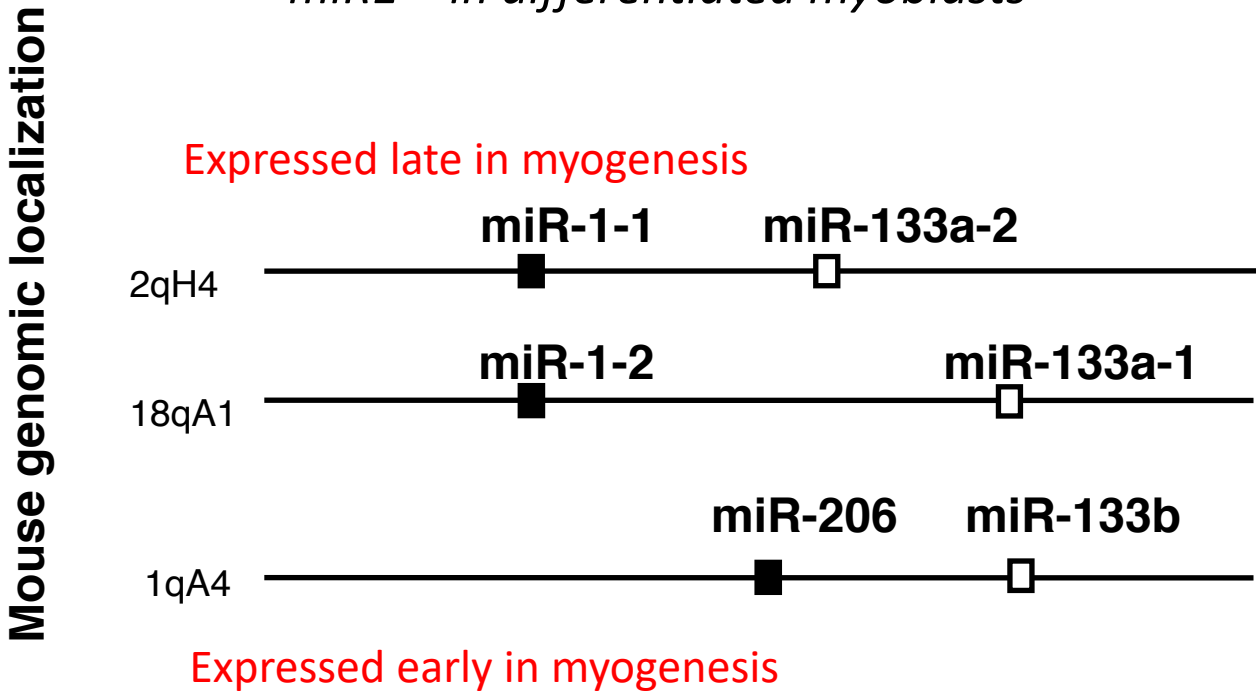
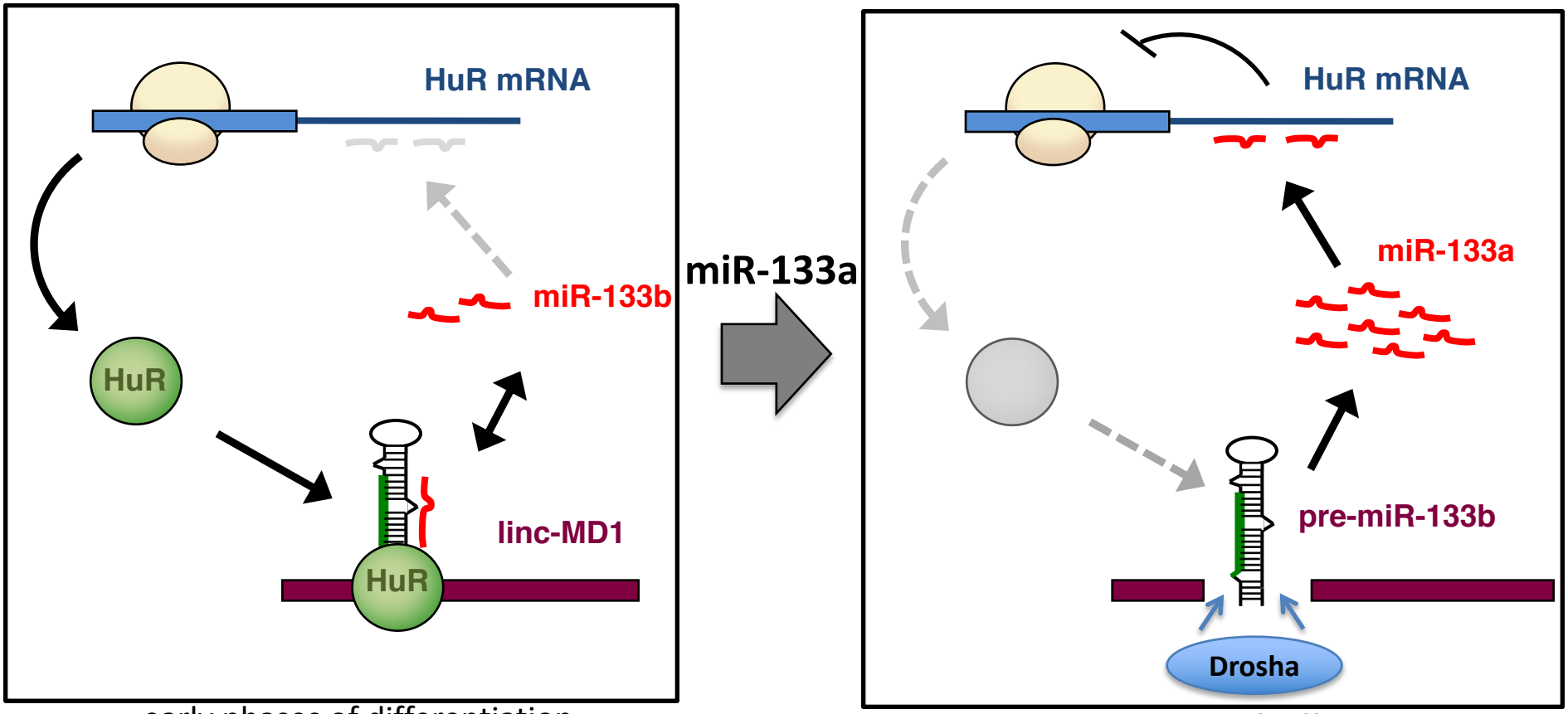
miR-206 – in activated precursor cells
miR1 – in differentiated myoblasts



A feed forward positive loop between HuR and linc-MD1



early phases of differentiation

late phases of differentiation

differentiation

Legnini et al., Mol *Cell* - 2014