microRNAs as regulators of myogenic differentiation and cell size

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microRNAs regulate the development of myogenic progenitors, and the formation of skeletal muscle fibers. However, the role microRNAs play in controlling the growth and adaptation of post-mitotic musculature is less clear. We show that inhibition of the established pro-myogenic regulator miR-206 can promote hypertrophy and increased protein synthesis in post-mitotic cells of the myogenic lineage. We have observed that histone deacetylase 4 (HDAC4) is a target of miR-206 in the regulation of myogenic differentiation. We confirmed that inhibition of miR-206 de-repressed HDAC4 accumulation in cultured myotubes. Importantly, inhibition of HDAC4 activity by valproic acid or sodium butyrate prevented hypertrophy of myogenic cells otherwise induced by inhibition of miR-206. To test the significance of miRNA-206 as a regulator of skeletal muscle mass *in vivo*, we designed recombinant adeno-associated viral vectors (rAAV6 vectors) expressing miR-206, or a miR-206 "sponge," featuring repeats of a validated miR-206 target sequence. We observed that over-expression or inhibition of miR-206 in the muscles of mice decreased or increased endogenous HDAC4 levels respectively, but did not alter muscle mass or myofiber size. We subsequently manipulated miR-206 levels in muscles undergoing follistatin-induced hypertrophy or denervation-induced atrophy (models of muscle adaptation where endogenous miR-206 expression is altered). Vector-mediated manipulation of miR-206 activity in these models of cell growth and wasting did not alter gain or loss of muscle mass respectively. Our data demonstrate that although the miR-206/HDAC4 axis operates in skeletal muscle, the post-natal expression of miR-206 is not a key regulator of basal skeletal muscle mass or specific modes of muscle growth and wasting. Our studies support a context-dependent role of miR-206 in regulating hypertrophy that may be dispensable for maintaining or modifying the adult skeletal muscle phenotype - an important consideration in relation to the development of therapeutics designed to manipulate microRNA activity in musculature.