TACSM Abstract

Release of MicroRNA15a/16 From Skeletal Muscle During Exercise Regulates Proteostasis in Muscle and Cancer

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ABSTRACT

Proteostasis, the intricate process of maintaining the proteome, is a critical matter for cellular health. The regulation of the multiple intersecting metabolic pathways comprising the proteostatic network is correspondingly complex and incompletely understood; however, a new and intriguing candidate in understanding this process has emerged in the form of microRNA (miRNA), small RNA species which are capable of regulating hundreds of genes at once by binding to and degrading mRNA transcripts. We have previously shown that muscle contraction results in the release of two miRNA species (miR15a/16) from skeletal muscles, and that a perfusate rich in these miRNAs slows growth in cultured pancreatic cancer cells. **PURPOSE**: To investigate the role of miR15a/16 in regulating muscle and cancer proteostasis. **METHODS**: The online miRPath (v.4.0) server was used to assess which cellular pathways (KEGG database) miR15a/16 regulate. Separately, we probed the ExTraMeta database for associations between our target miRNA and exercise training status and used the K-M plotter tool to determine the effect of miR15a/16 on pancreatic cancer patient survival. Finally, to directly assess the role of the miRNA in altering cellular protein metabolism, we measured cellular protein synthesis rates in response to miRNA knockout in cultured human skeletal muscle myotubes, and miRNA overexpression in the PANC1 pancreatic cancer cell line. **RESULTS**: miR15a/16 play a role in regulating several proteostatic pathways, including the anabolic mTOR pathway and the catabolic processes of autophagic and ubiquitin-proteasome mediated proteolysis (all $p<0.05$). Meta-analysis of 20 studies demonstrated a pattern of reduction in muscle miR15a levels with training ($p<0.05$); the same analysis was not available for miR16. In pancreatic cancer, high levels of miR15a/16 were beneficial to patient survival, with an increase in median survival time from 17 months (low) to 50 months (high) ($p<0.05$). Silencing of miR15a/16 in skeletal muscle led to a 50% increase in protein synthesis rate ($p<0.05$); on the other hand, overexpression of these miRNAs in pancreatic cancer reduced protein synthesis by 60% ($p<0.05$). **CONCLUSION**: We believe these results to be among the first to identify miR15a/16 as key regulators of the cellular proteostatic network. These results indicate that exercise training tends to reduce miR15a/16 content, and that targeting these miRNAs may be able to recapitulate some of the effects of exercise in skeletal muscle. Conversely, the loss of these same molecules is associated with worse survival in pancreatic cancer patients and restoring them to the cancer cell leads to a dramatic suppression of anabolic activity. The implications are two-fold: one, that the release of miR15a/16 from skeletal muscle may present a mechanism by which exercising muscle may promote its own growth while simultaneously prohibiting the growth of aggressive cancer, and two, that exogenously-delivered miRNA-based treatment may present a viable therapeutic avenue to regulate cellular proteostasis.