

## Muscular Contractions Facilitate Systemic Circulation of MicroRNA that Impact Cancer

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### ABSTRACT

Currently there is an evolving appreciation for exercise- combined therapies prescribed by clinicians for breast cancer patients; however there remains a lack of explanation of biological regulation of exercise on breast cancer, and the role that contracting skeletal muscle, the mechanistic machinery of exercise, has in the documented improved prognosis of exercising breast cancer patients. MicroRNAs (miRNA) are small non-coding RNAs found in abundance in skeletal muscle that have been proposed as possible myokines. Exogenous miRNA have post-transcriptional abilities allowing them to act as negative gene regulators of gene expression such as those in the mammalian target of rapamycin (mTOR) pathway. We have unique preliminary findings that myokines released during electrically-stimulated muscle contraction of hemicorpus-prepared rats affects the anabolic activity and capacity of breast cancer cells. When MCF-7 cancer cells were treated with perfusate collected during muscle contraction, a significant inhibition of proliferation was noted alongside diminished mTOR activity and global rates of protein synthesis.

**PURPOSE:** The purpose of this study was to profile microRNA released into circulation during lower limb muscular contractions that may influence the anabolic signaling of breast cancer cells. **METHODS:** Female Wistar rats underwent a hemicorpus hindlimb perfusion preparation with and without electrically-stimulated muscular contractions. RT-PCR analysis of select microRNAs, known to impact cellular anabolism, was performed on both muscle and perfusate samples collected pre- and post-contraction (Non-Stim=4, E-Stim=4, respectively). **RESULTS:** A total of 52 microRNA were identified across all samples, with an average of 65 microRNAs detected per sample. We also noted a significant differential expression of 8 microRNA between E-Stim and Non-Stim samples within animals ( $p < 0.05$ ), and 15 microRNAs between E-Stim and Non-Stim groups ( $p < 0.05$ ) were determined. Expression of mir16-5p was 4% higher in hindlimb muscle exposed to E-Stim compared to Non-Stim ( $p > 0.05$ ), and was 147% higher in E-Stim perfusate samples compared to Non-Stim ( $p < 0.05$ ). **CONCLUSION:** Our results suggest that skeletal muscle is a rich endogenous source of microRNA, including those associated with altered mTOR pathway gene expression. Muscular contraction comparable to resistance exercise facilitates the release of microRNA into systemic circulation which supports exercise facilitating cross-talk between muscle and other tissues, including cancer.