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# Exercise-Driven miRNA Seed Sequence Therapy for Colorectal Cancer Control

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BACKGROUND:
Colorectal cancer (CRC) remains a major global health burden. Exercise suppresses tumor progression through mediators such as myokines, metabolites, and miRNAs, and several miRNAs are known to be upregulated in skeletal muscle following physiological stimuli. Although these exercise-responsive miRNAs can enter circulation and exert tumor-regulatory effects, the therapeutic potential of miRNAs sharing an identical seed sequence has not been well characterized. While the seed region determines target specificity, a seed-sequence based approach could simultaneously repress multiple tumor-promoting genes with high biological precision. This study aimed to evaluate a synthetic siRNA designed to mimic the conserved seed sequence found in exercise-driven miRNAs (Ex siR) as a strategy to reproduce anti-cancer effects in CRC.
METHODS:
CT26 murine CRC cells were cultured and transfected with each vehicle, Scrambled siRNA and Ex siR according to their groups. Cell viability (CCK-8) and migration (wound healing assay) were assessed. RNA-sequencing was performed to characterize transcriptomic changes following seed-sequence–based silencing, followed by differential gene expression and pathway enrichment analyses.
RESULTS:
FAM-labeled siRNA imaging confirmed efficient intracellular uptake. Ex siR significantly reduced cell viability at 72 hours compared with both untreated and scrambled siRNA controls ($p < 0.001$). Migration was markedly impaired, with delayed wound closure relative to scrambled siRNA ($p = 0.007$). RNA-sequencing revealed broad transcriptional repression, including 412 downregulated genes such as Crhr1, Tgfbi, and Actg2. Pathway analyses indicated enhanced apoptosis and p53 signaling, alongside suppression of EMT-related, migration-associated, and extracellular matrix remodeling pathways.
CONCLUSION:
Seed-sequence–based siRNA intervention effectively attenuates CRC cell viability and migration while repressing multiple oncogenic networks. These findings suggest that exercise-derived seed-sequence mimetics may represent a promising therapeutic strategy for leveraging exercise-associated tumor-suppressive mechanisms. Further in vivo studies will be important to establish this approach as a feasible therapeutic strategy to extend the exercise-driven tumor-suppressive benefits.

## Keywords

Colorectal cancer (CRC), Exercise-driven miRNAs, Seed-sequence based regulation, siRNA therapy

## Conflict of Interest & Ethical Approval

yes

## Abstract submitters declaration

yes

**Author:** Mr KIM, Jeremy J. (Seoul National University, South Korea)

**Co-authors:** Prof. MOON, Hyo Youl (Seoul National University); Ms LEE, Jieun (Seoul National University, South Korea); Mr SHIN, Minyoung (Seoul National University, South Korea); Mr KIM, Sangyun (Seoul National University, South Korea); Mrs KIM, Tae Yeon (Seoul National University, South Korea); Mr PARK, Taeeon (Seoul National University, South Korea)

**Presenter:** Mr KIM, Jeremy J. (Seoul National University, South Korea)

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