MicroRNAs (miRNAs) are pivotal post-transcriptional regulators of gene expression. These endogenous small non-coding RNAs play significant roles in tumorigenesis and tumor progression. miR-142-3p expression is dysregulated in several breast cancer subtypes. We aimed at investigating the role of miR-142-3p in breast cancer cell invasiveness applying a range of microscopic techniques combined with functional analysis. Supported by transcriptomic Affymetrix array analysis and confirmatory investigations at the mRNA and protein level, we demonstrate that overexpression of miR-142-3p in MDA-MB-231, MDA-MB-468 and MCF-7 breast cancer cells leads to downregulation of Integrin-αV, RAC1, WASL (N-WASP) and CFL2, molecules implicated in cytoskeletal regulation and cell motility. ROCK2, IL6ST, KLF4, PGRMC2 and ADCY9 were identified as additional targets in a subset of cell lines. Decreased matrigel invasiveness was associated with the miR-142-3p-induced expression changes. Confocal immunofluorescence microscopy, nanoscale atomic force microscopy and digital holographic microscopy revealed a restructuring of the intracellular actin cytoskeleton as well as a reduced cell volume and size. A more cortical actin distribution and a loss of membrane protrusions were observed in cells overexpressing miR-142-3p. Luciferase activation assays confirmed direct miR-142-3p-dependent regulation of the 3' UTR of ITGAV and WASL. siRNA-mediated depletion of ITGAV and WASL resulted in a significant reduction of cellular invasiveness, highlighting the contribution of these factors to the miRNA-dependent invasion phenotype. Our data identify ITGAV and several additional cytoskeleton-associated molecules as novel invasion-promoting targets of miR-142-3p in breast cancer. With its tumor suppressive potential, miR-142-3p is a promising candidate for future approaches of miRNA-based anti-metastatic cancer therapy.

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