Title	MiR-141 not only modulates anoikis resistance of ovarian cancer cells but also alters pre-metastatic niche for ovarian cancer cell metastatic colonization
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MIR-141 NOT ONLY MODULATES ANOIKIS RESISTANCE OF OVARIAN CANCER CELLS BUT ALSO ALTERS PRE-METASTATIC NICHE FOR OVARIAN CANCER CELL METASTATIC COLONIZATION

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INTRODUCTION: Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy worldwide. This disease is generally called the 'silent killer' because there are no symptoms and thus, the majority of patients are found in advanced stages accompanied by extensive metastasis. Most deaths from this cancer are attributed to metastatic progression. The cancer metastasis is determined by the priming of metastatic niche and the intrinsic properties of cancer cells to adapt the microenvironemntal stresses. However, the associated molecular mechanisms remain unclear.

MATERIAL AND METHOD: The miRCURY™ LNA, cDNA, and proteomic array profilings in combination with a series of biochemical and functional analyses were performed to identify miR-141 as a putative miRNA in regulating anokis resistance of ovarian cancer cells through KLF12/survivin signaling. Both in vitro cell culture and in vivo mouse model showed miR-141 is an secretary miRNA, while immunofluorescent, qPCR, Proteome Profiler Human XL Cytokine Array Kit and functional analyses demonstrated miR-141 was able for cell-to-cell communication to alter host cells as a premetastatic niche.

RESULTS AND DISCUSSION: Using miRCURY™ LNA Array profiling in combination with a series of biochemical and functional analyses, we identified Hsa-miR-141 (miR-141) was highly expressed in advanced serous subtype ovarian cancers. The overexpressed miR-141 could enhance cell survival of ovarian cancer cells against anoikis by targeting Krüppel-related zinc finger protein AP-2rep (KLF12). Restoration of KLF12 in miR- 141-expressing cells remarkably reduced, or knockdown of KLF12 similar to miR- 141 overexpression augmented, anoikis resistance of ovarian cancer cells through alteration of survival-associated factor, survivin. Luciferase reporter assay using survivin promoter luciferase plasmid (luc-survivin) indicated that survivin could be transcriptionally inhibited by KLF12. Intringuingly, miR-141 was found to be secreted from ovarian cancer cells and taken up by hFF-1 fibroblast cells. Ovarian cancer cells cultured in miR-141-expressing fibroblast cell medium displayed increased cell growth and cell migration in the presence of GROa and EMMPRIN chemokines.

CONCLUSION: MiR-141 not only plays a key role in altering cancer cell plasticity against anoikis but also can reprogram stroma to be a pre-metastatic niche facilitating the ovarian cancer metastatic colonization.