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MicroRNA-204-5p inhibits breast cancer progression and metastasis by targeting PI3K/Akt signaling pathway

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MicroRNAs (miRNA) are involved in crucial biological processes such as cell proliferation, differentiation and apoptosis and the dysregulation of miRNA has been demonstrated in initiation and progression of a variety of human malignancies, including breast cancer. Several studies suggested that that down-regulation of miR-204-5p is associated with poor prognosis and metastasis of breast cancer by regulating proliferation, apoptosis, migration, invasion of breast cancer cells *in vitro*, however, the underlying mechanisms of *in vivo* anti-tumor or anti-metastatic activity of miR-204-5p remains to be elucidated. Here, we identified differentially expressed miRNAs between primary breast tumors and normal adjacent tissues using small RNA sequencing. Among them, miR-204-5p was the most significantly down-regulated in all of 17 breast tumor tissues compared with corresponding normal pairs. To investigate the role of miR-204-5p on breast cancer progression, we first established stable breast cancer cell lines overexpressing miR-204-5p. MiR-204-5p suppressed tumor growth and metastasis in both syngeneic 4T1 murine allograft breast cancer model and MDA-MB-231 xenograft model *via* inhibiting proliferation, migration and invasion of breast cancer cells. With RNA-seq and the integrative analysis of TCGA data, we observed that there was significant inverse correlation between miR-204-5p expression and PI3K/Akt/mTOR signaling pathway. After analyzing down-regulated genes and target prediction *in silico*, we found that *PIK3CB*, a catalytic subunit of PI3K, was highly down-regulated in miR-204-5p overexpressing cells and experimentally validated that *PIK3CB* was a direct target of miR-204-5p. Also, knockdown of *PIK3CB* impaired breast cancer cell proliferation and migration. Moreover, miR-204-5p decreased the mobilization and recruitment of CD11b+ myeloid-derived suppressor cells, which facilitated cancer cell metastasis through regulating mTOR signaling pathway, via down-regulating the expression of *CCL20*, *VEGFA* and *CSF1*. In conclusion, miR-204-5p inhibits the initial progression of breast cancer and metastasis by blocking proliferation, migration as well as invasion. These findings indicate that miR-204-5p may be a novel therapeutic strategy against breast cancer progression and metastasis.

Biography

Bok Sil Hong has completed her PhD in 2011 from Pohang University of Science and Technology (POSTECH). She is currently a Research Professor of Seoul National University Hospital, Center for Medical Innovation. Her main research field is about the significant roles of miRNAs on breast cancer progression. She has published more than 15 papers regarding the cancer biology and progression.

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