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Extracellular ATP drives breast cancer cell migration and metastasis via S100A4 production by cancer cells and fibroblasts

Ying Liu, Yue-Hang Geng, Hui Yang, Han Yang, Yan-Ting Zhou, Hong-Quan Zhang, Xin-Xia Tian, Wei-Gang Fang

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**Abstract**

Our previous work has demonstrated that extracellular ATP is an important pro-invasive factor, and in this study, we tapped into a possible mechanism involved. We discovered that ATP could upregulate both the intracellular expression and secretion of S100A4 in breast cancer cells and fibroblasts. Apart from stimulating breast cancer cell motility via intracellular S100A4, ATP enhanced the ability of breast cancer cells to transform fibroblasts into cancer-associated fibroblast (CAF)-like cells, which in turn secreted S100A4 to further promote cancer cell motility. Both apyrase and niclosamide treatments could inhibit metastasis of inoculated tumors to lung, liver and kidney in mice model, and CAFs from these treated tumors exhibited weakened migration-stimulating capacity for breast cancer cells. Collectively, our data indicate that extracellular ATP promotes the interactions between breast cancer cells and fibroblasts, which work collaboratively via production of S100A4 to exacerbate breast cancer metastasis.

**Keywords**: Extracellular ATP, S100A4, fibroblast, tumor microenvironment, breast cancer metastasis