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The microbiome affects hormonal therapy in breast cancer

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Background/Aims

Microbiomes are associated with breast cancer, and breast cancer is closely related to estrogen. Among symbiotic bacteria in the human body, microbiomes which produce estrogen-metabolizing enzymes called estrobolome. This study identified the microbiome in breast cancer and normal group and found microbiome which was abundant in the breast cancer group but poor in the normal group. We hypothesized that these bacteria would potentially affect the hormone treatment of breast cancer and tamoxifen treatment. We report the bacteria and its mechanism by which affect tamoxifen efficacy.

Methods

The 347urine samples in female (127 breast cancer patients and 220 normal individuals) were collected. The mean age in urine samples 51.8 in cancer groups and 59.2 years in control groups. These urine samples were analyzed by NGS using a universal bacterial primer of 16S rDNA. Metagenomic analysis of urine samples was performed at phyla to genus-level. Target bacteria which is abundant in breast cancer of luminal type was selected. Tamoxifen or K.pneumoniae-derived EVs plus tamoxifen was used in the MCF7 cells, and we compared cell survival, cell cycle, and signaling molecules in each group. Human estrogen receptor-positive cells (MCF7) were cultured and bacterial extracellular vesicles(EVs) were isolated from Klebsiella pneumoniae, the target bacteria. For cell-cycle analysis, the cells were treated with distilled water as a control, EVs of K.pneumoniae at 10, 100, 1000 ng/ml for 72 h. Quantitative Real-Time PCR and western blotting for signaling molecule analysis were performed after treatment of EVs in breast cancer cells.

Results

Microbiome between breast cancer and normal group was showed the significantly different. Among these results, Klebsiella was more abundant in luminal A type, estrogen-receptor positive breast cancer and less in the normal group. The efficacy of tamoxifen was verified by comparing the results between cells treated with tamoxifen alone and those treated with tamoxifen and bacterial EVs. When K.

pneumoniae-derived EVs were used alone, the growth of MCF7 cells was not suppressed significantly. However, K. pneumoniae EVs co-treated with tamoxifen inhibited the cell growth of MCF7 by two-folds compared with tamoxifen treatment alone. When K. pneumoniae EVs and tamoxifen were used together, cyclin E2 transcription was down-regulated, and protein levels of P21

Conclusions

In conclusion, these results show that K.pneumoniae may affect the patients who have estrogen -receptor positive breast cancer according to metagenomic analysis. K. pneumoniae-derived EVs enhanced the anti-estrogen effect of tamoxifen through down-regulation of survival signaling molecules in estrogen positive breast cancer cells.