Study reveals molecular basis for endocrine therapy-resistant breast cancer

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Mitsuyoshi Nakao, Director of the Institute of Molecular Embryology and Genetics in Kumamoto University and Associate Professor Noriko Saitoh revealed that a cluster of defined, non-coding RNAs are mechanistically involved in endocrine therapy resistance in human breast cancer cells. Furthermore, resveratrol, a kind of polyphenol, was found to repress these RNAs and inhibit the proliferative activity of breast cancer cells which had acquired resistance. The work was published in *Nature Communications* on April 29th, 2015.

Breast cancer is one of the most common types of cancer in women. In recent years, both early diagnosis and emerging therapies have been improved by the progress of medical technology. However, the fact that many patients suffer from metastasis and later recurrence of this disease is an important issue.

The keys to help understand the nature of breast cancer cells are estrogens and estrogen receptors. These molecules together present a "lock-and-key" theory for breast cancer therapy. About 60~70% of breast cancers are estrogen receptor-ƒ¿ (ER)-positive and highly depend on estrogen for cellular growth and survival. Thus, endocrine therapies, such as those using an aromatase inhibitor, block estrogen action and are clinically the most effective for ER-positive breast cancers. Unfortunately, these treatments are often followed by disease recurrence because most breast tumors are initially responsive to these therapies but then develop resistances through unknown mechanisms. Cancer recurrence is further associated with metastasis and invasion. For this reason, identification of the mechanism of therapy resistance has been strongly anticipated.

To analyze the cancer cell adaptation process, the research group used the human breast cancer cell line MCF7. These cells are ER-positive and can continue growth even after long term estrogen deprivation (LTED), similar to cancer cells that are resistant to endocrine therapy. It was determined that the expression of the ER gene (ESR1) was up-regulated during this adaptation in the LTED cells, and that novel ncRNAs, important in LTED cell adaptation, are produced from the ESR1 gene locus and the up-regulated ESR1 gene. Fluorescence in situ hybridization (FISH) analyses showed that these ncRNAs, termed Eleanors (ESR1 locus enhancing and activating non-coding RNAs), were localized at the site of actively transcribed ESR1 locus, resulting in the formation of distinct RNA foci in the nucleus. It was further revealed that resveratrol, a kind of polyphenol, exerted a repressive effect on the Eleanors via the ER and down-regulated the ESR1 gene which inhibited the proliferative activity of the LTED cells.

These findings uncovered the molecular basis for endocrine therapy-resistant breast cancer, showing the essential role of a new type of ncRNA-mediated regulation of the ESR1 gene locus.

In summary, Eleanors ncRNAs are actively involved in the epigenetic adaptation of ER-positive breast cancer cells via high expression of the ESR1 gene. These findings highlight the ncRNA-mediated mechanisms in cancer cell adaptation, which may be diagnostic and therapeutic targets for endocrine therapy-resistant breast cancer.

Source:
Kumamoto University