DATE: Day 5 Month 5 Year 2018

SUMMARY of
2017 RESEARCH RESULTS REPORT
For International Collaborative Research with IPR, Osaka University

Research Title		Experimental and Theoretical Detection of Phase Transition in Endocrine Resistance in Breast Cancer
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Summary

Breast cancer is one of the most common diseases in modern society and overcoming this disease is a challenging task in worldwide. Seventy percent of breast cancer are categorized as estrogen receptor (ER)-dependent tumor and initially respond to endocrine therapy using such as tamoxifen. However, about 30-40 % of tamoxifen-responsive tumor eventually acquires endocrine resistance within 15 years after initial diagnosis after long-term treatment of the drug. Due to this reason, molecular mechanisms of tamoxifen resistance have been intensively studied both *in vivo* and *in vitro*. Nevertheless, a deterministic factor that can modulate the endocrine resistance is not identified yet. Based on this fact, one can assume that drug resistance of breast cancer might be caused by modification of the molecular networks associated with many genes rather than by changes of a few molecules. Therefore, we hypothesis that drug resistance is a result of state changes in the time-course cellular transition in which gene networks are rewired to adapt to new environment rather than relaying on the old network. Specifically, we hypothesis that there is a tipping point just before the drastic state change (or drastic network rewiring) resulting in the drug resistance.

However, it is a challenging task to determine the tipping point of endocrine resistance and further detect the associated molecules. To meet this challenge, we previously developed a computational framework called dynamic network biomarker (DNB) analysis, which is able to identify such tipping point theoretically by analyzing: (1) increase of averaged correlation coefficients of molecular behaviors and (2) drastic increase of the averaged standard deviations within the network (DNB) together with (3) drastic decrease in the correlation coefficients of molecular behaviors outside of the DNB (protein or gene expressions). In this study, we applied the DNB analysis for time-course transcriptome data obtained from tamoxifen-treated breast cancer cells to quantitatively identify the tipping point of a drastic system transition as well as the DNB genes that play key roles in acquiring drug resistance.

Specifically, we analyzed time-course mRNA sequence data generated from the tamoxifen-treated estrogen receptor (ER)-positive MCF-7 cell line, and identified the tipping point of endocrine resistance with its leading molecules. The results show that there is interplay between gene mutations and DNB genes, in which

the accumulated mutations eventually affect the DNB genes that subsequently cause the change of transcriptional landscape, enabling full-blown drug resistance. Survival analyses based on clinical datasets validated that the DNB genes were associated with the poor survival of breast cancer patients.

***Deadline: May 18, 2018**
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