New computational method reveals chemoresistance drug targets

30 January 2018

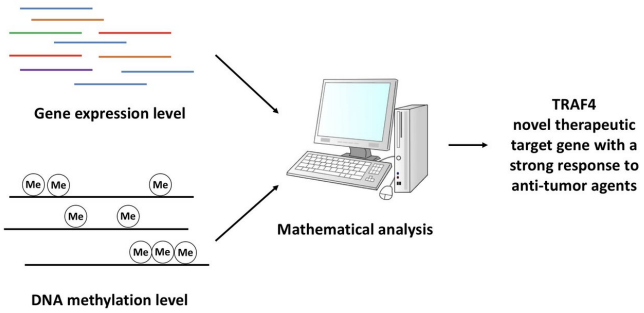

Fig.1. Mathematical analysis between gene expression levels and DNA methylation levels. Credit: Osaka University

Osaka – In cancer, one of the most important features is the methylation of deoxycytosine to form 5-methylcytosine (5mC). DNA methylation is a process by which methyl groups (structural units of organic compounds consisting of three hydrogen atoms bonded to a carbon atom) are added to the DNA molecule.

The occurrence and distribution pattern of 5mC have been shown to be crucial for gene regulation and can serve as important biomarkers for diagnostics. Therefore, investigating the relationship between DNA methylation and transcription (the first step of gene expression) is important for the interpretation of cellular responses and development of novel therapeutic strategies.

Extensive DNA methylation and transcription analyses have provided large quantities of data; however, it is difficult to identify critical genes related to cancer development from these data. To that end, a team of Osaka University researchers transformed the large volume of data into a smooth function using Gaussian functions to extract appropriate information from the data – information that serves as a representative value of 5mC methylation.

"Tumors contain a subpopulation of cells, called cancer stem cells (CSCs), which are self-renewing and tumorigenic and play a role in the resistance against chemotherapy and radiotherapy," explains Masamitsu Konno, first author of the study reported in *Scientific Reports*. "We therefore aimed to determine the efficient methods of identifying therapeutic targets using a CSC model of the enzyme ornithine decarboxylase to characterize intracellular events based on the 5mC."

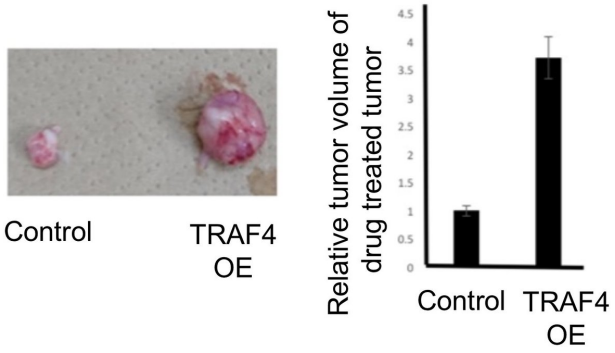

Fig.2. Drug sensitivity the control tumor and TRAF4 overexpressed tumor. Credit: Osaka University

The new computational approach integrates gene expression level and methylation modification data, which allows the researchers to successfully identify TRAF4 as an important gene for chemoresistance. Through the method, the effectiveness of drugs for human gastrointestinal cancer, including esophageal cancer, was also determined. Abnormal TRAF4 expression has been

reported in certain cancers, including breast, lung, and prostate cancers, but this is the first study to show that TRAF4 is important for possible regulation of functions in CSCs of human esophageal cancer.

"Our mathematical method can be used to simultaneously quantify and identify chemoresistant potential targets in gastrointestinal cancer stem cells," corresponding author Yuichiro Doki says. "Our results not only provide valuable information for the development of new therapeutics for esophageal cancer, but they also support the rationale for the large-scale screening of therapeutic targets of CSC drug development."

More information: Masamitsu Konno et al. Computational trans-omics approach characterised methylomic and transcriptomic involvements and identified novel therapeutic targets for chemoresistance in gastrointestinal cancer stem cells, *Scientific Reports* (2018). DOI: 10.1038/s41598-018-19284-3