

News Release

Title

The Discovery of an Oncometabolite Contributing to the Resistance to Nutrient Starvation

Key Points

- In malnourished cancer tissues, it was found that glutamate deprivation (*1) was the nutrient starvation especially related to malignant alteration of cancers.
- Cancer cells react to glutamate deprivation specifically by accumulating oncometabolite and become resistant to nutrient starvation. It was found that this mechanism and oncometabolite correlate with the prognosis of patients.
- This finding strongly suggests that there is a need to establish new cancer treatment from the perspective of nutrition science including disorders of glutamate metabolism.

Summary:

Solid cancer has incomplete angioarchitecture and has impaired flow of blood, causing hypoxia, malnutrition, low pH, and these tumor microenvironments promote changes in the epigenome, changes in energy metabolism, and metastasis/invasive capacity. It is known these contribute to poor prognosis such as malignant alteration of cancers, acquiring resistance to treatment, and relapse/metastasis. However, it has not been previously made clear how cancer cells that adopted to environment deprived of oxygen and nutrition had specific metabolic pathways. Group of researchers consisting of Tsuyoshi Osawa, a specially appointed associate professor at the Research Center for Advanced Science and Technology (RCAST) at The University of Tokyo, Professor Emeritus Tatsuhiko Kodama, Professor Teppei Shimamura from Nagoya University, and Professor Tomoyoshi Soga from Keio University clarified the following mechanism. They found that malnourished cancer cells react to glutamate deprivation through reduced expressions of PCYT2 (*2) which is an enzyme regulating metabolism, and by accumulating phosphoethanolamine (pEtN) (*4) within cells, which is an intermediate metabolite of synthetic pathway (*3) of PE lipids, the expression of PCYT2 (*2) is reduced in response to glutamate deprivation, thereby gaining resistance to nutrient starvation. The research findings were published in the electronic journal "Cell Reports" on October 1, 2019 at 11:00 am. (Eastern Daylight Time). This research was supported by Japan Agency for Medical Research and Development (AMED)'s "Innovative Cancer Medical Practice Research Project" and Grant-in-Aid for Scientific Research by Ministry of Education, Culture, Sports, Science and Technology.

Research Results

The research team has reported previously that the core of solid cancer tended to have hypoxia/malnutrition/low pH and these tumor microenvironments promote changes in the epigenome, changes in energy metabolism, and metastasis/invasive capacity contributing to poor prognosis such as malignant alteration of cancers and poor prognosis. In the research, culture system imitating malnourished state was used to predict changes in metabolism in cancer cells under amino acid deprivation among malnourished states and conducted transcriptome analysis (*5), metabolome analysis (*6), and Trans-omic Analysis (*7). As a result, it was found that when cancer cells are deprived of glutamate, they specifically accumulate phosphoethanolamine of oncometabolite and acquire resistance to nutrient starvation. Further, from analysis using cultivated cells and laboratory mice, it was found PCYT2, which is a rate limiting of enzyme of PE lipid synthesis pathway, reacts to glutamate deprivation and gets reduced. As a result, it became clear that malnourished cancer cells acquire resistance to nutrient starvation by accumulating phosphoethanolamine which is an intermediate metabolite of synthetic pathway of PE lipids (Figure 1) and relates to the prognosis of patients.

This is the first research that suggests glutamate deprivation among nutrient starvation is related to malignant alteration of cancer. In recent years, the importance of amino acid metabolism abnormality has been focused in cancer research but the knowledge obtained from this research findings suggest that there is a need to establish new cancer treatment from the perspective of nutrition science including disorders of glutamate metabolism. The discovery strongly suggests there is a need to establish new cancer treatment.

(*1) Glutamine:

An amino acid having an amide in the side chain and a structure in which the hydroxy group of glutamic acid is replaced with an amino group.

(*2) PCYT2:

A regulatory enzyme for phosphatidylethanolamine and plasmalogen biosynthesis.

(*3) Cell membrane phospholipid (PE) synthesis pathway:

A Biosynthesis pathway of cell membrane phospholipid (phosphatidylethanolamine)

(*4) Phosphoethanolamine:

Intermediate metabolite of PE synthesis pathway. Cancer metabolite (oncometabolite).

(*5) Transcriptome:

The set of all RNA molecules in one cell or a population of cells. The genome, which is the base sequence information of all DNA in a cell, is basically the same for all cells in the same individual, but the transcriptome differs for each cell and condition.

(*6) Metabolome:

The complete set of small-molecule chemicals found within a biological sample.

(*7) Trans-mics analysis

A technique that comprehensively analyzes biological phenomena by analyzing molecular groups (DNA, RNA, proteins, metabolites, lipids, etc.) in the living body.

Publication

Phosphoethanolamine Accumulation Protects Cancer Cells under Glutamine Starvation through Downregulation of PCYT2

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https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Cell_Rep_191002.pdf