Editorial Commentary

Metabolomics combined with mathematical analysis reveals metabolic pathways specific to metastatic cancers

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Intracellular metabolism of cancer is important not only for the survival of cancer cells but also in facilitating their invasion and metastasis potential (1-3). Cancer metabolism is known to differ from normal cellular metabolic processes, as exemplified by the Warburg effect (4,5). Metastases typically exhibit harsh environments characterized by reduced oxygen and nutrient availability compared to primary tumors (6,7), and thus require different metabolic pathways than those in primary tumors. Previous reports have shown differences in both the metabolic environment and metabolic pathways between primary and metastatic cancer sites (8-10). In this study, Mathur *et al.* placed emphasis on investigating the relationship between breast cancer metastasis and intracellular metabolism (11), because the existing genetic classification of breast cancer subtypes was inadequate in fully elucidating the metastatic potential (12).

A computational analysis involving a cohort of metastatic breast cancer cases sourced from public databases (13) revealed that driver gene mutations, such as those in PI3KCA and P53, and key clinical information may not be determinative factors in defining the metastatic site. The comparison of metabolomics results between the parental MDA-MB231 cells and the brain metastasis-oriented BrM2 and lung metastasis-oriented LM2 sublines revealed differences between the parental and subline strains, especially with regard to glucose metabolism. Based on mathematical analysis and *in vitro* studies, a notable prominence of lactate efflux was observed in LM2. In addition, lactate dehydrogenase (LDH) activity/pyruvate dehydrogenase (PDH) activity ratio was associated with lactate efflux. The high LDH/PDH ratio was also observed in breast cancer patients with lung metastasis. Furthermore, insights from pancreatic cancer cell lines indicated that cancer cells with high lactate efflux capacity may harbor a high lung metastatic potential across various organs.

The authors' findings not only demonstrate the adaptive nature of the intracellular metabolism of cancer cells to the metastatic environment but also indicate the potential for predicting the specific organ for metastasis based on the metabolic pathways of cancer cells in the primary tumor. This paves the way for the development of novel treatment methods targeting cancer cell metabolic pathways specific to metastatic organs. Future issues that require resolution include a more detailed analysis of the mechanisms that determine the activation of metabolic pathways specific to the metastatic organs identified in this study and the elucidation of universal metabolic pathways specific to metastatic organs other than the lungs.

In addition to glucose and amino acid metabolism,

fatty acid metabolism is also important in intracellular metabolism of metastatic cancers (14-16), and it has been pointed out that stromal cells, such as adipocytes surrounding cancer cells, may contribute to cancer cell metabolism owing to substantial alterations in the microenvironment at metastatic sites (17). Further development of research on the intracellular metabolism of cancer is anticipated in the near future.

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