Angiogenesis, formation of new blood vessels, is essential for tumor progression, invasion, and metastasis. Vascular endothelial growth factors (VEGFs) and their receptors (VEGFRs) are primary regulators of angiogenesis. Anti-VEGF antibodies (e.g., bevacizumab) and small molecular inhibitors of VEGFRs (e.g., sunitinib and sorafenib) were validated as the first cancer therapeutic agents targeting the tumor microenvironment. However, the effectiveness of anti-angiogenic treatments is limited to certain types of cancer. In addition, they may not completely eradicate tumor growth and may elicit malignant progression by, for example, inducing resistance to chemotherapy. Thus, the molecular mechanism underlying the elimination of such resistant and refractory cancer cells needs to be elucidated. The adaptation of cancer cells to tumor microenvironments such as in response to hypoxia, nutrient deficiency, acidosis, and reactive oxygen species can be achieved via alteration of metabolic states to glycolysis, glutaminolysis, and other metabolic pathways, but metabolic pathways utilized under hypoxia and nutrient starvation is unknown.

To elucidate metabolic pathways under hypoxia and nutrient starvation, we conducted integrated analysis of epigenome, transcriptome and metabolome and found that cancer cells survived under hypoxia and nutrient starvation utilizing phospholipid metabolism. Cancer cells resistant to hypoxia and nutrient starvation stimulated AKT phosphorylation, anchorage independent growth, cell migration and invasion in culture and increased angiogenesis and infiltration of macrophages into tumor tissues in vivo partly under epigenetic regulations. Using mRNA-Seq, ChIP-Seq, and metabolome analysis, we found that ethanolamine phosphate was most accumulated under hypoxia and nutrient starvation by down-regulation of the following rate-limiting enzyme PCYT2 within the Kennedy pathway. Moreover, inhibition of PCYT2 increased accumulation of ethanolamine phosphate and stimulated tumor growth both in vitro and
in vivo, suggesting that phospholipid polar head in Kennedy pathway can play an important role in cancer cell survival under nutrient starvation. Our results form the foundation of a strategy to attack hypoxia- and nutrient starvation-resistant cancer cells as an approach to leverage conventional chemotherapy and limit resistance to them.


Tsuyoshi Osawa, Ph.D.
2006-2007 Research fellow, Division of Genetics, IMS, The University of Tokyo
2007-2011 Assistant Professor, Department of Oncology, Tokyo Medical and Dental University
2011- Assistant Professor, Systems Biology and Medicine, RCAST, The University of Tokyo

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