IN THEIR ARTICLE, published in this issue of the American Journal of Physiology-Cell Physiology, Takahashi and Sato (7) point to the possibility that anaerobic respiration depends on complex II activity in mammalian cells, especially cancer cells. Fumarate respiration is established in parasites and shellfish but has not been unequivocally demonstrated in mammalian cells. What cancer cells are eating to generate energy for survival without oxygen and glucose is one challenging subject.

Cancer cells depend on glycolysis for their energy production, even during sufficient oxygen supply, and this dependence on glycolysis for energy production, i.e., the Warburg effect, has long been believed to be one of the most general characteristics of cancer (8). On the other hand, tumor angiogenesis is also strongly activated in most cancer tissues through activation of hypoxia-inducible factor (HIF)-1-dependent and-independent pathways, and tumor angiogenesis is often closely associated with poor prognosis for patients with various types of cancer (5). However, many clinical investigations have revealed that most cancer tissues are strongly hypoxic, despite vigorous angiogenesis and the preference of cancer cells for glycolysis. Therefore, cancer tissue hypoxia is assumed to be a result of insufficient blood supply. Tumor vasculature might be subjected to structural distortion by continuous tumor growth and death, resulting in structural and functional immaturity. The main energy production pathway of mammalian cells in an anaerobic environment is believed to be glycolysis, but, in the case of tumor hypoxia, glucose and other nutrient supplies might also be limited. Information about how cancer cells produce energy to maintain their proliferation and/or life under such harsh conditions is limited (2, 3).

Several authors have proposed the possibility of anaerobic respiration by renal cells and cancer cells, but its biochemical mechanisms and significance remain to be established (5, 6). Takahashi and Sato (7) used an elegant experimental system to demonstrate the possibility of an alternative anaerobic respiration. They developed a two-dimensional tissue model in which a monolayer of cultured cells expressing green fluorescent protein was placed under a coverslip so that oxygen is supplied only from the edge of the coverslip. In this system, an oxygen gradient was formed and visualized as the red shift of fluorescence, which depends on oxygen tension (6). When mitochondrial membrane potential was also visualized by a cationic fluorescent dye, the point at which the oxygen supply became limiting for mitochondrial function could be established. Using this system, they showed that the maximum distance for diffusion of oxygen was ~500 μm from the oxygen source (the edge of the coverslip), at which point mitochondrial membrane potential was abolished [the anoxic front (AF)]. When prolyl hydroxylase domain-containing proteins were inhibited by dimethyloxalylglycine (DMOG), the AF was extended to 1,500–2,000 μm, and the effect was much more prominent in a cancer cell line than in a fibroblast-like cell line. DMOG pretreatment significantly reduced tissue oxygen gradients, indicating sustained mitochondrial membrane potential with reduced respiration. In addition, DMOG effects were completely abolished by pharmacological inhibition of complex II, but not complex III, suggesting that complex II (probably with complex I) sustains mitochondrial membrane potential in the absence of oxygen (anaerobic respiration) in cells in which PHD activity is inhibited.

Recently, the importance of α-ketoglutarate-dependent dioxygenases in biology has been widely accepted, and this is especially true for the HIF-1 pathway in cancer and epigenetic regulation of cellular function. In the work of Takahashi and Sato (7), DMOG was used to activate hypoxic adaptation, and “cellular anaerobic respiration” was found to be activated. HIF-1 is the most important and well-studied transcription factor regulating a wide variety of cellular adaptations to the hypoxic environment. However, α-ketoglutarate-dependent dioxygenases include a large number of family members, and DMOG is not highly specific for the prolyl hydroxylases that regulate HIF-1α. The recent discovery of isocitrate dehydrogenase mutations, which produce large increases in the levels of the “onco-metabolite” D-2-hydroxyglutarate, raised the following question: How does this metabolite exert its oncogenic effect? HIF-1 activation is a strong candidate, but more extensive genetic and biochemical analyses, including effects on TET dioxygenases, histone demethylases, and prolyl hydroxylases, are needed to explore the biological relevance of D-2-hydroxyglutarate (1) and the work of Takahashi and Sato (7).

The work of Takahashi and Sato (7) points to the possibility that anaerobic respiration depends on complex II activity in mammalian cells, especially cancer cells, and this is one of the most interesting possibilities. Fumarate respiration is established in parasites and shellfish but has not been unequivocally demonstrated in mammalian cells (4). What cancer cells are eating to generate energy for survival without oxygen and glucose is one challenging subject. Additional genetic and biochemical studies are needed.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.
AUTHOR CONTRIBUTIONS

H.E. drafted the manuscript; H.E. approved the final version of the manuscript.

REFERENCES