

FIGURE 72-8 Warburg versus oxidative phosphorylation. In most normal tissues, the vast majority of cells are differentiated and dedicated to a particular function within the organ in which they reside. The metabolic needs are mainly for energy and not for building blocks for new cells. In these tissues, ATP is generated by oxidative phosphorylation that efficiently generates about 36 molecules of ATP for each molecule of glucose metabolized. By contrast, proliferative tumor tissues, especially in the setting of hypoxia, a typical condition within tumors, use aerobic glycolysis to generate energy for cell survival and generation of building blocks for new cells.

Mutations in genes involved in the metabolic process occur in a number of cancers. Among the most frequently found to date are mutations in isocitrate dehydrogenases 1 and 2 (IDH1 and IDH2). These have been most commonly seen in gliomas, AMLs, and intrahepatic cholangiocarcinomas. These mutations lead to the production of an oncometabolite (2-hydroxyglutarate [2HG]) instead of the normal product α -ketoglutarate. Although the exact mechanisms of oncogenesis by 2HG are still being elucidated, α -ketoglutarate is a key cofactor for a number of dioxygenases involved in controlling DNA methylation. 2HG can act as a competitive inhibitor for α -ketoglutarate, leading to alterations in methylation status (primarily hypermethylation) of genes (leading to epigenetic changes) that can have profound effects on a number of cellular processes including differentiation. Inhibitors of mutant IDH1 and IDH2 are approved for treating IDH mutant AML and are in clinical trials for glioblastomas and cholangiocarcinomas.

Much needs to be learned about the specific differences in metabolism between cancer cells and normal cells; however, even with the currently limited state of knowledge, modulators of metabolism are being tested clinically. The first of these is the antidiabetic agent metformin, both alone and in combination with chemotherapeutic agents. Metformin inhibits gluconeogenesis and may have direct effects on tumor cells by activating AMPK, a serine/threonine protein kinase that is downstream of the LKB1 tumor suppressor, and thus inhibiting mTOR complex 1 (mTORC1). This leads to decreased protein synthesis and proliferation. Studies to date have not yet established metformin to have a clear role as an anticancer agent.