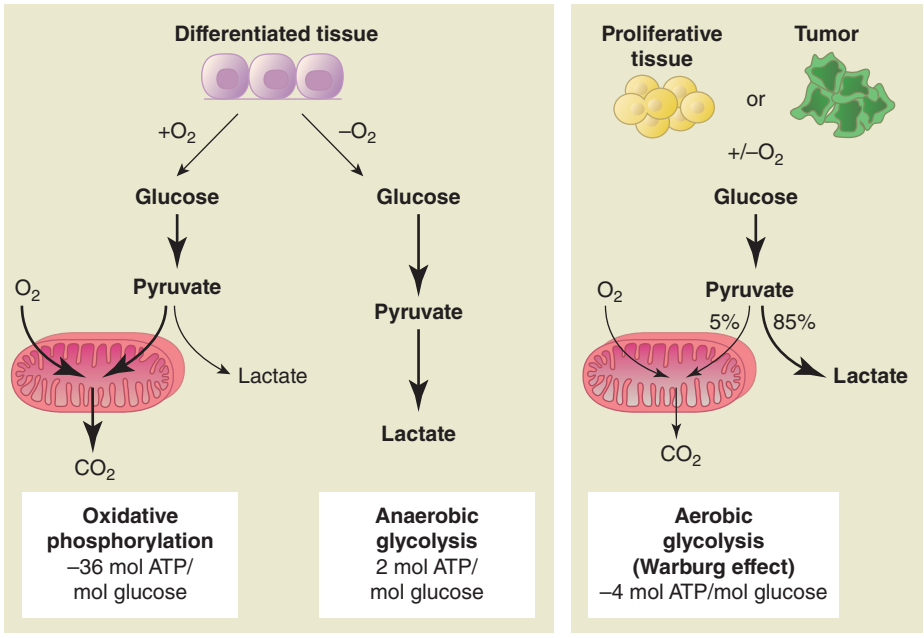

FIGURE 102e-8 Warburg effect versus oxidative phosphorylation. In most normal tissues, the vast majority of cells are differentiated and dedicated to a particular function within the organ in which they reside. The metabolic needs are mainly for energy and not for building blocks for new cells. In these 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 metastatic 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, AML, 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 (epigenetic changes) that can have profound effects on a number of cellular processes including differentiation. Inhibitors of mutant *IDH1* and *IDH2* are being developed.

Much needs to be learned about the specific differences in metabolism between cancer cells and normal cells; however, 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 the 5′-adenosine monophosphate-activated kinase (AMPK), a serine/threonine protein kinase that is downstream of the LKB1 tumor suppressor, and thus inhibiting mTORC1. This leads to decreased protein synthesis and proliferation. A second approach being tested involves dichloracetate (DCA), an inhibitor of pyruvate dehydrogenase kinase (PDK). PDK inhibits pyruvate dehydrogenase in cancer cells, leading to a switch from mitochondrial oxidative phosphorylation of glucose to cytoplasmic glycolysis (the Warburg effect). By blocking PDK, DCA inhibits glycolysis. Additional approaches targeting tumor metabolism will likely emerge.

TUMOR MICROENVIRONMENT, ANGIOGENESIS, AND IMMUNE EVASION

Tumors consist not only of malignant cells but also of a complex microenvironment including many other types of cells (e.g., inflammatory cells), ECM, secreted factors (e.g., growth factors), reactive oxygen and nitrogen species, mechanical factors, blood vessels, and lymphatics. This microenvironment is not static but rather is dynamic and continually evolving. Both the complexity and dynamic nature of the microenvironment enhance the difficulty of treating tumors. There are also a number of mechanisms by which the microenvironment can contribute to resistance to anticancer therapies.

One of the critical elements of tumor cell proliferation is delivery of oxygen, nutrients, and circulating factors important for growth and survival. The diffusion limit for oxygen in tissues is ~100–200 μm, and thus, a critical aspect in the growth of tumors is the development of new blood vessels, or angiogenesis. The growth of primary and metastatic tumors to larger than a few millimeters requires the recruitment of blood vessels and vascular endothelial cells to support their metabolic requirements. Thus, a critical element in growth of primary tumors and formation of metastatic sites is the *angiogenic switch*: the ability of the tumor to promote the formation of new capillaries from preexisting host vessels. The angiogenic switch is a phase in tumor development when the dynamic balance of pro- and antiangiogenic factors is tipped in favor of vessel formation by the effects of the tumor on its immediate environment. Stimuli for tumor angiogenesis include hypoxemia, inflammation, and genetic lesions in oncogenes or tumor suppressors that alter tumor cell gene expression. Angiogenesis consists of several steps, including the stimulation of endothelial cells (ECs) by growth factors, degradation of the ECM by proteases, proliferation and migration of ECs into the tumor, and the eventual formation of new capillary tubes.

Tumor blood vessels are not normal; they have chaotic architecture and blood flow. Due to an imbalance of angiogenic regulators such as VEGF and angiopoietins (see below), tumor vessels are tortuous and dilated with an uneven diameter, excessive branching, and shunting. Tumor blood flow is variable, with areas of hypoxemia and acidosis leading to the selection of variants that are resistant to hypoxemia-induced apoptosis (often due to the loss of p53 expression). Tumor vessel walls have numerous openings, widened interendothelial junctions, and discontinuous or absent basement membrane; this contributes to the high vascular permeability of these vessels and, together with lack of functional intratumoral lymphatics, causes increased interstitial pressure within the tumor (which also interferes with the delivery of therapeutics to the tumor; Figs. 102e-9, 102e-10, and 102e-11). Tumor blood vessels lack perivascular cells such as pericytes and smooth-muscle cells that normally regulate flow in response to tissue metabolic needs.

Unlike normal blood vessels, the vascular lining of tumor vessels is not a homogeneous layer of ECs but often consists of a mosaic of ECs and tumor cells with upregulated genes seen in ECs and vessel formation that can occur in hypoxic conditions because of their plasticity; the concept of cancer cell–derived vascular channels, which may be lined by ECM secreted by the tumor cells, is referred to as *vascular mimicry*. During tumor angiogenesis, ECs are highly proliferative and express a number of plasma membrane proteins that are characteristic of activated endothelium, including growth factor receptors and adhesion molecules such as integrins.

MECHANISMS OF TUMOR VESSEL FORMATION

Tumors use a number of mechanisms to promote vascularization, subverting normal angiogenic processes for this purpose (Fig. 102e-9). Primary or metastatic tumor cells sometimes arise in proximity to host blood vessels and grow around these vessels, parasitizing nutrients by co-opting the local blood supply. However, most tumor blood vessels arise by the process of *sprouting*, in which tumors secrete trophic