- Acquired biallelic loss-of-function mutations of *PTCH1* are seen frequently in sporadic basal cell carcinomas and medulloblastomas

***VHL***: encodes a component of a ubiquitin ligase that is responsible for degradation of hypoxia-induced factors (HIFs), transcription factors that alter gene expression in response to hypoxia

- Germline loss-of-function mutations cause von Hippel-Lindau syndrome, autosomal dominant disorder associated with a high risk of renal cell carcinoma and pheochromocytoma
- Acquired biallelic loss-of mutations are common in sporadic renal cell carcinoma

## Growth-Promoting Metabolic Alterations: The Warburg Effect

**Even in the presence of ample oxygen, cancer cells demonstrate a distinctive form of cellular metabolism characterized by high levels of glucose uptake and increased conversion of glucose to lactose (fermentation) via the glycolytic pathway.** This phenomenon, called the *Warburg effect* and also known as *aerobic glycolysis*, has been recognized for many years (indeed, Otto Warburg received the Nobel Prize in 1931 for discovery of the effect that bears his name). Clinically, the "glucose-hunger" of tumors is used to visualize tumors via positron emission tomography (PET) scanning, in which patients are injected with $^{18}$F-fluorodeoxyglucose, a nonmetabolizable derivative of glucose that is preferentially taken up into tumor cells (as well as normal, actively dividing tissues such as the bone marrow). Most tumors are PET-positive, and rapidly growing ones are markedly so.

Warburg's discovery was largely neglected for many years, but over the past decade metabolism has become one of the most active areas of cancer research. Metabolic pathways (like signaling pathways) in normal and cancer cells are still being elucidated and the details are complex, but at the heart of the Warburg effect lies a simple question: why is it advantageous for a cancer cell to rely on seemingly inefficient glycolysis (which generates two molecules of ATP per molecule of glucose) instead of oxidative phosphorylation (which generates up to 36 molecules of ATP per molecule of glucose)? While pondering this question, it is important to recognize that rapidly growing normal cells, such as in embryonic tissues, also rely on aerobic fermentation. Thus, "Warburg metabolism" is not cancer specific, but instead is a general property of growing cells that becomes "fixed" in cancer cells.

The answer to this riddle is simple: **aerobic glycolysis provides rapidly dividing tumor cells with metabolic intermediates that are needed for the synthesis of cellular components, whereas mitochondrial oxidative phosphorylation does not.** The reason growing cells rely on aerobic glycolysis becomes readily apparent when one considers that a growing cell has a strict biosynthetic requirement; it must duplicate all of its cellular components—DNA, RNA, proteins, lipid, and organelles—before it can divide and produce two daughter cells. Recall that the net effect of oxidative phosphorylation is to take a single molecule of glucose, $C_6H_{12}O_6$, and combine it with six molecules of $O_2$ to produce six molecules of $H_2O$ and six molecules of $CO_2$, which are lost through respiration. Thus, while "pure" oxidative phosphorylation yields abundant ATP, it fails to produce any carbon moieties that can be used to build cellular components that are needed for growth (proteins, lipids, and nucleic acids). Even cells that are not actively growing must shunt some metabolic intermediates away from oxidative phosphorylation in order to synthesize macromolecules that are needed for cellular maintenance.

By contrast, in actively growing cells only a small fraction of the cellular glucose is shunted through the oxidative phosphorylation pathway, such that on average each molecule of glucose that is metabolized produces approximately four molecules of ATP (instead of the two molecules that would be produced by "pure" glycolysis"). Presumably, this balance in glucose utilization (heavily biased toward aerobic fermentation, with a bit of oxidative phosphorylation) hits a metabolic "sweet spot" that is optimal for growth. It follows that growing cells do rely on mitochondrial metabolism. However, the main function of mitochondria in growing cells is not to generate ATP, but rather to carry out reactions that generate metabolic intermediates that can be shunted off and used as precursors in the synthesis of cellular building blocks. For example, lipid biosynthesis requires acetyl-CoA, and acetyl-CoA is largely synthesized in growing cells from intermediates such as citrate that are generated in mitochondria.

So how is this profound reprogramming of metabolism, the Warburg effect, triggered in growing normal and malignant cells? As might be guessed, **metabolic reprogramming is produced by signaling cascades downstream of growth factor receptors, the very same pathways that are deregulated by mutations in oncogenes and tumors suppressor genes in cancers.** Thus, whereas in rapidly growing normal cells aerobic glycolysis ceases when the tissue is no longer growing, in cancer cells this reprogramming persists due to the action of oncogenes and the loss of tumor suppressor gene function. Some of the important points of crosstalk between pro-growth signaling factors and cellular metabolism are shown in Fig. 7-32 and include the following:

- **PI3K/AKT signaling**. PI3K/AKT signaling upregulates the activity of glucose transporters and multiple glycolytic enzymes, thus increasing glycolysis; promotes shunting of mitochondrial intermediates to pathways leading to lipid biosynthesis; and stimulates factors that are required for protein synthesis.
- **Receptor tyrosine kinase activity**. In addition to transmitting growth signals to the nucleus, receptor tyrosine kinase signaling also influences metabolism. Rapidly dividing cells, both normal and malignant, express the M2 isoform of pyruvate kinase, which catalyzes the last step in the glycolytic pathway, the conversion of phosphoenolpyruvate to pyruvate. Receptor tyrosine kinases phosphorylate the M2 isoform of pyruvate kinase, a modification that attenuates its enzymatic activity. This creates a damming effect that leads to the build-up of upstream glycolytic intermediates, which are siphoned off for synthesis of DNA, RNA, and protein. Of note, in contrast to growing tissues and cancer cells, post-mitotic tissues with high demand for ATP such as the brain