



In cancer cells, increased rates of glycolysis and the low-activity kinase PKM2, which slows down the last step of this metabolic pathway, allow intermediates to be siphoned off for the production of nucleotide and amino acid precursors.

In cancer cells, glutamine taken in from the extracellular environment powers the Krebs cycle even when glucose is being diverted toward increased glycolysis.

In cancer cells, additional amino acids are obtained by collecting and breaking down extracellular proteins into their component parts.

### METABOLIC REPROGRAMMING

To support their unchecked proliferation, cancer cells often make metabolic adjustments to increase the supply of precursors to the necessary building blocks of the cell, such as amino acids, nucleotides, and lipids. Many of these altered metabolic pathways could serve as targets for novel anticancer therapies.

Unlike normal cells, cancer cells metabolize high levels of glucose and perform glycolysis even in the presence of oxygen. Increased glycolytic rates lead to the accumulation of much needed precursors for biosynthetic reactions. Glycolytic intermediates are siphoned off to the pentose phosphate pathway **1**—which generates NADPH and pentoses (5-carbon sugars)—as well as to pathways for serine/

glycine biosynthesis **2**, ultimately leading to the production of nucleotides. Cancer cells also employ a low activity pyruvate kinase isoform, PKM2, which slows down the last step of glycolysis.

In mitochondria, the metabolic process known as the Krebs cycle also provides key precursors for the synthesis of amino acids and nucleotides as well as lipid precursors in both normal and cancer cells. Among these, aspartate is a critical precursor for both protein and nucleotide biosynthesis **3**. In proliferating cancer cells, an ample supply of glutamine from the extracellular environment supports the production of Krebs cycle precursors **4**. Some cancer cells use a process called macropinocytosis to ingest extracellular proteins, which then serve as amino acid sources essential for growth **5**.