Malignant cells exhibit metabolic changes when compared to their normal counterparts, owing to both genetic and epigenetic causes. Many of these alterations are in place to support intensive cell proliferation, which implies that the metabolic profile of cancer cells resembles that of non-transformed, rapidly dividing cells. Recent evidence also suggests that the metabolic rewiring of each neoplasm is specific and supports all facets of malignant transformation, rather than constituting yet another general hallmark of cancer. During the past decade, the metabolic circuits of cancer cells have been characterized with increasing precision, and the therapeutic potential of strategies to target these pathways has been intensively investigated. Moreover, several conventional chemotherapeutics operate as de facto metabolic inhibitors, which suggests that a therapeutic window for drugs that target cancer cell metabolism does exist. A novel number of metabolic inhibitors are about to enter clinical trials for cancer therapy. Such a strategy has the potential to convert a central aspect of tumour biology into the Achilles heel of malignant cells.

**Metabolic targets for cancer therapy**

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**Facts on oncometabolism**

The metabolism of cancer cells is rewired to allow for malignant transformation. Enzymes involved in metabolic processes that are found in normal cells adapt to changing environmental conditions. For example:

- **Surrogate glucose sources**: Multiple metabolites can be used as glucose surrogates, such as glucuronate, lactate, and succinate. These are converted into acetyl-CoA, 3-ketoisovalerate, and pyruvate, respectively, and are then further oxidized and metabolized in the TCA cycle and oxidative phosphorylation.

- **Suppressive effects on mitochondrial respiration**: Inhibition of mitochondrial respiration impairs the production of ATP, a critical energy source for cellular functions. This leads to a decrease in ATP levels, which can promote cell death or cell cycle arrest, thereby inhibiting the proliferation of cancer cells.

- **Enhanced glucose utilization**: Cancer cells exhibit increased glucose uptake and utilization, a process known as the Warburg effect. This increased glucose metabolism leads to the production of lactate, which is excreted into the extracellular environment, allowing cancer cells to maintain their metabolic requirements.

- **Drug targets**: Metabolic pathways that are altered in cancer cells provide potential drug targets for therapeutic intervention. These include enzymes involved in glucose metabolism, such as glucose-6-phosphate dehydrogenase (G6PDH), and enzymes involved in lipid metabolism, such as farnesyl diphosphate synthase (FPPS).

**Metabolic modulators with antineoplastic effects**

- **Targeting metabolic pathways**: Metabolic pathways that are altered in cancer cells provide potential drug targets for therapeutic intervention. These include enzymes involved in glucose metabolism, such as glucose-6-phosphate dehydrogenase (G6PDH), and enzymes involved in lipid metabolism, such as farnesyl diphosphate synthase (FPPS).

- **Clinical application**: The combination of metabolic inhibitors with other therapeutics, such as chemotherapeutics, can lead to improved therapeutic efficacy and reduced side effects.

**Potential for personalized medicine**: The metabolic profile of each individual cancer cell is unique, and this can lead to differences in therapeutic response. Thus, the development of personalized metabolic therapies that target specific metabolic pathways in individual patients is an area of active research.

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