Cancer Metabolism as a Therapeutic Target: Metabolic Synthetic Lethality

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Drugs targeting different metabolic pathways induced in tumors may be used in combination with one another to induce synthetic lethality in cancer cells, while preserving the survival of normally proliferating cells.

Interest in targeting metabolism as a possible cancer therapy has been renewed in recent years as research increases our understanding of the altered metabolic profile of cancer cells compared with that of normal cells. As mentioned by Drs. Batra, Rosen, and Shanmugam, metabolic reprogramming allows tumor cells to survive and proliferate in the hostile tumor environment. Alterations in tumor cell metabolism lead to higher energy production, induction of anabolic pathways, and maintenance of cellular redox potential. These mechanisms are essential for the survival and proliferation of tumor cells. Metabolic processes are regulated by genetic events that render cancer cells dependent on certain nutrients, such as glutamine and lipids. Moreover, hypoxia in cancer cells that are distant from their oxygen supply will lead to the induction of hypoxia-inducible factor 1α (HIF-1α), a transcription factor that is responsible for changes in metabolism that support the survival of cells in hypoxic tumor areas. Several aspects of metabolism are altered in tumor cells—including glucose and glutamine metabolism, as the authors have mentioned—but we would like to point out that lipid metabolism also has a crucial role in tumorigenesis.

As noted in the review by Dr. Batra and colleagues, survival processes that are coupled with metabolic reprogramming could be used for therapeutic targeting, but the most important challenge would be to specifically target the metabolism of tumor cells without affecting that of noncancerous cells. The metabolism changes in cancer cells in hypoxic tumor areas may render these cells more vulnerable to metabolic targeting.

Targeting Cancer Cell Metabolism

Several studies offer evidence that hypoxia mediates resistance to chemotherapy. For instance, anti-angiogenic therapies have been shown to induce hypoxia within tumors, resulting in both increased local invasion and distant metastatic spread.[1] Thus, a better understanding of the biology of hypoxia induced by these treatments, and of metabolic reprogramming, would lead to improvements in existing therapies; it would also aid in the search for new targets that might be used to overcome resistance to anti-angiogenic treatment.[2] Inhibition of specific metabolic pathways induced by hypoxia could represent a crucial constituent in the discovery of efficient anticancer therapies.

As suggested by the authors, highly glycolytic cancer cells may be particularly sensitive to inhibition of glucose metabolism, especially when glucose and oxygen are limited in the tumor microenvironment. Numerous studies have been performed with glycolytic inhibitors,[3,4] or inhibitors of specific glycolytic enzymes, such as phosphoglycerate mutase (PGM), hexokinase 2 (HKII), or lactate dehydrogenase A (LDH-A).[5-7] Nevertheless, these therapeutic strategies have not shown significant results as anticancer treatments clinically. Other glycolytic targets described in the review, such as PFKFB3, pyruvate kinase M2 (PKM2), or phosphoglycerate dehydrogenase (PHGDH), seem essential for the survival of various cancer cells and have been targeted by inhibitory drugs in several preclinical studies.[8,9]

In addition, targeting glutamine metabolism could be an efficient way to reduce cancer cell survival.[10] Cancer cell lines are extremely sensitive to glutamine starvation; for example, inhibition of phosphate-activated glutaminase (GLS2) with a small-molecule inhibitor suppresses oncogenic transformation without affecting the growth of normal cells.[11] The glutamine-analogue acivicin, in association with glutaminase, synergistically inhibits the proliferation and invasion of some cancer cell types.[12] Furthermore, tumor cells with isocitrate dehydrogenase (IDH) mutations are addicted to glutamine as a source for the production of 2-hydroxyglutarate (2-HG). Inhibition of GLS1 by an
inhibitory drug reduces the growth of glioblastoma cells expressing mutant but not wild-type IDH1.[13]

Reactivation of mitochondrial function could be another pathway that might be targeted in anticancer therapy. The HIF-1α target pyruvate dehydrogenase kinase 1 (PDK1) is inhibited by the drug dichloroacetate (DCA). DCA decreases tumor cell proliferation, increases cell death, and inhibits tumor growth.[14] DCA has also been tested in clinics in patients with glioblastomas, leading to reactivation of the mitochondrial function and generation of reactive oxygen species.[15]

Lipid metabolism is another essential metabolic route that could be targeted in cancer cells. In adult normal tissues, the majority of fatty acids are acquired from the circulation. In contrast, tumor cells synthesize high levels of fatty acids, even when high levels of lipids are present in the circulation—and numerous lipogenic enzymes, such as fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC), are induced or upregulated in tumors.[16] The importance of lipogenesis for cell growth and proliferation has been demonstrated by studies showing the effect of its inhibition in cancer cells using pharmacological agents or siRNA to target FASN or ACC.[17,18] Inhibition of stearoyl-CoA desaturase 1 (SCD1), a fatty acid desaturase, also induces cell death in various cancer cell types.[19,20]

**Metabolic Synthetic Lethality**

Alteration of one single pathway in the metabolic network may induce compensatory pathways to generate alternative sources that can compensate for the loss of certain metabolites. Metabolic synthetic lethality occurs when simultaneous mutations in two different metabolic genes together are lethal, while a mutation in either of the individual genes alone is tolerable for normal growth. The simultaneous suppression of several genes that together have the potential for synthetic lethality may open new avenues for anticancer treatment.

The combination treatment of metformin and 2-deoxyglucose, a specific glycolysis inhibitor, impaired tumor growth in mouse xenograft models.[21] The combination of an LDH-A inhibitor with the nicotinamide adenine dinucleotide (NAD+) synthesis inhibitor FK866 greatly reduced the NAD+ cellular pool and led to lymphoma regression.[22] Synthetic lethality screens targeted at metabolic enzymes could be useful tools that might add to the number of metabolic targets for anticancer therapy, and could be exploited to overcome resistance to conventional chemotherapy agents, such as bevacizumab (Avastin). A potential target is glycogen phosphorylase liver form (PYGL), which showed increased expression following bevacizumab treatment in an in vivo xenograft model.[23] Combination treatment with inhibitors targeting PYGL and/or other HIF-dependent metabolic enzymes essential for survival in hypoxia, and an anti-angiogenic drug, could be of great interest as a metabolic cancer therapy.

**Conclusion**

Drugs targeting different metabolic pathways induced in tumors may be used in combination with one another to induce synthetic lethality in cancer cells, while preserving the survival of normally proliferating cells. Notably, there are hundreds of different types of cancer, and the specific metabolic pathways to target may differ from one type of tumor to another; this may lead to the development of tumor-specific therapies. The next decade will be very exciting, as both basic and clinical research in the metabolic field may lead to markedly improved cancer characterization and therapy.

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