Serine Biosynthesis Regulates Folate Availability in Cancer Cells

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Metabolism is clearly altered in proliferating cancer cells, which reprogram certain metabolic pathways to support the conversion of available nutrients into biomass. By gaining a better understanding of tumor metabolism is altered to support cell proliferation, it may be possible to identify new potential therapeutic targets. Recent research points to nucleotide metabolism, particularly the serine biosynthesis pathway, as key mediators of cancer cell proliferation.

**Role of Phosphoglycerate Dehydrogenase (PHGDH) in Oncogenesis**

Proliferative metabolism is characterized by an increased rate of glycolysis. Pyruvate kinase catalyzes the conversion of phosphoenolpyruvate (PEP) to pyruvate. High pyruvate kinase activity decreases serine synthesis and results in nucleotide depletion. Tumor cells demonstrate a strong selection for the expression of the less active isof orm of pyruvate kinase, M2 (PKM2). To support continued proliferation, however, cells utilizing the less active PKM2 isof orm must rely on alternate pathways with separate regulatory features to convert PEP to pyruvate.

In a report published in *Nature Genetics* in 2011, a research team led by Jason W. Locasale, PhD, found that some cancer cells divert a relatively large amount of glycolytic carbon into serine and glycine metabolism through phosphoglycerate dehydrogenase (PHGDH). The PHGDH gene is located in a chromosomal region (1p12) that is amplified in multiple tumor types, most commonly in melanoma. The expression of PHGDH is also increased in some breast cancers, where PHGDH overexpression is indicative of poor disease outcomes.

Increased PHGDH expression is associated with increased serine synthesis from glucose. However, serine synthesis from glucose does not appear to be the major source of serine for most cells. Tests evaluating the serine contribution from glucose showed that only 10-15% of serine is made de novo, even in cells with an amplified serine biosynthesis pathway. Moreover, the intracellular serine that is produced reaches complete equilibrium with the extracellular media. These findings suggest that the majority of the serine that cells utilize is extracellular.

**Role of Folate Metabolism**

Folate metabolism is compartmentalized in mammalian cells, with different enzyme isoforms in the mitochondria and cytosol that catalyze the same reactions. However, because folates are not permeable to the mitochondrial membrane, only cytosolic folate is available for nuclear thymidine synthesis. PHGDH-amplified cells demonstrate more folate cycling than non-amplified cells, underscoring the potential key role of folate metabolism in cancer cell survival.

**Preclinical Models of PHGDH Inhibition**

Another recent line of research has focused on the effects of inhibiting PHGDH and serine biosynthesis on cancer cell metabolism. In PHGDH-amplified cell lines, PHGDH inhibition adversely effects thymidine synthesis. Further, the inhibition of serine biosynthesis impacts cell cycle progression. Although PHGDH inhibitors appear to alter the growth of tumors formed from PHGDH-amplified cells, better models are needed to study these interactions in vivo. PHGDH expression appears to accelerate the growth and progression of cancer cells in other tumor models, particularly in mouse models of BRAF-mutated melanoma and BRCA1-mutated breast cancer. A mouse model of PHGDH-amplified cancer is currently under development.

**New Insights into Cellular Respiration**

One final area of emerging research involves the mechanisms of cellular respiration and their roles in tumor proliferation. Respiration-deficient cells are pyruvate auxotrophs, meaning that they must be provided supraphysiological levels of pyruvate to proliferate. Electron acceptors are required to make biomass, and providing electron acceptorsallows cells to proliferate in the presence of mitochondrial poisons. One of the most abundant products of tricarboxylic acid cycle (TCA cycle) is aspartate, which is necessary for nucleotide synthesis. Aspartate supports cellular proliferation in the absence of respiration. Conversely, proliferating cells require respiration to produce aspartate.
**Future Directions**

To date, many of these preliminary findings regarding cancer cell respiration, serine biosynthesis, and folate metabolism are hypothesis-generating. Additional research on the diversity of cancer metabolism phenotypes may reveal important clues about why certain chemotherapy regimens and anticancer therapies are more effective in particular settings.

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**References**

