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MINI-SYMPOSIUM: CANCER METABOLISM IN BRAIN TUMORS

Metabolic Reprogramming in Brain Cancer: A Coordinated Effort

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INTRODUCTION

Metabolic reprogramming is a central hallmark of cancer (4). In a seminal observation made nearly a century ago, the German biochemist, Otto Warburg, demonstrated that cancer cells convert the majority of glucose they take up into lactate even in the presence of sufficient oxygen to support oxidative phosphorylation. This observation spawned decades of research in which cancer was considered to be fundamentally a disease of metabolic dysregulation. The molecular era ushered in a new perspective in which cancer was considered first and foremost to be a genetic disease arising from mutations in oncogenes and tumor suppressors. Remarkably, functional studies of altered genetic networks have yielded a powerful new insight—genetic alterations cause in cancer in part by altering cellular metabolism. Many of these new insights integrating cancer genetics and cancer metabolism have been conducted in glioma cells, rendering this disease a critical focal point as researchers try to understand how tumor cells reprogram their metabolism to drive tumor formation, progression and drug resistance.

Many tumor cells, including most glioma cells studied, increase glucose uptake to meet the increased energetic and biosynthetic demands imposed by rapid tumor growth. In parallel, these glioma cells have developed additional biochemical adaptations that enable them to (i) leverage the glucose-derived carbons for production of ribose, glycerol, serine and glycine; (ii) utilize the glucose-derived carbons for lipid synthesis through the activity of ATP citrate lyase; and (iii) secrete the excess glucose-derived carbons as lactate, indicating that the Warburg effect alone cannot account for the full spectrum of metabolic changes required for tumor growth (10). Glutaminolysis, the catabolism of glutamine to support tumor cell proliferation, is also a central feature of cancer metabolic reprogramming, providing (i) a source of nitrogen for nucleotide and amino acid synthesis; (ii) a mechanism to produce NADPH for lipid and nucleotide synthesis; and (iii) an alternative carbon source to supply tricarboxylic acid (TCA) cycle intermediates (5). Tumor cells also require large amounts of lipid for membrane biogenesis, signal transduction and potentially as an energy source. De novo lipogenesis is a metabolic hallmark of cancer, including in gliomas (3, 6), which can be augmented by uptake of exogenous lipids (2).

In this mini-symposium, we examine cancer metabolism as a central driving force of glioma pathogenesis. Gliomas remodel their metabolism to ensure maximal flexibility in order to grow, produce energy and survive. These adaptions are designed to meet the intertwined demands of building biomass, maintaining redox and getting energy. Metabolic reprogramming in glioma can be mediated by several factors. These include critical glycolytic enzymes such as pyruvate kinase M2 (PKM2, discussed by Liu and Vander Heiden) (7), central regulators of metabolism such as mTORC2 (reviewed by Masuei *et al*) (8) and mutations in metabolic enzymes such as isocitrate dehydrogenase 1/2 (IDH 1/2, discussed by Wahl and Venneti) (9). These metabolic alterations drive many aspects of glioma biology, including tumor formation (mutant IDH1/2), growth (PKM2 and mTORC2) and drug resistance (mTORC2). Further, these metabolic changes create imaging opportunities for noninvasive diagnosis, patient stratification and monitoring of treatment response (reviewed by Chaumeil *et al*) (1). Finally, metabolic reprogramming provides unanticipated therapeutic vulnerabilities that can serve as novel therapeutic targets to combat gliomas. This collection of review article provides critical insights into glioma biology from the perspective of cancer metabolism and highlights many of the further studies that are needed to dissect the molecular networks to inform the development of new treatments.

This mini-symposium will attempt to present and integrate the current state of our understanding of metabolic reprogramming in gliomas. These reprogramming changes may create new ways to image tumors in patients noninvasively to stratify them for treatment and to monitor their responses to therapy. Further, these metabolic changes may create unanticipated and potentially clinically actionable targets that may inform new treatments for glioma patients.

REFERENCES

1. Chaumeil MM, Lupo JM, Ronen SM (2015) Magnetic resonance (MR) metabolic imaging in glioma. *Brain Pathol* **25**:769–780.
2. Currie E, Schulze A, Zechner R, Walther TC, Farese RV Jr (2013) Cellular fatty acid metabolism and cancer. *Cell Metab* **18**:153–161.
3. Guo D, Prins RM, Dang J, Kuga D, Iwanami A, Soto H *et al* (2009) EGFR signaling through an Akt-SREBP-1-dependent,

rapamycin-resistant pathway sensitizes glioblastomas to antilipogenic therapy. *Sci Signal* **2**:ra82.
4. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. *Cell* **144**:646–674.
5. Hensley CT, Wasti AT, DeBerardinis RJ (2013) Glutamine and cancer: cell biology, physiology, and clinical opportunities. *J Clin Invest* **123**:3678–3684.
6. Lewis CA, Brault C, Peck B, Bensaad K, Griffiths B, Mitter R *et al* (2015) SREBP maintains lipid biosynthesis and viability of cancer cells under lipid- and oxygen-deprived conditions and defines a gene signature associated with poor survival in glioblastoma multiforme. *Oncogene* **34**(40):5128–5140.
7. Liu V, Vander Heiden MG (2015) The role of pyruvate kinase M2 in cancer metabolism. *Brain Pathol* **25**:781–783.
8. Masui K, Cavenee WK, Mischel P (2015) mTORC2 and metabolic reprogramming in GBM—at the interface of genetics and environment. *Brain Pathol* **25**:755–759.
9. Wahl D, Venneti S (2015) 2-Hydoxyglutarate: D/Riving pathology in gLiomaS. *Brain Pathol* **25**:760–768.
10. Ward PS, Thompson CB (2012) Metabolic reprogramming: a cancer hallmark even Warburg did not anticipate. *Cancer Cell* **21**:297–308.