Measurement Methodologies for Assessing the Glycolysis Effect in the Discrimination and Therapy of Brain Gliomas

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ABSTRACT

Primary brain tumors refer to those developing from the various types of cells that compose the brain. Gliomas represent about 50% of all primary brain tumors and include a variety of different histological tumor types and malignancy grades. The World Health Organization (WHO) classifies gliomas into four histological types and four grades. The goal of molecular classification using advanced pattern recognition tools is to identify subgroups of tumors with distinct biological and clinical features and initiate the challenge of classifying complex gliomas of similar histology and malignancy status into distinct categories. The aim of this paper is i) present the measurement procedures and analysis methodologies, ii) summarize the currently available knowledge related to the utilization of ’omics’ measurements in the discrimination of brain gliomas, and iii) provide a scientific basis for future medical practice in the discrimination and treatment of brain gliomas based specifically on the metabolic process of glycolysis. In particular, the paper explores the idea of the glycolysis pathway as a critical concept for the development of therapeutic strategies for brain gliomas.

Keywords: Genomics, Glioma Classification, Glycolysis Markers, Glycolysis Measurements, Metabolomics, Proteomics

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1. INTRODUCTION

Gliomas are the most frequent primary malignant brain tumors in adults, which generally have a poor prognosis. The worldwide incidence rate of malignant brain tumors is estimated at 3.7 per 100,000 in males and 2.6 per 100,000 in females. It shows a higher incidence in developed countries (males, 5.8 and females, 4.1 per 100,000) than in less developed countries (males, 3.0 and females, 2.1 per 100,000), based on the Globocan 2002 data of the International Agency for Research on Cancer (McCarthy, Schellinger, Propp, Kruchko, & Malmer, 2009).

Gliomas are derived from glial cells of astrocytic, oligodendroglial and ependymal origin. According to the fourth edition of the World Health Organization (WHO) classification of tumors of the Central Nervous System, published in 2007, gliomas are classified into four histological types: astrocytoma, oligodendrogloma, oligoastrocytoma and ependymoma. These categories are based on morphological similarities of the tumor cells with non-neoplastic glial cells and the presence of particular architectural features and are further divided in four grades (grade I-IV), with increasing grade reflecting an increase in tumor aggressiveness and worse prognosis. The astrocytic tumors are most common and include the most malignant type of glioma in adults, the glioblastoma (glioblastoma multiforme-GBM). Apart from these common glioma types, a number of rare malignant glioma entities and variants, as well as several types of mixed glial and neuronal tumors, are detected particularly in children and young adults, which are not discussed in this study (Michotte, Neyns, Chaskis, Sadones, & In ’t Veld, 2004; Louis et al., 2007; Riemschneider, Jeuken, Wesseling, & Reifenberger, 2010; Jones & Holland, 2011).

Despite extensive research over the past forty years, little improvement progress in mortality rates has been made for patients diagnosed with malignant glioma. The intra- and inter-tumoral heterogeneity and the diffuse infiltration of tumor cells into normal brain tissue complicate the effective therapy and surgical resection, respectively and partially explain the poor outcome (Jones & Holland, 2011). Thus, the heterogeneity of gliomas creates the need for improved classification, novel therapies and means for selecting patients for individualized therapy. The functional approach of molecular classification includes new ‘omics’ technologies, such as genomics, proteomics, and metabolomics (Petrik, Loosemore, Howe, Bell, & Papadopoulos, 2006). ‘Omics’ generate complex data, analysed using advanced pattern recognition tools to identify molecular signatures of different glioma types. Using biomarker signatures over traditionally histological characterization has resulted in a more effective subgrouping of brain tumors and of gliomas in particular, thus increasing the diagnostic accuracy or serving as potential drug targets. Importantly, molecular classification has shed more light on the biological mechanisms and molecular pathways involved in gliomagenesis which in turn is the key to developing effective therapies (Jones & Holland, 2011; Petrik, Loosemore, Howe, Bell, & Papadopoulos, 2006).

Over the last decade a lot of research has focused on the identification of genetic alterations that play a vital role in brain glioma pathology. Most recent studies (Shiraishi, & Tabuchi, 2003; Furnari et al., 2007; Ohgaki & Kleihues, 2009) conclude to a specific set of gene markers that has become a diagnostic standard to describe the type and grade of this complex and lethal cancer. Towards a better understanding of the interactions of these genes and the stage of their involvement in glioma grade progression, a genetic pathway in the form of a super network called glioma pathway, has become available in KEGG (Kyoto Encyclopedia of Genes and Genomes). Within this network, specific pathways exemplify the role of oncogenes and tumor suppressor genes in crucial biological processes of the cell.

Besides the genomic considerations, ongoing research focuses on classifying groups of gliomas on the basis of metabolic markers and of glycolytic markers in particular (Locasale et al., 2011; Wolf et al., 2011; Kounelakis, 2010), based on the importance of cellular energy
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