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Review

# Mitochondrial energy metabolism and apoptosis regulation in glioblastoma

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ABSTRACT

Glioblastoma is the most aggressive form of gliomas and is associated with short survival. Recent advancements in molecular genetics resulted in the identification of glioma genomic, epigenomic and transcriptomic hallmarks, and multidimensional data allowed clustering of glioblastomas into molecular subtypes. Parallel with these developments, much scientific attention has been attracted by the exploration of two functional processes linked to mitochondrial regulation. One of these processes involves genomic and mitochondrial gene mutations, mitochondrial protein expression modifications and altered metabolic regulation that define glioblastoma. The second mitochondrially-centered process involves complex molecular interactions and pathways that influence the extrinsic or the intrinsic mechanisms of apoptosis regulation and may underlie the uncontrolled spreading, recurrence and drug resistance of glioblastoma. While the available data are not yet comprehensive, these two complex processes represent important aspects of tumor cell biology, which may provide complementary opportunities for therapeutic manipulations of this highly resistant tumor type.



## Contents



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## 1. Introduction

Gliomas are graded I–IV by the World Health Organization. Glioblastoma (GBM) is the most advanced (grade IV), most aggressive and most frequent form of gliomas (Dunn et al., 2012). Tissue diagnosis of GBM is defined based on histomorphology along with the presence of cell proliferation, necrosis and angiogenesis. The 5-year survival rate is 4.5%, while the 10 year survival rate is 2.7% for patients with GBM (Griguer and Oliva, 2011). The standard of care includes wide surgical resection, irradiation and chemotherapy. The recent addition of the alkylating agent, temozolomide (TMZ) to radiotherapy increased the 2-year survival from 10.4% (radiotherapy alone) to 26.5% (radiotherapy+TMZ), and resulted in a 14.6 month increased median survival (Griguer and Oliva, 2011). Unfortunately, the tumor eventually recurs in all patients, but there are variations in the progression free survival dependent upon the patient's age, gender, extent of surgical removal of pathology, and the tumor biology and genetics, microenvironmental factors and the presence of residual cancer stem cells (CSC). Much effort has been made to better define markers of GBM variability and individual molecular targets for therapy.

At histological level, GBMs are notoriously heterogeneous. The tumor cells are characterized by pleiomorphism, glioblastoma stem cells (GSC) may be present in varying numbers, and primitive neuroectodermal or mesenchymal elements often admix with glial elements (Phillips et al., 2006; Prayson, 2009; de Almeida Sassi et al., 2012). Histological heterogeneity is observed not only among, but also within GBMs. A new definition of inter-tumor heterogeneity was recently proposed based on multi-dimensional molecular (genomic, transcriptomic and epigenomic) studies carried out by The Cancer Genome Atlas Network (TCGA). The TCGA analyses showed clustering of GBMs into four subgroups, namely proneural, neural, classical and mesenchymal, that correlate with biological properties of tumors and measures of clinical outcome (The Cancer Genome Atlas, 2008; Verhaak et al., 2010). Analyses of data from microarray studies identified 38 genes predicting GBM survival (Colman et al., 2010), which could be confined to a 9-gene-expression panel with utility in clinical practice. To provide an even simpler GBM classifying tool, Le Mercier et al. (2012) tested the expressions of EGFR, PDGFRA and p53 proteins by quantitative immunohistochemistry in formalin-fixed, paraffin-embedded clinical specimens. Based on these three markers alone, the separation of two GBM subtypes was feasible: (1) The classical subtype with EGFR+, p53- and PDGFRA- staining; and (2) the proneural subtype with p53+ and/or PDGFRA+ staining. These observations reproduced main points of previous genomic and transcriptomic studies and offered prognostic significance (Verhaak et al., 2010; Le Mercier et al., 2012).

Somatic mutations and expression variations in the EGFR gene received probably the most attention among all molecular markers, since this transmembrane molecule is essential in glioma cell biology while also amenable to therapeutic interventions with tyrosine kinase inhibitors, monoclonal antibodies, EGFR vaccines, and RNA-based therapies (Kalman et al., 2013). Mutations in the EGFR gene in GBM are mainly located in its extracellular domain, and include deletions, insertions and missense mutations. Among them, the EGFRvIII mutant with a deletion involving exons 2–7 is the most frequent pathogenic variant detected in approximately 30% of GBMs. In normal conditions, after the engagement of EGFR and its ligand (*e.g.* the epidermal growth factor, TNFα or amphiregulin), the intracellular tyrosine kinase domain of the receptor activates a cascade of signaling molecules and through that, regulates cell proliferation, survival, apoptosis, migration, and gene transcription (Kalman et al., 2013). The mutated EGFR is constitutively active and contributes to uncontrolled cell proliferation and altered cell biology. Targeting overexpressed wild type or mutated EGFR is an attractive therapeutic approach in those GBMs in which a sufficient proportion of cells are positive for these molecules (Kalman et al., 2013). For both prognostic and therapeutic purposes, intratumor distribution of molecular markers has great clinical relevance (Scottoriva et al., 2013). We recently reviewed the literature concerning the degree and nature of intratumor molecular heterogeneity in the context of tumor behavior and response to therapies and proposed that such evaluation of individual tumors may form a basis for clinical decisions (Eder and Kalman, 2014).

The complexity and interdependence of somatic alterations that define GBM biology is increasingly recognized. We discuss here two pathways involving complex mitochondrial functions linked to tumorigenesis. One of the pathways integrates genomic and mitochondrial (mt)DNA mutations, metabolic changes and tumor formation. The second pathway links altered gene expression and decreased apoptosis together with uncontrolled cell proliferation and tumor formation. Recognizing unique features of mitochondrial genetics, energy metabolism and apoptosis regulation in GBM has the practical relevance of offering new or supplementary targets for therapy.

## 2. Mitochondrial genetics and function

### 2.1. *Mitochondrial genetics*

Mitochondria are cytoplasmic organelles bounded by two distinctly different membranes and comprised of four different physical and functional compartments. The inner mitochondrial membrane is highly convoluted to form cristae thereby increasing the surface area and thus the bioenergetic capacity of the organelle. Mitochondria in oxidatively active cells have more extensive cristae. In addition to being the energy- generating center of the cell by synthesizing ATP via