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Functional and Therapeutic Implications of Mitochondrial Network and Mitochondria-Associated Membranes: The Glioma's Case

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<http://dx.doi.org/10.5772/intechopen.77224>

Abstract

Even today, despite the surgery, radiotherapy, and chemotherapy, gliomas prognosis is still poor. There is a great need to develop new therapies. The understanding of the structural and functional characteristics of mitochondrial network (MN) and mitochondria-associated membranes (MAM) in gliomas is essential for the design of future therapeutic strategies. A huge range of ultrastructural findings is observed in MN and MAM in the human gliomas. These findings imply that a majority of glioma cells are incompetent to produce an adequate amount of energy by means of oxidative phosphorylation and compensatory increases in glycolytic ATP production. Regarding MAM, a “MAM-rich” cell (well-differentiated glioma cells) and “MAM-deficient” cells (glioma like-stem cells) exist. The quantity of MAM could be linked to the functional or metabolic state of the different glioma cells. MAM-resident mTORC2 is a major regulator tumor growth and drug resistance. If sufficient nutrients are present, glioblastoma cells maintain mTORC2 signaling to drive cell proliferation and survival. Consequently, the replacement of fermentable fuels like glucose with non-fermentable fuels like ketone bodies becomes a logical approach. The vision must be targeting the cellular signaling pathways and metabolic reprogramming. Whatever the modality, a holistic and feasible approach must be developed.

Keywords: mitochondria, mitochondria-associated membranes, glioma, glioblastoma, metabolic reprogramming, mTORC2

1. Introduction

In the next lines, we do a brief journey through some aspects of gliomas, included epidemiological, clinical, neuroradiological, neuropathological, ultrastructural, therapeutics, and biologic behavior. An emphasis regarding the functional and therapeutics implications (metabolic therapy approach) of mitochondrial network (MN) and mitochondria-associated membranes (MAM) in astrocytomas is presented.

The MN has been implicated in the process of carcinogenesis, which includes alterations of cellular metabolism and cell death pathways. Defects in mitochondrial function have been suspected to play an important role in the development and progression of cancer [1].

Accumulating evidence indicates that MAMs are a subcellular “hot spot” for the intracellular signaling [2, 3]. Recent research has highlighted and broadened the functional roles of MAM in a variety of cellular processes from lipid synthesis/transport, Ca^{2+} signaling, and ER stress, to mitochondrial shape and autophagy/mitophagy and to inflammation and cell immunity [3, 4]. MAM dysfunction has been associated with several types of cancer [5]. Research from the past decade has identified the MAM as a potentially central regulator of tumor cell metabolism, as exemplified by the presence of critical tumor suppressors and oncoproteins on this structure [6]. The involvement of MAM in cancer has not been thoroughly investigated. Consequently, there is a huge open window for pathophysiological understanding and novel treatment modalities related to MN and MAM functions.

Recently, we provide evidence showing MN and MAM ultrastructural aspects in a range of human astrocytomas, including pilocytic astrocytoma diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma [7–10]. Probably, this represents a contribution to the structural basis of functional roles of MN and MAM in astrocytic tumors as well as therapeutics implications.

2. Epidemiological and clinical aspects

Diffuse astrocytic tumors comprise approximately 60% of primary intracranial tumors. These tumors can arise at any age in children and the very elderly, although incidence increases substantially with advancing age. The median age is 30–40 for diffuse astrocytoma, 40–50 for anaplastic astrocytoma, and 50–60 years for glioblastoma. Older patients are also more likely to have higher grade gliomas, especially glioblastoma. The last one is the most frequent neoplasm in this category, accounting for approximately 80% of the diffusely infiltrative astrocytomas [11, 12].

The clinical presentation of the diffuse astrocytomas varies according to the sites of involvement and the rate of growth. The most common clinical symptoms are new-onset seizures, changes in behavior, motor deficits, and signs/symptoms of increased intracranial pressure (headache, nausea, vomiting, and papilledema). High-grade astrocytoma tend to have a short history with rapid progression, whereas low-grade astrocytoma are more indolent, often with insidious onset and a long, protracted clinical course [11, 12].

3. Neuroimaging

Astrocytomas are most commonly seen on magnetic resonance imaging MRI as ill-defined, deep-seated, or predominantly subcortical cerebral hemispheric masses. MRI sequences, where signal hyperintensity reflects vasogenic edema generated in response to diffuse infiltration by individual tumor cells. Secondary signs of mass effect include midline shift, ventricular compression, and sulcal effacement. Glioblastoma commonly show a rim-enhancing pattern with a central low-density region of necrosis surrounded by irregular, variable thickness rim of contrast enhancement. This rim-enhancing component is always surrounded by T2- or FLAIR signal hyperintensity that represents an associated diffusely infiltrating neoplasm [11, 12] (**Figure 1**).

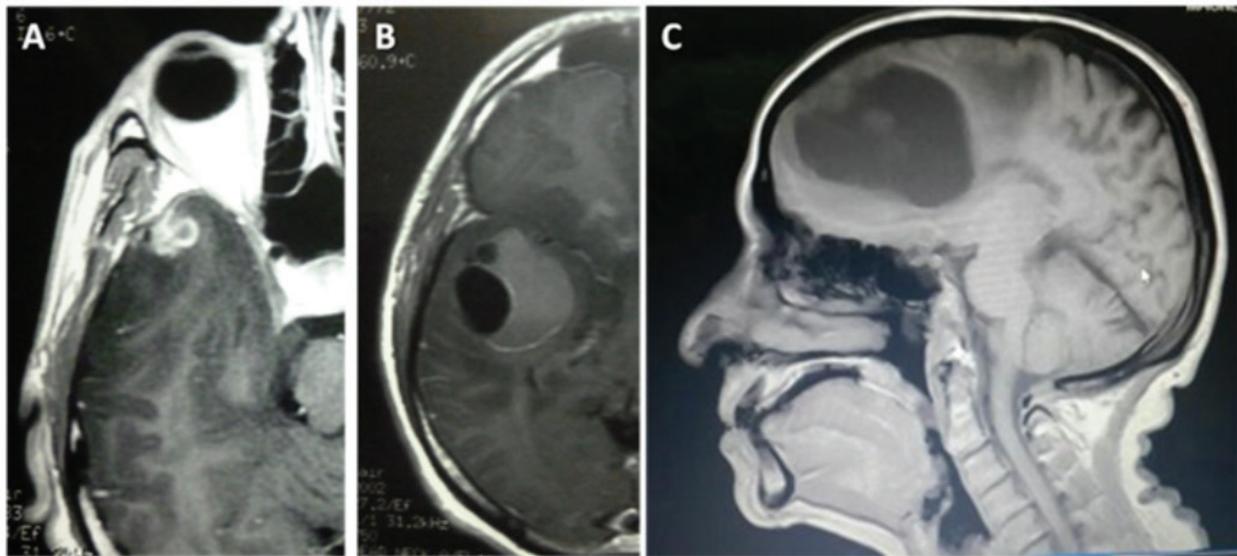


Figure 1. Glioblastoma MRI. (A) Initial MRI from a 50-year-old male patient with seizures and a temporal lobe glioblastoma. (B) The same patient three months later. (C) A huge frontal lobe giant cell glioblastoma from a 65-years-old female patient with changes in behavior.

4. Neuropathological aspects of gliomas

4.1. Gross pathology

Diffuse astrocytomas are ill-defined and subtly discolored, with secondary mass effects. These tumors are most often centered in the subcortical white matter but have a tendency to infiltrate widely and include the cerebral cortex, deep gray structures, and even the contralateral hemisphere. Glioblastoma are classically heterogeneous, with foci of necrosis, and hemorrhage [11, 12].

4.2. Histopathology

Gliomas constitute a heterogeneous group of primary central nervous system tumors. The term astrocytoma includes tumors with astrocytic differentiation. They may have a wide spectrum of

cell types in pure or mixed form. The classical tumor cells may show elongated, irregular hyperchromatic nuclei, often with no discernible cytoplasm, and embedded in a dense fibrillary matrix, mixed with cells that display visible eosinophilic cytoplasmic processes. However, cellular diversity, such as gemistocytic cell, protoplasmic cell, sarcomatous cell, epithelioid cell, granular cell, giant cell, or small cell is eventually observed. Glioblastoma display microvascular hyperplasia and tumor necrosis (pseudopalisading areas or infarct-like areas) [11, 12] (**Figure 2**).

The infiltrative or diffuse forms of astrocytoma are composed of individual tumor cells that infiltrate widely throughout the brain parenchyma with a cellular density and degree of anaplasia that increase with tumor grade. They are characterized by invasive growth such that nonneoplastic cells are often intermixed and may even predominate in some areas. The secondary structures of Scherer include subpial condensation, perineuronal satellitosis, and perivascular aggregation. The extreme end of the infiltrative spectrum, previously assigned as gliomatosis cerebri; it involves multiples lobes of the brain, often bilaterally and frequently extending into the brain stem, cerebellum, and even the spinal cord [11, 12].

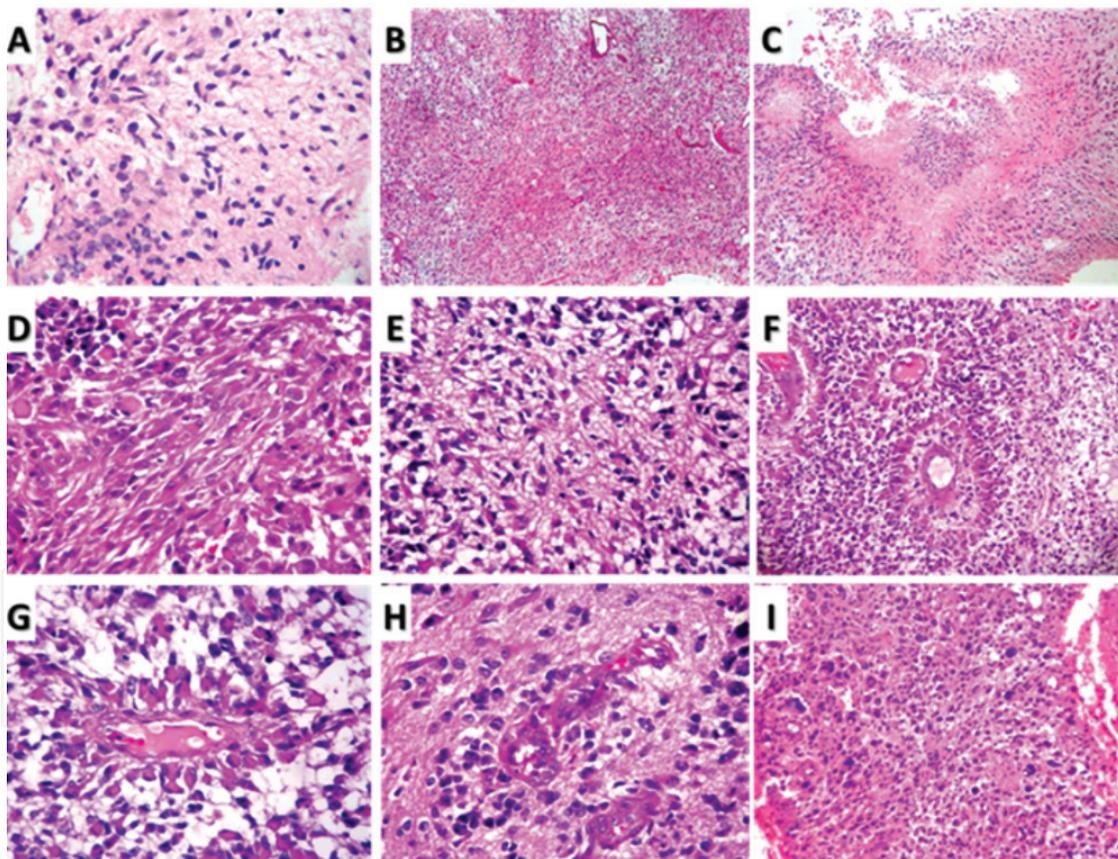


Figure 2. Histopathology. (A) Diffuse astrocytoma. Tumor cells show elongated, irregular hyperchromatic nuclei, with no discernible cytoplasm and embedded in a dense fibrillary matrix, mixed with cells that display visible eosinophilic cytoplasmic processes. (B) Glioblastoma displays a hypercellular-solid neoplasm with fuzzy or ill-defined margins, with diffuse parenchymal infiltration. (C) Glioblastoma: a pseudopalisading necrosis area. (D) Glioblastoma: an epithelioid-like cell area. (E) Glioblastoma: hypercellularity, tumor cells show elongated, irregular hyperchromatic nuclei, with no discernible cytoplasm and embedded in a dense fibrillary matrix, mixed with cells that display visible eosinophilic cytoplasmic processes. (F and G) Glioblastoma: cooption blood vessels surrounded by tumor gemistocytic cells. (H) Glioblastoma displaying microvascular hyperplasia. (I) Giant-cell glioblastoma corresponding to **Figure 1C**.

4.3. The 2016 World Health Organization classification of tumors of the central nervous system

According to the 2016 World Health Organization classification of tumors of the central nervous system [13], the diffuse gliomas include the WHO grade II and grade III astrocytic tumors, the grade II and III oligodendrogliomas, the grade IV glioblastomas, as well as the related diffuse gliomas of childhood. Then, all diffusely infiltrating gliomas (whether astrocytic or oligodendroglial) are grouped together: based not only on their growth pattern and behaviors but also more pointedly on the shared genetic driver mutations in the *IDH1* and *IDH2* genes. This approach leaves those astrocytomas that have a more circumscribed growth pattern, lack IDH gene family alterations, and frequently have *BRAF* alterations (pilocytic astrocytoma, pleomorphic xanthoastrocytoma) or *TSC1/TSC2* mutations (subependymal giant cell astrocytoma) distinct from the diffuse gliomas.

The WHO grade II diffuse astrocytomas and WHO grade III anaplastic astrocytomas are now each divided into IDH-mutant, IDH-wildtype, and NOS categories. It is recommended that WHO grading is retained for both IDH-mutant and IDH-wildtype astrocytomas, although the prognosis of the IDH-mutant cases appears more favorable in both grades.

Glioblastomas are divided into: (1) glioblastoma, IDH-wildtype (about 90% of cases), which corresponds most frequently with the clinically defined primary or de novo glioblastoma and predominates in patients over 55 years of age [14]; (2) glioblastoma, IDH-mutant (about 10% of cases), which corresponds closely to so-called secondary glioblastoma with a history of prior lower grade diffuse glioma and preferentially arises in younger patients [14]; and (3) glioblastoma, NOS, a diagnosis that is reserved for those tumors for which full IDH evaluation cannot be performed.

5. Biologic behavior

Today, gliomas still represent a serious and discouraging brain tumor; despite the diversity of treatment modalities, generally, the prognosis for patients is still poor (i.e., fatality and sequelae). Even with surgical resection and aggressive treatment with chemotherapy and radiotherapy, the prognosis for patients with astrocytomas remains very poor [15].

6. The mitochondrial network, mitochondria-associated membranes, glioma ultrastructural pathology, and their functional and therapeutic implications

Both the endoplasmic reticulum and mitochondria are highly dynamic organelles, forming networks that may undergo rapid changes in the size, length, and shape, depending on metabolic and Ca^{2+} buffering needs, or in response to different cellular insults [16].

6.1. Mitochondrial network

Ultrastructurally, mitochondrion is an organelle constituted by a peripheral and inner membrane. The peripheral membrane encloses the entire contents of the mitochondrion, and internal membrane forms a series of folds, called cristae, which project inward toward the interior space of the organelle. The area between the peripheral and inner membranes is designated as intermembrane space, and the area enclosed by the internal membrane is labeled as a mitochondrial matrix. Functionally, the outer membrane includes the apoptosis antagonists and agonists and fission/fusion mitochondrial proteins. The inner membrane contains all the respiratory enzyme complexes and the three electron transporters, necessary for oxidative phosphorylation. In major mammalian tissues, 80–90% of ATP is generated by mitochondria in the process of oxidative phosphorylation [17, 18]. The mitochondrial matrix contains the enzymatic system of β -oxidation and tricarboxylic acid cycle. Mitochondria in living human cells display large, elongated and branched structures, actually entitled as mitochondrial network, extending throughout the cytosol and in close contact with the nucleus, the endoplasmic reticulum, the Golgi complex and the cytoskeleton, and is continually remodeled by both fusion and fission events [19].

In some cell types, mitochondria exist as single and randomly dispersed organelles; in other cells, mitochondria may also exist as dynamic networks that often change shape and subcellular distribution. Depending on the cell type, mitochondria localized in different site-specific regions of a cell may display dissimilar morphology and biochemical properties [20].

6.2. Mitochondria-associated membranes

MAM is a membranous and protein structure (inter-membranous structure) composed by three pieces: (1) endoplasmic reticulum membrane; (2) mitochondrial membrane (outer mitochondrial membrane); and (3) tethers (proteins). Consequently, it displays biological membranous processes such as molecules trafficking and signaling events.

To date, MAM is considered as a fundamental cellular structure tightly regulated and with multifaceted roles that include Ca^{2+} signaling, lipid synthesis and exchange, metabolic control, and others. MAM formation might depend on several factors relating to differences in cell demands or microenvironment stimuli [2, 21].

6.3. Mitochondrial network and mitochondria-associated membranes abnormalities in human astrocytomas

Regards to the mitochondrial network, lucent-swelling mitochondria with disarrangement and distortion of cristae and partial or total cristolysis is predominant in the astrocytoma cells. In a minor proportion of astrocytoma cells, the presence of mitochondria with dense matrix displayed in closed groups exists [7–10].

Considerable variations in MAM ultrastructure is observed in the glioma tissue with respect to density, length, and width of the interfacing ER and mitochondrial membranes (**Figure 3**). In some astrocytoma cells, the MAM displayed a network or “work station”

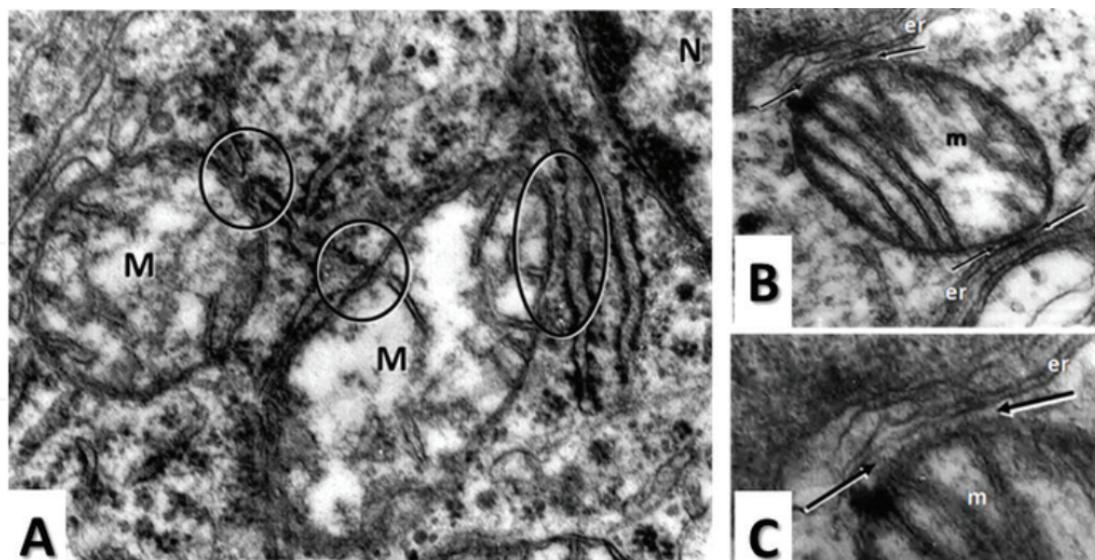


Figure 3. (A–C) Glioblastoma cells displays variable organization of endoplasmic reticulum membrane associated with mitochondria (circles, ellipses, and arrows). M/m denotes mitochondria; er: endoplasmic reticulum profiles. N: cellular nucleus. Lucent-swelling mitochondria with disarrangement and distortion of cristae, and partial or total cristolysis, are seen.

(an area with high density of MAM and predicted the functional activity). Close or direct association (mitochondria-endoplasmic reticulum interface <30 nm) and detached or disrupted (>30 nm) associations is present. The shortest span of MAM was 96 nm, and the longest was 652 nm [10].

In the ultrastructural perspective, we identified two remarkable cell types: (1) poorly differentiated glioma stem cells and (2) well-differentiated glioma cells. The first one exhibits a poorly developed mitochondrial network and scarce MAM (named by us “MAM-deficient cells”). The second contains a well-developed MN and numerous MAM (named by us “MAM-enriched cells”). MAM displayed a network or “work station” in some well-differentiated glioma cells [10] (**Figure 4**).

Previously, we suggest that the MAM could be involved in the invasive properties of glioma cells. Human glioma cell invadopodia show mitochondria with a dense matrix condensed configuration, indicating an active state. The mitochondria were frequently in close contact with an extended smooth endoplasmic reticulum displaying an endoplasmic reticulum subfraction associated with mitochondria MAM. Fluorescent microscopy confirmed that D54 and U251 glioma cells growing *in vitro* also contained filopodia with mitochondria (**Figure 5**). The U251 glioma cells’ filopodia that penetrated through 1.2- μ m pores of transwell chambers also contained mitochondria, suggesting that the mitochondria are actively involved in the invasion process [9].

In the vascular microenvironment components of gliomas, the mitochondrial network exhibit similar changes to describe in tumoral cells. The mitochondria display mainly two patterns: (1) swelling associated with disarrangement of cristae and partial or total cristolysis and (2) condensed configuration [8].

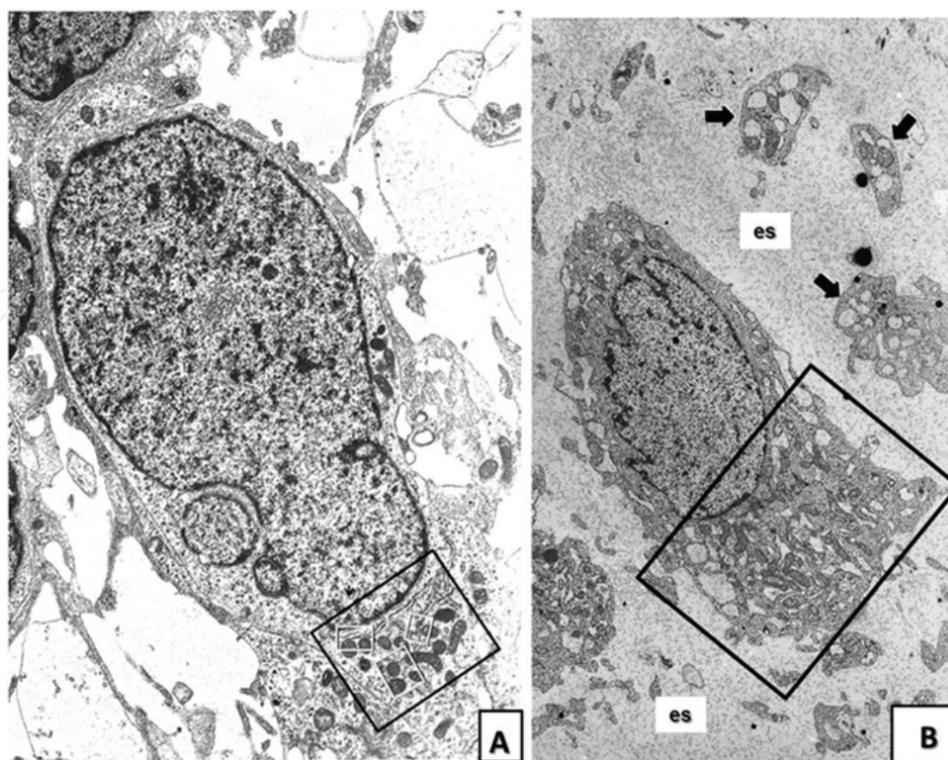


Figure 4. (A) Glioma like-stem cell exhibited, adjacent to nuclei, an endoplasmic reticulum an endoplasmic reticulum profile, and a small amount of electron-dense mitochondrion displayed a “MAM network” (black rectangle) with six direct interorganellar close associations with small span (white rectangles). (B) Well-differentiated tumor cell displays electron-lucent mitochondrion (m) in close association with multiple endoplasmic reticulum profiles establishing multiple MAM (rectangle) conforming a huge “MAM network”. Similar fashion is observed in three cellular processes (arrows); es: denotes extracellular space.

6.4. Functional and therapeutics implications

In the case of astrocytomas, the dense mitochondria could be capable of producing energy by oxidative phosphorylation, and lucent-swelling mitochondria with disarrangement and distortion of cristae and partial or total cristolysis are incapable of generating energy by oxidative phosphorylation. Possibly, the astrocytoma cells that hold dense mitochondria are able to generate sufficient ATP concentration by oxidative phosphorylation. In contrast, the astrocytoma cells that contain lucent swelling mitochondria with disarrangement and distortion of cristae and partial or total cristolysis are incompetent to produce an adequate amount of ATP by mitochondrial respiration. These findings suggest that the majority of astrocytoma cells are incompetent to produce an adequate amount of energy by means of oxidative phosphorylation [7–9]. The glycolytic inhibition and inhibition or down-regulation of mitochondrial respiration would be a potential tool for future therapeutic strategies in cases of human astrocytic tumors.

Mitochondria are present at the invadopodia and their apparent function appears linked with the ROS generation and subsequent activation of several pathways essentials for glioma invasiveness. Mitochondria are a major source of ROS, which occurs mainly at complexes I and III of the respiratory chain. In cancer cells, mitochondria can generate ROS and redox signals, specifically via an increase in the NAD^+/NADH ratio [22]. H_2O_2 induces Akt (protein kinase B) activation, and their pathway is redox regulated. Akt activation correlated with the

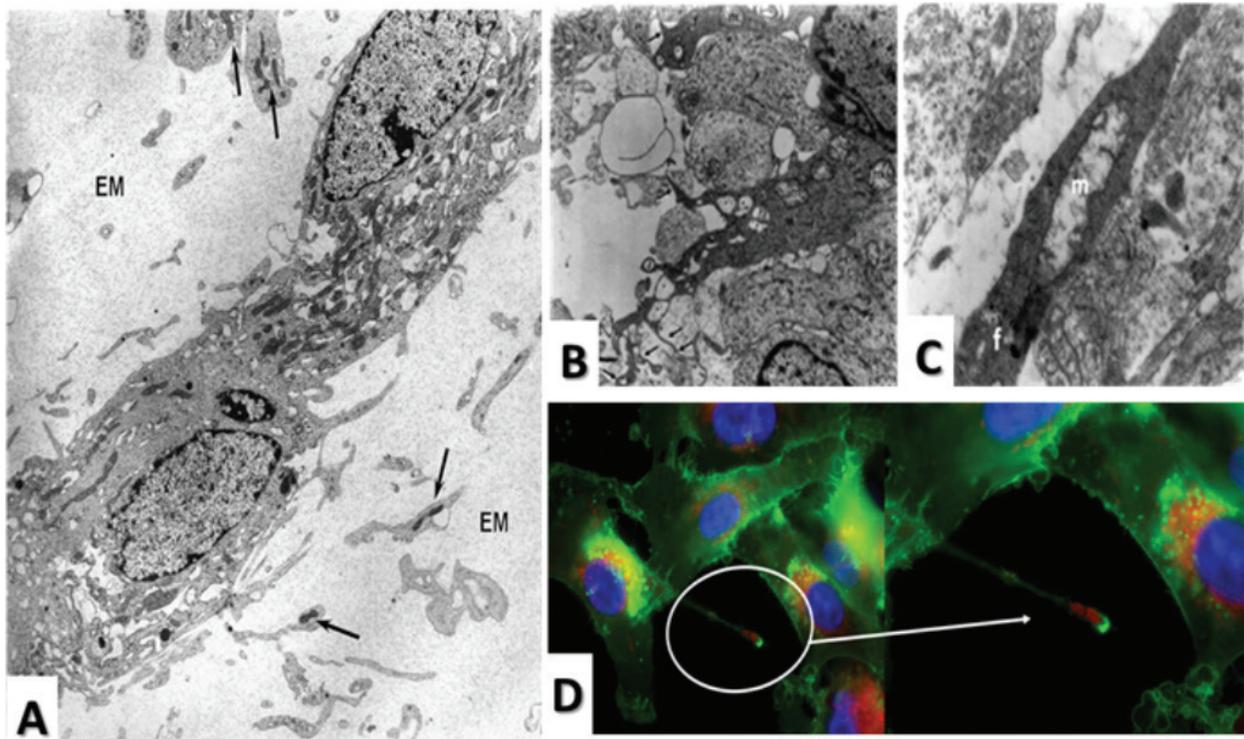


Figure 5. (A) Two glioblastoma multiforme cells exhibit several invadopodia that contain mitochondria with dense matrix condensed configuration (arrows). The cytosol shows multiple mitochondria with similar morphologies and physically adjacent to distended endoplasmic reticulum MAM. EM: denotes extracellular matrix. (B and C) Glioma cells filopodias (f). M denotes: mitochondria; * designates: dilated endoplasmic reticulum cystem; arrows indicate: filiform projections. (D) Under fluorescent microscopy, U251 glioma cells stained with MitoTracker Red (label the mitochondria). The mitochondria are in the filopodia (circle and arrow). Green: actin filaments. Blue: nuclei. (personal communication and courtesy from Martin R. Jadas, Diagnostic & Molecular Health Care Group, Veterans Affairs Medical Center, Long Beach, California, USA, Neuro-Oncology Program, Chao Comprehensive Cancer, University of California–Irvine, Orange, California, and USA; and Pathology and Laboratory Medicine, Med. Sci. I, University of California, Irvine, California, USA).

increased tumorigenicity, stem cell-ness, and invasiveness of invasive glioblastoma cells [23]. Molina et al. [23] reported that the glioma cells with high Akt activation actively invaded the surrounding parenchyma along blood vessels and with matter tracts. In human astrocytomas, the co-option vessel shows invadopodia with mitochondria that display dense matrix condensed configuration [9]. This finding possibly represents the ultrastructural basis of the molecular process expressed above, which permits the invasiveness of glioblastoma cells. On another hand, the PI3K-Rac and PI3K-3/Akt pathways are involved in the production of ROS that accumulates at the membrane ruffles [24], ROS production stimulates cytoskeletal reorganization required for a migratory response. Migrating glioma cells show activation of the PI3K/Akt pathway, and PI3K inhibitors have been tested experimentally, resulting in a decrease in migration [25]. Therefore, Inhibition of mitochondrial ROS generation may represent another important therapeutic target to most gliomas.

The degree of development of MN and quantity of MAM could be linked to the functional or metabolic state of the different tumor cells found in human astrocytic tumors. Then, the well-differentiated glioma cells (or “MAM-enriched cells”) could be more active in these processes than the poorly differentiated glioma stem cells (or “MAM deficient cells”) [10]. A recent study

showed that glioma stem cells are less glycolytic than differentiated glioma cells, consuming lower levels of glucose, and producing lower amounts of lactate while maintaining higher ATP levels compared with their differentiated progeny [26]. Another study, by means of transmission electron microscopy, analysis revealed that the number of mitochondria with distinct cristae and electron-dense matrices increased significantly in the non-stem differentiated glioma cells when compared to their undifferentiated glioma stem cells. The final conclusion was that glioma stem cells prefer a relatively higher glucose metabolism, which implies that they utilize different mitochondrial biosynthesis and metabolic pathways when compared to differentiated glioma cells [27]. Other research established that glioma stem cells displayed diminished endoplasmic reticulum-mitochondria contacts compared to glioma differentiated cells. Forced endoplasmic reticulum-mitochondria contacts in glioma stem cells increased their cell surface expression of sialylated glycans and reduced their susceptibility to cytotoxic lymphocytes. The final conclusion was that endoplasmic reticulum-mitochondria contacts control surface glycan expression and sensitivity to killer lymphocytes in glioma stem-like cells [28].

The length of the interface is changing under different biochemical conditions [29, 30]. Apparently, the execution of the physiological programs is dependent on the length of the MAM, since the structural plasticity of the MAM cleft accompanies changes in cell metabolism [29]. Changing the thickness of MAM would impact on the activity of several enzymes of the Krebs cycle and on the strength of the IP3R Ca^{2+} signaling pathway [30]. Furthermore, the variability of the ultrastructural aspects observed on astrocytic tumors suggests a dynamic regulation of the interorganellar junction that can be modified by functional requirements needed to adapt to different cell demands. Solid and glycolytic tumor tissue is frequently characterized by a loss of normal MAM architecture and formation [6]. Today, altered Ca^{2+} signaling at the MAM is recognized as a hallmark of cancer cells that shifts their metabolism to glycolysis and increases their resistance to cell death [31]. MAM-resident mTORC2 controls the MAM integrity and mitochondrial functions [4, 32] and is the core of MAM signaling hub that controls growth and metabolism. Recent studies suggest that mTORC2 can promote glioblastoma growth and chemotherapy resistance in cancer cells as well as controlling genome stability and tumor metabolism including glycolysis, glutaminolysis, lipogenesis, and nucleotide and reactive oxygen species metabolism [33]. Glucose is required to activate mTORC2 and promote tumor growth [33] by means an auto-activation loop of mTORC2, rendering glioblastoma resistant to EGFR, PI3K, or AKT-targeted therapies. Then, if sufficient nutrients are present, glioblastoma cells maintain mTORC2 signaling to drive cell proliferation, and survival [33, 34]. mTORC2 markedly increases glycolysis in glioblastoma [33]. Consequently, replacement of fermentable fuels like glucose and glutamine with non-fermentable fuels like ketone bodies becomes a logical approach to management [35, 36]. The dietary intervention prevents glioma cells accessing their preferred fuel source, i.e., glucose [37–40], and consequently, the signal transduction of mTORC2, cell proliferation and survival are diminished [35]. Therefore, impairments in glucose availability can be devastating for glioma survival [26].

The current standard of care for glioblastoma patients consists of maximal safe resection, followed by radiotherapy, and concurrent chemotherapy with Temozolomide [15, 41, 42]. Despite substantial clinical research efforts over the past decades, therapeutic progress

has been marginal [43]; added benefits from Temozolomide [44] and bevacizumab [45] are modest, and patient overall survival remains poor. Increasing recognition of the metabolic peculiarities of cancer has prompted investigations of nutritional strategies targeting glycemic modulation in cancer treatment, predominantly through the use of high-fat and low-carbohydrate diets (ketogenic diets; KDs), but also caloric restriction (CR), intermittent fasting (IF), and other combinatorial dietary protocols [46, 47]. All of these strategies induce a physiological state of systemic ketosis that metabolically compensates for the therapeutic reduction of carbohydrate intake and a concurrent decrease in blood glucose levels [47]. Both glycemic reduction and systemic ketosis are established key metabolic correlates of these nutritional strategies and are thought to mediate their therapeutic efficacy [35, 47]. The reduced availability of glucose as an energy substrate has been shown to selectively starve glioma cells both in vitro and in vivo [48–54]. Glioma cells are metabolically maladapted to utilize ketone bodies [48, 52, 55]. Unlike highly selective pharmacological blocking agents, KMT might produce a global dampening of insulin-related signaling with potentially more efficacy and less side effects [56]. On a functional level, several preclinical studies could demonstrate that ketogenic metabolic therapy (in particular, KD treatment, and/or CR) induces a metabolic shift in malignant brain tissue toward a proapoptotic, antiangiogenic, anti-invasive, and anti-inflammatory state accompanied by a marked reduction in tumor growth in vivo [57]. According to the current literature, ketogenic metabolic therapy is a safety and feasible alternative for malignant glioma. Cumulative clinical trials suggest that ketogenic metabolic therapy is emerging as a potential therapeutic option and might be combinable with existing anti-neoplastic treatments for malignant glioma [57]. Recently, a press-pulse therapeutic strategy for cancer management was presented [58]. The press-pulse therapeutic strategy for cancer management is illustrated with calorie-restricted ketogenic diets used together with drugs and procedures that create both chronic and intermittent acute stress on tumor cell energy metabolism, while protecting and enhancing the energy metabolism of normal cells. Optimization of dosing, timing, and scheduling of the press-pulse therapeutic strategy will facilitate the eradication of tumor cells with minimal patient toxicity. This therapeutic strategy can be used as a framework for the design of clinical trials for the non-toxic management of most cancers [58].

7. Conclusions

There is a great need to develop new therapies for gliomas. The ultrastructural findings observed in MN and MAM in the human gliomas indicate that: (1) The majority of glioma cells are incompetent to produce adequate amount of energy by means of oxidative phosphorylation and compensatory increases in glycolytic ATP production and (2) The variability of the ultrastructural aspects of MAM observed on astrocytic tumors suggests a dynamic regulation of the interorganellar junction that can be modified by functional requirements needed to adapt to different cell demands. These findings possibly represent the ultrastructural basis of the metabolic processes of glioma cells. MAM-resident mTORC2 controls the MAM integrity and mitochondrial functions, and mTORC2 can promote growth and chemotherapy resistance in cancer cells as well as tumor metabolism including glycolysis, glutaminolysis,

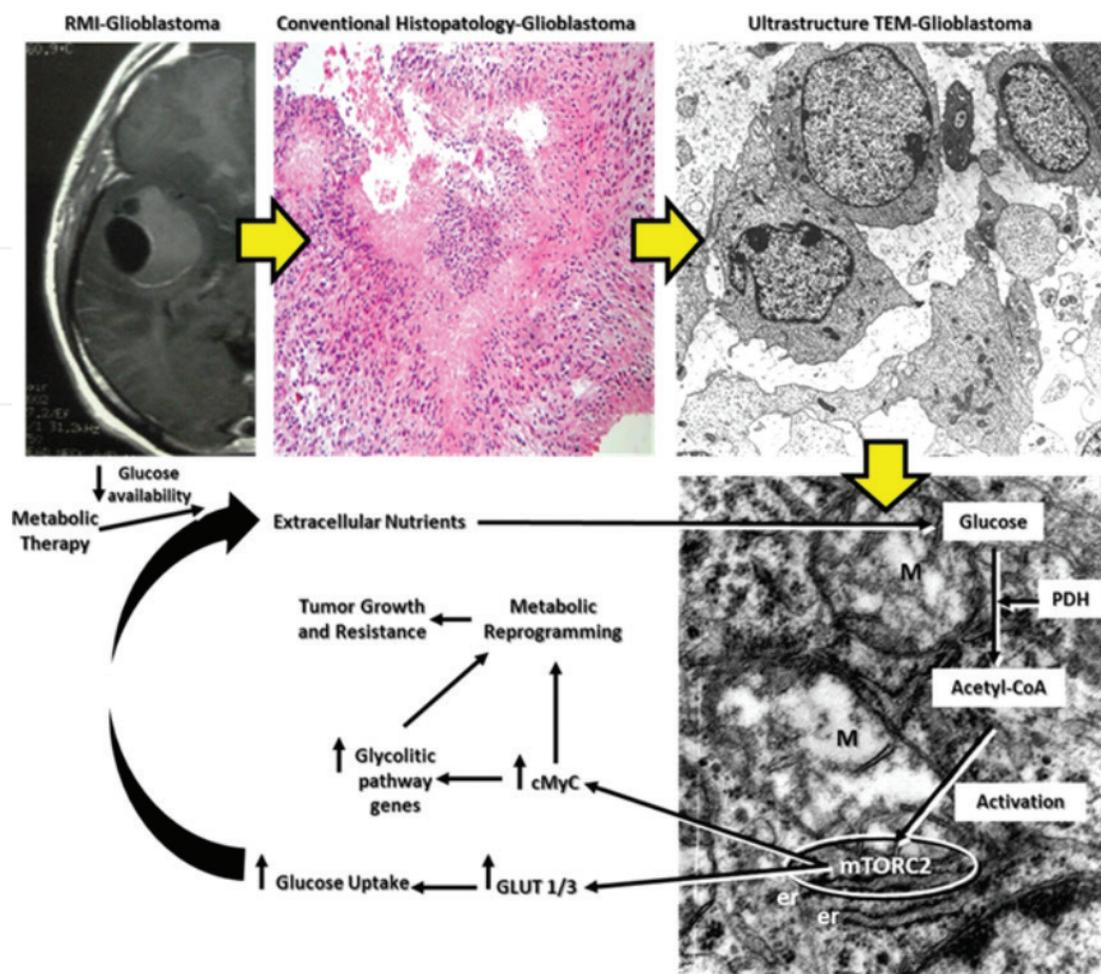


Figure 6. General visualization of the glioma pathology, metabolic aspects and, their metabolic therapy approach. Glucose derived from extracellular nutrients is required to activate mTORC2 and promote tumor growth and resistance. Glucose is converted in acetyl-CoA for the pyruvate dehydrogenase (PDH) action. Acetyl-CoA produces the activation of mTORC2 by acetylation of RICTOR. mTORC2 signaling facilitates the metabolic reprogramming, tumor growth, and resistance. This is a nutrient availability-dependent process, by means an auto-activation loop of mTORC2. The metabolic therapy approach, limit the availability of glucose and consequently, the signal transduction of mTORC2, cell proliferation, and survival are diminished (ellipse denotes MAM).

lipogenesis, and nucleotide and reactive oxygen species metabolism. Considering that therapeutic progress has been marginal, ketogenic metabolic therapy in the context of the press-pulse therapeutic strategy is emerging as a potential therapeutic option (**Figure 6**).

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