Short Commentary

Gabriel Arismendi-Morillo*, Tomas Duraj, Derek C. Lee, Purna Mukherjee and Thomas N. Seyfried

From mitochondrial cristae pathobiology to metabolic reprogramming in cancer: the α and ω of Malignancies?

https://doi.org/10.1515/oncologie-2025-0379
Received September 1, 2025; accepted October 20, 2025;
published online November 14, 2025

Abstract: Mitochondrial cristae pathobiology, involving partial or total cristolysis, is a hallmark of human and mammalian cancer. This feature represents the basis of metabolic dysfunction in neoplastic cells. Consequently, most cancer cells with mitochondrial cristae defects would be incapable of producing adequate amounts of energy through oxidative phosphorylation. ATP production through increased glucose-driven cytosolic and glutamine-driven mitochondrial substrate-level phosphorylation thus becomes necessary to compensate for OxPhos insufficiency. The aim of this article is to offer a brief perspective on the link between the mitochondrial cristae pathobiology and the metabolic reprogramming in cancer cells, whose origin is linked to chronic mitochondrial cristae lesion (named α) and its eventual resolution by means of a progressive and continuous process of tumor cell death (named ω), induced by metabolic targeting. Dietary and pharmacological metabolic therapies that restrict the utilization of glucose and glutamine in tumor cells while elevating circulating ketone bodies represent a non-toxic therapeutic strategy for cancer management. Metabolic therapy can induce a persistent state of energy stress with a consequent increase in tumor cell death and reduction of tumor mass while improving the energy efficiency of non-neoplastic cells. Recent clinical studies suggest that ketogenic metabolic therapies may be therapeutically useful and well-tolerated in the long term.

Keywords: mitochondrial cristae; substrate-level phosphorylation; oxygen consumption; lipid droplets

Introduction

Epidemiological impact, drug resistance, and toxic effects of therapy are important aspects of cancer. According to *Global Statistics 2022 (GLOBOCAN 2022)*, cancer is a leading cause of death [1]. There were an estimated 19.9 million new cases and 9.7 million cancer deaths worldwide in 2022. An estimated 35 million new cases are projected to occur in 2050 [1]. A variable mortality rate is observed depending on the cancer subtype (Table 1). The most prevalent cancer sites are lung, breast, colorectum, and prostate, together signifying 40.9 % of all cancers and reaching 38.8 % of all deaths [1]. Individuals with multimorbidity or polypharmacy have a greater risk of cancer than healthy cohorts. Deaths from early-onset cancers are also on the rise [2].

Drug resistance can arise in large part from the acidification of the tumor microenvironment following the release of lactate and succinate waste products of glucose and glutamine fermentation [3]. Mechanisms vary between individual chemotherapeutic agents, but coincide in compensatory glutathione detoxification, P-glycoprotein upregulation, enhanced autophagy, DNA damage repair, and cell cycle arrest [4, 5]. Adverse effects are common following standard chemoradiotherapy that include, but are not limited to, central nervous system toxicity, pseudoprogression, vascular malformation, ischemia, gastrointestinal distress, chronic inflammation, muscle swelling, pneumonia, myocardial damage and hepatic failure, among others [6–8]. This circumstance increases the risk of drug-drug interactions, hospitalization, toxicity, cessation of management, and mortality [9–13].

Otto Warburg et al. first championed aberrant energy metabolism as the central issue in cancer initiation and progression [14]. Based primarily on biochemical measurements, Warburg postulated that damaged mitochondria linked to insufficient oxygen-dependent respiration caused compensatory ATP production through lactic acid fermentation in cancer cells [15]. The widespread adoption of electron microscopy over the last half century has deepened our understanding of canonical ultrastructure,

***Corresponding author: Gabriel Arismendi-Morillo**, Biological Research Institute, Faculty of Medicine, 4001, Maracaibo, Venezuela and Department of Medicine, Faculty of Health Sciences. DeustoMED. University of Deusto, 48007, Bilbao (Bizkaia), Spain, E-mail: g.arismendi@deusto.es
Tomas Duraj, Derek C. Lee, Purna Mukherjee and Thomas N. Seyfried, Biology Department, Boston College, Chestnut Hill, MA, USA

Table 1: Cancer mortality in 2022.

Cancer type	Mortality, %
Pancreas	91.4
Liver	87.5
Esophagus	87.1
Brain, central nervous system	77.2
Lung	73.2
Stomach	68.1
Ovary	63.7
Leukemia	62.6
Cervix uteri	52.6
Colorectum	46.9
Non-hodgkin lymphoma	45.5
Blader	39.8
Kidney	35.8
Female breast	28.8
Hodgkin lymphoma	27.5
Prostate	27.1

Adapted from reference [1].

including the dynamic yet regulated organization of cristae [16–18]. In this review, we aim to link the pathobiology of mitochondrial cristae (The α) observed in cancer cells to compensatory bioenergetic pathways (*i.e.*, cytoplasmic and mitochondrial substrate level phosphorylation) and tumor cell death induced by ketogenic metabolic therapy (The ω, *i.e.*, blocking the utilization of metabolites that fuel cytosolic and mitochondrial substrate-level phosphorylation).

Loss of canonical cristae structure is associated with increased dependency on substrate-level phosphorylation (The A)

According to the mitochondrial metabolic theory of carcinogenesis, most major cancers arise from a two-step bioenergetic transition [19–21]. The first transition involves a chronic, sublethal injury of the mitochondrial structure, function, or number by ambient factors, ultimately compromising the functional efficiency of oxidative phosphorylation (OxPhos) [20, 21]. The electron transport chain (complexes I-IV) and ATP synthase (complex V) are localized to cristae [21, 22]. The efficiency of ATP synthesis is intimately linked to the structure of cristae and to the content and composition of cardiolipin, a phospholipid enriched in the inner mitochondrial (cristae) membrane [23]. Indeed, mitochondrial shape is necessary for the proper assembly and stabilization of super complexes, multi-protein assemblies of complexes I-IV, that drive OxPhos [22–24]. Moreover, invagination within the inner mitochondrial membrane is essential for complex V dimerization and efficiency [24–26]. Abnormalities in cristae shape (unfolded, disarray, cristolysis) will lower OxPhos efficiency and, in turn, impair cellular metabolism [22, 24]. The super complexes of the OxPhos system are disorganized when cristae are unfolded, thus making the electron transport chain less efficient (*i.e.*, decreased coupling of ADP phosphorylation and oxygen consumption) [24]. Cristolysis is linked to the metabolic reprogramming of cancer cells involving the compensatory shift to cytosolic and mitochondrial substrate-level phosphorylation flux, driven primarily by glucose and glutamine, respectively [21, 27]. The disarrangement of mitochondrial cristae, such as partial or total cristolysis, is in large part responsible for the shift from OxPhos-linked ATP synthesis to substrate-level phosphorylation-linked ATP synthesis that is the metabolic hallmark of cancer (Figure 1) [21, 27–29].

The second transition involves the upregulation of the glycolysis and the glutaminolysis pathways, which become necessary to replace the diminished energy synthesis from OxPhos with energy synthesis through substrate-level phosphorylation (Figure 2) [21]. Indeed, voracious glucose uptake is a hallmark of cancer cells; over 85 % of the glucose consumed by cancer cells does not reach the mitochondria to be completely oxidized by the Krebs cycle [30]. Instead, it is used for biosynthesis and ATP production through cytosolic substrate-level phosphorylation. Much of the remaining glucose carbons are found outside the cell as lactate [31]. Hypoxia inducible factors (HIFs) and c-MYC are master transcriptional regulators of the glycolysis and glutaminolysis pathways, respectively [32, 33]. HIFs and c-MYC targeting compounds are under active investigation and may serve as a new approach toward selective chemotherapies [34–36].

The ultrastructural correlation of OxPhos insufficiency is found in changes in mitochondrial-endoplasmic reticulum contact sites (MERCS) [37]. The activity of several enzymes of the Krebs cycle and the inositol triphosphate receptor (IP3R) Ca^{2+} signaling pathway are linked with the integrity and thickness of MERCS [38]. Furthermore, the variability of MERCS can be modified by functional requirements needed to adapt to different cell demands [38]. The MERCS-resident mammalian target of rapamycin complex 2 (mTORC2) controls MERCS integrity and mitochondrial function. mTORC2 is the core of the MERCS signaling hub that controls growth and metabolism [38–41]. mTORC2 is linked to glycolysis and glutaminolysis [42]. Glucose is required to activate mTORC2 and promote

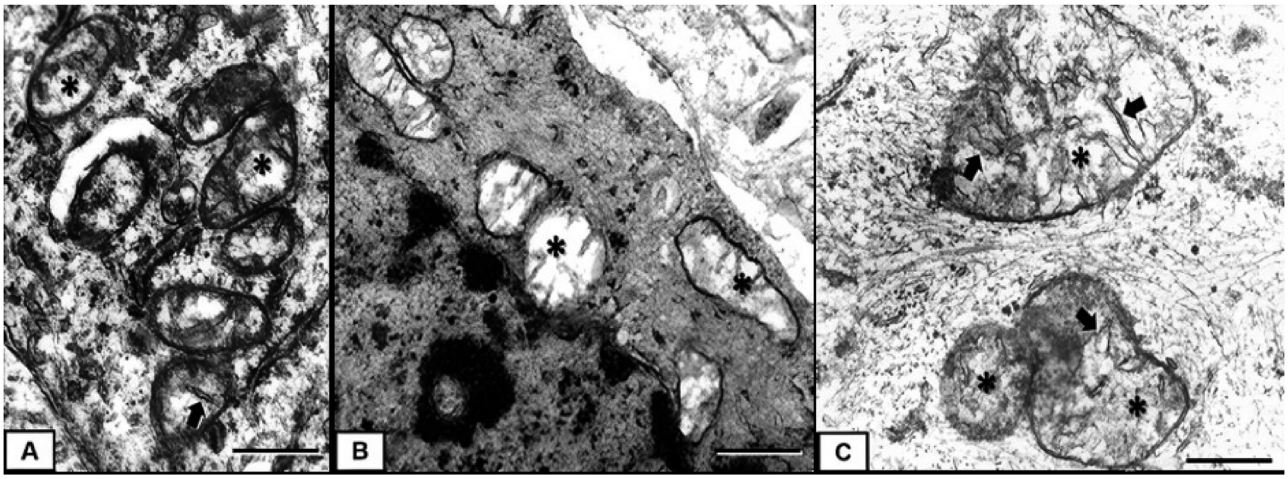

Figure 1: Mitochondria in human glioblastoma exhibits electron-lucent mitochondrial matrix (*) associated with disarrangement of cristae and partial or total cristolysis (bold arrows). (A) Scale Bar: 0.45 µm. (B) Scale Bar: 0.45 µm. (C) Scale Bar: 0.60 µm. Notes: (A) and (B) are adapted from reference [28]. (C) is adapted from reference [29].

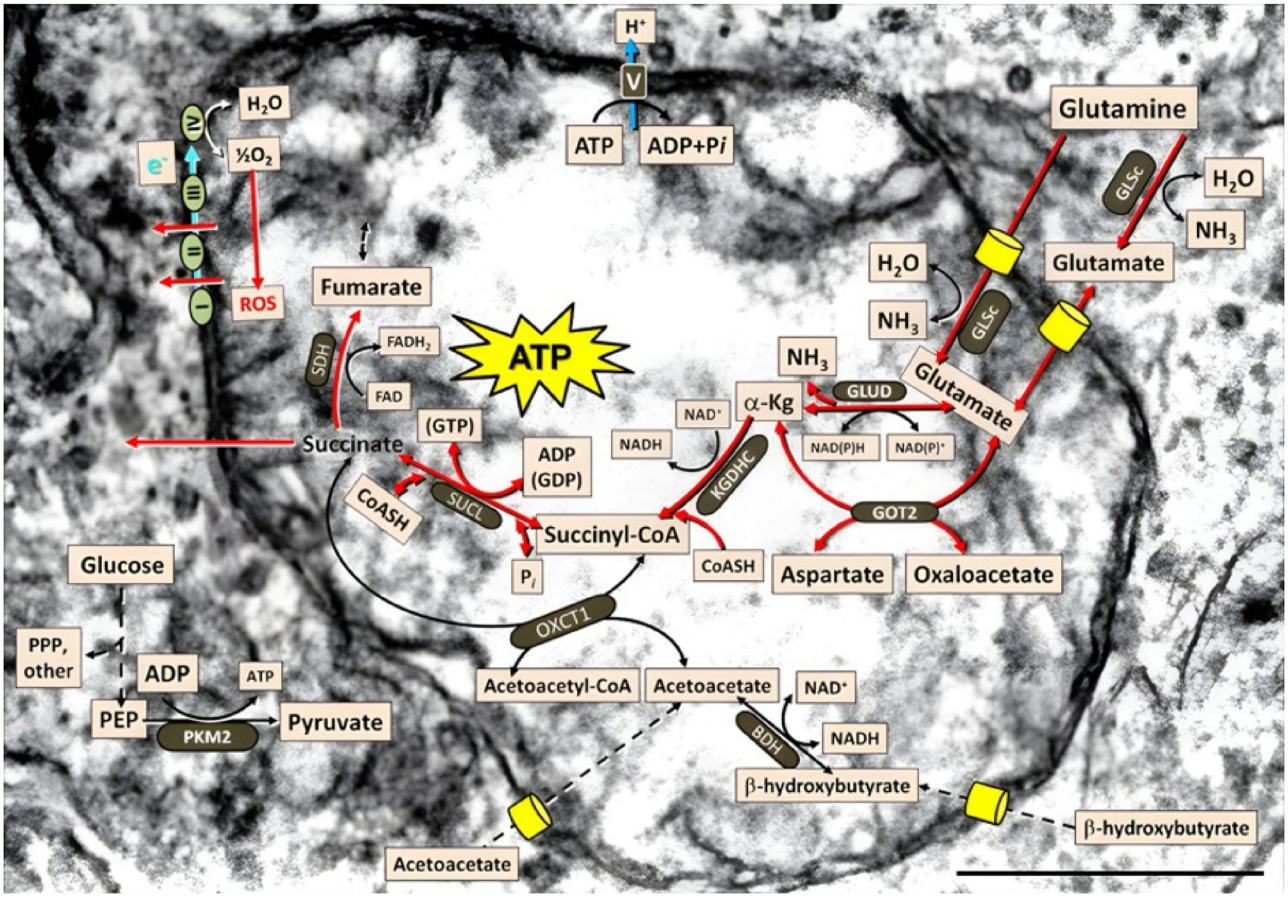

Figure 2: Glioblastoma mitochondrion with total cristolysis. ATP synthesis through substrate-level phosphorylation through fermentation pathways. Cristolysis is linked to the metabolic reprogramming of cancer cells involving the compensatory shift to cytoplasmic substrate-level phosphorylation using glucose and mitochondrial substrate-level phosphorylation using glutamine. These processes hold the ΔG'ATP hydrolysis at −56 kJ/mol, thus maintaining cancer cell viability in either the presence or the absence of oxygen. Scale Bar: 0.65 µm. Notes: Adapted from references [20] and [29].

tumor growth by means of an auto-activation loop of mTORC2. Cancer cells maintain active mTORC2 signaling to drive dysregulated cell proliferation and survival if sufficient nutrients are present in the microenvironment (Figure 3) [39]. mTORC2 activation elicits an increase in GLUT1/3 and *c*-MYC. The subsequent increase in glucose and glutamine utilization as metabolic substrates for biomass and ATP synthesis drives cell proliferation [43]. Therefore, the ultrastructural abnormalities in mitochondria and MERCS represent an aspect of the submicroscopic basis of the metabolic process of cancer cells and the compensatory energy through mitochondrial substrate-level phosphorylation (Figure 4). Glutamine-driven glutaminolysis, which enters the Krebs cycle at the point of alpha-ketoglutarate, provides the upstream metabolite for mitochondrial substrate-level phosphorylation [27]. Mitochondrial substrate-level phosphorylation occurs during the conversion of succinyl-CoA to succinate, which is catalyzed by succinyl-CoA ligase within the mitochondrial matrix. Accordingly, ^{13}C-succinate was observed in the extracellular matrix in cells cultured in ^{13}C-glutamine [27]. Furthermore, reversal of the Krebs cycle has been shown as a compensatory mechanism to regenerate NAD+ and use Krebs cycle intermediates as alternative electron acceptors under OxPhos inhibition [32, 33]. This concept supports Warburg's central hypothesis that ATP synthesis through OxPhos was intimately linked to mitochondrial structure [15]. The mitochondrial and MERCS morphological abnormalities appear dependent on the tumor microenvironment and do not seem to be specific for any tumor type [37].

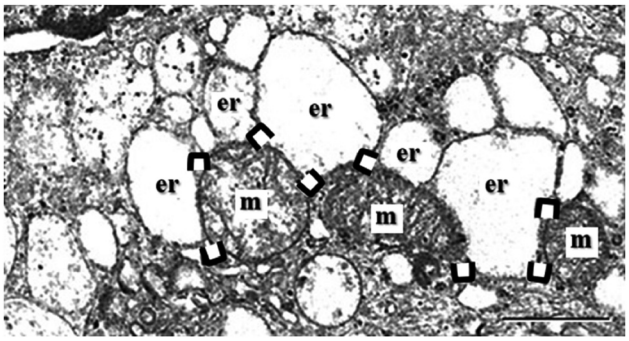

Figure 4: Variations in mitochondria-endoplasmic reticulum contact sites (MERCS) ultrastructure are observed in glioma. Mitochondria (m) and endoplasmic reticulum profiles (er) in direct association are seen (opposite U designates MERCS). Multiplicity in the density, length, and width of the MERCS are linked to cancer cell metabolic reprogramming (metabolic shifts to glycolysis, glutaminolysis, and reactive oxygen species metabolism). The MERCS diversity found in gliomas have also been observed in other cancers and include abnormalities in calcium homeostasis, proliferation, metastasis, and chemotherapeutic resistance. Scale Bar: 0.45 µm.

Metabolic therapies exploit structural changes in mitochondria to selectively target fermentable fuels and induce cancer cell death (the Ω)

The goal of oncology is to eradicate tumors without collateral toxicity to normal tissues. Acceptable limits of toxicity need

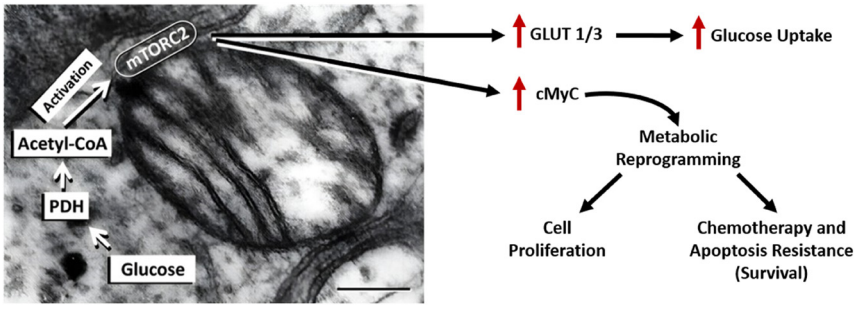

Figure 3: Glucose derived from extracellular nutrients is required to activate mTORC2 and promote tumor growth and resistance. Glucose is converted into acetyl-CoA by the pyruvate dehydrogenase complex (PDH) action. Acetyl-CoA produces the activation of mTORC2 by acetylation of RICTOR. mTORC2 signaling facilitates the metabolic reprogramming, tumor growth, and resistance. This is a nutrient availability-dependent process, by means of an auto-activation loop of mTORC2. The goal of metabolic therapy is to limit the availability or utilization of glucose and consequently the signal transduction of mTORC2, cell proliferation, and survival are diminished. Scale Bar: 0.166 µm. Note: Adapted from reference [37].

to be balanced with the potential for a successful outcome [44, 45]. Very low-carbohydrate diets, which are able to achieve nutritional ketosis by raising plasma beta-hydroxybutyrate and reducing plasma glucose, are a safe approach, especially when compared with traditional anti-cancer therapy [46, 47]. Dietary interventions have been shown to enhance anticancer therapy and improve cancer outcomes [48, 49]. Most preclinical and some clinical studies support the use of calorie-restricted ketogenic diets as an adjuvant cancer therapy [46–54]. Cancer cells exhibit increased reliance on the availability of glucose and glutamine for survival compared to healthy tissue due to mitochondrial cristolysis (Figures 2 and 3) [20, 21]. For example, renal cell carcinoma is increasingly recognized as a metabolic disease based on these metabolic phenotypes [55–57]. Furthermore, this metabolic reprogramming occurs across multiple types of cancer, suggesting a similar phenotype and origin [20, 21]. These fuels could be targeted using non-toxic metabolic therapies using diet-drug combinations [44]. Restricting both fermentable fuels by implementing a calorie-restricted ketogenic diet alongside pharmacological agents that inhibit glutaminolysis (The Ω, *i.e.,* blocking the utilization of metabolites that fuel cytosolic and mitochondrial substrate-level phosphorylation), while increasing nonfermentable fuels like ketone bodies, becomes a logical approach for management [47, 50]. Ketogenic dietary interventions can impair the ability of cancer cells to access necessary fuels, such as glucose, which can diminish the signal transduction of mTORC2, proliferation, and survival.

The simultaneous targeting of glycolysis and glutaminolysis pathways has been shown to significantly improve progression-free and overall survival [50]. There are preclinical and clinical studies reporting the effects of the ketogenic diet on tumor progression and survival in a vast number of tumor types including: glioblastoma, astrocytoma, medulloblastoma, neuroblastoma, leukemia, carcinoma of prostate, colon, breast, lung, kidney, liver, ovarian, endometrium, pancreas, pancreato-billary, bladder, gastric, melanoma, advanced metastatic disease and head and neck cancer. Overall, good safety and tolerability as well as an increase in quality of life have been reported in board range of cancers [44–62]. However, concerns remain about limitations in adherence, gastrointestinal distress, and changes in micronutrient consumption [59]. Poor dietary adherence with no significant reduction in circulating glucose levels could be responsible in part for the lack of therapeutic effect in some studies of GBM patients [60]. Additionally, weight loss can be a concern as it is often used as a marker for disease progression and cachexia [61]. Proper patient-specific nutritional counseling may help retain lean muscle mass and decrease adipose tissue [47], which can be viewed as healthy weight loss. It is imperative that clinicians and dieticians acknowledge and employ interventions to minimize these hurdles [47]. Regardless, promising preclinical and clinical data support the continued development of dietary interventions in cancer, which would be combined with standard treatments and metabolic inhibitors [44–62].

Pathobiological vision

The benefit of metabolic therapies against cancer is expressed pathologically as a significant tumor mass reduction (complete or partial response). This process is linked to tumor cell apoptosis (Figure 5). Metabolic therapy (simultaneous targeting of the glycolysis and glutaminolysis pathways) will starve the tumor cells of their essential fuels while also reducing inflammation in the tumor microenvironment (*i.e.,* therapeutic starvation). Inflammation is driven by low pH due to the accumulation of glucose-derived lactic acid and glutamine-derived succinic acid [63].

According to Potts' concept of environmental forcing and adaptability, tumor cells would be less able than normal cells to acclimate metabolically under low nutrient conditions due to their OxPhos insufficiency and somatic mutations [64, 65]. The relative metabolic stress induced by fasting or fasting-mimicking interventions such as the ketogenic diet (glucose, insulin and nutrient deprivation) is a potent activator of apoptosis. The apoptotic responses are the result of the interplay between the functional state of mitochondria and environmental signals. Metabolic stress induced by nutrient deprivation will induce proapoptotic signaling [66]. Prolonged periods of nutrient deprivation can induce cancer cell death (lethal metabolic shock and differential stress sensitization (Figure 5) [67]. The multiple genomic defects that occur in most tumor cells, together with mitochondrial dysfunction, will prevent the metabolic flexibility needed for rapid adaptation to nutrient stress, thus leading to tumor cell death through a combination of autophagy and autolytic cannibalism [68].

The differential effects of metabolic and non-metabolic cancer therapies on mitochondrial pathobiology remain largely unexplored. In order to achieve a deeper understanding of these aspects, it is imperative the study the molecular and ultrastructural pathology of mitochondria, mitochondrial cristae, mitochondrial contact site and cristae organizing system (MICOS), mitochondria-endoplasmic reticulum contacts (MERCS), as well as, cell death mechanisms in response to ATP and nutrient insufficiency (apoptotic cell death, autophagic-dependent cell death, autoptic cell death, ferroptosis, pyroptosis). At the same time, it will be necessary to expand the clinical testing

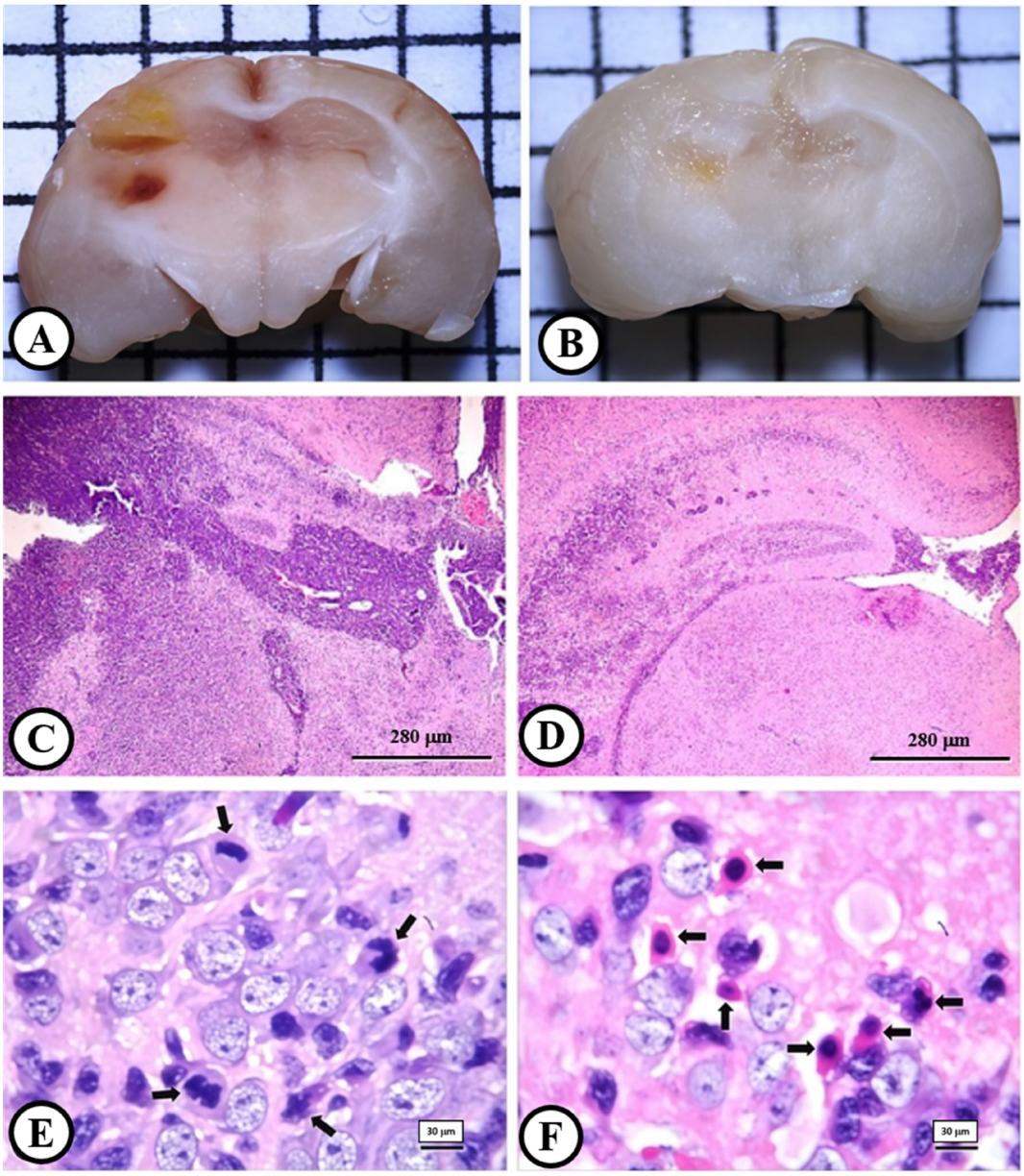

Figure 5: Tumor cell death by apoptosis is a remarkable finding of the effect of calorie-restricted ketogenic diet and glutamine targeting therapy. Gross and histopathological effects of VM-M3 glioblastoma high-grade glioma mouse model. (A) Macroscopic view of the brain with tumor (left side) in mice fed with a high-carbohydrate standard diet in unrestricted amounts. (B) Macroscopic view of the brain with a tumor (left side) in mice fed with a ketogenic diet in restricted amounts (calorie restriction). (C) Histopathological aspect of the neoplasm in mice fed with a high-carbohydrate standard diet in unrestricted amounts. (D) Histopathological aspect of the neoplasm in mice fed with a ketogenic diet in restricted amounts. Partial response (≈45 % reduction) is observed. (E) Densely packed tumor cells with abundant mitoses (arrows) are seen. (F) Abundant apoptotic tumor cells with eosinic cytoplasm and condensed chromatin (arrows) are seen. There are evident differences between untreated and treated subjects in both macroscopic and microscopic examination. The treatment is expressed by apoptotic induction in tumor cells. Note: Images (A–D) are original, (E) and (F) are adapted from reference [67].

of diet-drug combinations, such as, ketogenics diets and fasting alongside glycolysis and glutaminolysis inhibitors, to establish, the optimal administration protocols that leverage the structural and functional abnormalities described in tumor mitochondria.

Conclusions

The origin of cancer is linked to a persistent dysfunction of mitochondrial cristae. Loss of cristae will result in OxPhos insufficiency compensated by cytosolic and mitochondrial

substrate-level phosphorylation for ATP production, as evidenced by incompletely oxidized end products of the glycolysis and the glutaminolysis pathways. Abnormalities in MERCS are present in many cancers and may play a vital role in regulating apoptotic signaling in dysfunctional mitochondria through mTORC2 and calcium signaling. Metabolic therapies could induce therapeutic starvation with subsequent pathological and clinical responses derived from the interplay between the functional state of mitochondria and their environmental signals. The underlying structural and metabolic abnormalities discussed above provide the rationale for exploring metabolic therapies in a wide range of cancer subtypes.

Acknowledgement: We thank the Foundation for Metabolic Cancer Therapies, CrossFit Inc., Dr. Joseph C. Maroon, Dr. Edward Miller, The Broken Science Initiative, Children with Cancer UK, The Corkin Family Foundation, Boston College Research Expense Fund, CONDES-University of Zulia, Maracaibo-Venezuela. To Technicians Pedro Arteaga, Norkys Sanchez, and Gianny Arteaga (Maracaibo,Venezuela) for assistance with histopathological processing. To Technicians Pedro Salas (Campus Los Perozo, Francisco de Miranda University (UNEFM), Santa Ana de Coro, Venezuela) and Juan Pablo Hernández (Faculty of Medicine, University of Zulia, Maracaibo, Venezuela) for the assistance with Transmission Electron Microscopes.

Research ethics: Not applicable.

Informed consent: Not applicable.

Author contributions: All authors read and approved the information presented in the manuscript. Gabriel Arismendi-Morillo and Thomas N. Seyfried conceived and designed the manuscript. Derek C. Lee, Tomas Duraj and Purna Mukherjee revised the manuscript.

Use of Large Language Models, AI, and Machine Learning Tools: None declared.

Conflicts of Interest: None.

Research funding: This manuscript received no specific grant from any funding agency in the public, commercial, or not-profit sectors.

Data availability: Not applicable.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2022;74:229–63.
2. Zhao J, Xu L, Sun J, Song M, Wang L, Yuan S, et al. Global trends in incidence, death, burden and risk factors of early-onset cancer from 1990 to 2019. BMJ Oncol 2023;2:e000049.
3. Vasan N, Baselga J, Hyman DM. A view on drug resistance in cancer. Nature 2019;575:299–309.
4. Ortiz M, Wabel E, Mitchell K, Horibata S. Mechanisms of chemotherapy resistance in ovarian cancer. Cancer Drug Resist 2022;5:304–16.
5. Liu YP, Zheng CC, Huang YN, He ML, Xu WW, Li B, et al. Molecular mechanisms of chemo- and radiotherapy resistance and the potential implications for cancer treatment. MedComm (2020) 2021;2:315–40.
6. Albano D, Benenati M, Bruno A, Bruno F, Calandri M, Caruso D, et al. Imaging side effects and complications of chemotherapy and radiation therapy: a pictorial review from head to toe. Insights Imaging 2021;12:76.
7. van den Boogaard WMC, Komninos DSJ, Vermeij WP. Chemotherapy side-effects: not all DNA damage is equal. Cancers (Basel) 2022;14:627.
8. Guida JL, Ahles TA, Belsky D, Campisi J, Cohen HJ, DeGregori J, et al. Measuring aging and identifying aging phenotypes in cancer survivors. J Natl Cancer Inst 2019;111:1245–54.
9. Alnaim LS, Almalki HM, Almutairi AM, Salamah HJ. The prevalence of drug-drug interactions in cancer therapy and the clinical outcomes. Life Sci 2022;310:121071.
10. Ramasubbu SK, Mahato SK, Agnihotri A, Pasricha RK, Nath UK, Das BD, et al. Prevalence, severity, and nature of risk factors associated with drug-drug interactions in geriatric patients receiving cancer chemotherapy: a prospective study in a tertiary care teaching hospital. Cancer Treat Res Commun 2021;26:100277.
11. Lavan AH, O'Mahony D, Buckley M, O'Mahony D, Gallagher P. Adverse drug reactions in an oncological population: prevalence, predictability, and preventability. Oncologist 2019;24:e968–e977.
12. Livshits Z, Rao RB, Smith SW. An approach to chemotherapy-associated toxicity. Emerg Med Clin North Am 2014;32:167–203.
13. Dilalla V, Chaput G, Williams T, Sultanem K. Radiotherapy side effects: integrating a survivorship clinical lens to better serve patients. Curr Oncol 2020;27:107–12.
14. Warburg O, Wind F, Negelein E. The metabolism of tumors in the body. J Gen Physiol 1927;8:519–30.
15. Warburg O. On the origin of cancer cells. Science 1956;123:309–14.
16. Daems WT, Wisse E. Shape and attachment of the cristae mitochondrial in mouse hepatic cell mitochondria. J Ultrastruct Res 1966;16:123–40.
17. Mannella CA. Consequences of folding the mitochondrial inner membrane. Front Physiol 2020;11:536.
18. Adams RA, Liu Z, Hsieh C, Marko M, Lederer WJ, Jafri MS, et al. Structural analysis of mitochondria in cardiomyocytes: insights into bioenergetics and membrane remodeling. Curr Issues Mol Biol 2023;45:6097–115.
19. Seyfried TN, Shelton LM. Cancer as a metabolic disease. Nutr Metab 2010;7:7.
20. Seyfried T, Chinopoulos C. Can the mitochondrial metabolic theory explain better the origin and management of cancer than can the somatic mutation theory? Metabolites 2021;11:572.
21. Seyfried T, Arismendi-Morillo G, Mukherjee P, Chinopoulos C. On the origin of ATP synthesis in cancer. iScience 2020;23:101761.
22. Baker N, Patel J, Khacho M. Linking mitochondrial dynamics, cristae remodeling and supercomplex formation: how mitochondrial structure can regulate bioenergetics. Mitochondrion 2019;49:259–68.
23. Kiebish MA, Han X, Cheng H, Chuang JH, Seyfried TN. Cardiolipin and electron transport chain abnormalities in mouse brain tumor mitochondria: lipidomic evidence supporting the warburg theory of cancer. J Lipid Res 2008;49:2545–56.

24. Cogliati S, Enriquez JA, Scorrano L. Mitochondrial cristae: where beauty meets functionality. Trends Biochem Sci 2016;41:261–73.
25. Daum B, Walter A, Horst A, Osiewacz HD, Kühlbrandt W. Age-dependent dissociation of ATP synthase dimers and loss of inner-membrane cristae in mitochondria. Proc Natl Acad Sci U S A 2013;110: 15301-6.
26. Rampelt H, Wollweber F, Licheva M, de Boer R, Perschil I, Steidle L, et al. Dual role of Mic10 in mitochondrial cristae organization and ATP synthase-linked metabolic adaptation and respiratory growth. Cell Rep 2022;38:110290.
27. Lee DC, Ta L, Mukherjee P, Duraj T, Domin M, Greenwood B, et al. Amino acid and glucose fermentation maintain ATP content in mouse and human malignant glioma cells. ASN Neuro 2024;16:2422268.
28. Arismendi-Morillo G. Electron microscopy morphology of the mitochondrial network in human cancer. Int J Biochem Cell Biol 2009; 41:2062–8.
29. Arismendi-Morillo GJ, Castellano-Ramirez AV. Ultrastructural mitochondrial pathology in human astrocytic tumors: potentials implications pro-therapeutics strategies. J Electron Microsc 2008;57: 33–9.
30. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the warburg effect: the metabolic requirements of cell proliferation. Science 2009;324:1029–33.
31. Zhang W, Guo C, Jiang K, Ying M, Hu X. Quantification of lactate from various metabolic pathways and quantification issues of lactate isotopologues and isotopmers. Sci Rep 2017;7:8489.
32. Podar K, Anderson KC. A therapeutic role for targeting c-Myc/Hif-1-dependent signaling pathways. Cell Cycle 2010;9:1722–8.
33. Trejo-Solís C, Castillo-Rodríguez RA, Serrano-García N, Silva-Adaya D, Vargas-Cruz S, Chávez-Cortéz EG, et al. Metabolic roles of HIF1, c-Myc, and p53 in glioma cells. Metabolites 2024;14:249.
34. Thumpati P, Rai SN, Prajapati C, Ramakrishna K, Singh SK. Targeting c-MYC G-Quadruplexes for cancer treatment with small molecules. Sci Pharm 2025;93:6.
35. Feng L, Sun C, Sun X, Zhao Y, Yu R, Kang C, et al. Identification of inhibitors targeting HIF-2α/c-Myc by molecular docking and MM-GBSA technology. J Recept Signal Transduct Res 2021;41:511–9.
36. Lu Z, Bi Y, Jiang J, Yao X, Hou G. Exploring the prognostic and therapeutic value of HIF1A in lung adenocarcinoma. Heliyon 2024;10: e37739.
37. Arismendi-Morillo G, Castellano-Ramírez A, Seyfried TN. Ultrastructural characterization of the Mitochondria-associated membranes abnormalities in human astrocytomas: functional and therapeutics implications. Ultrastruct Pathol 2017;41:234–44.
38. Csordás G, Várnai P, Golenár T, Roy S, Purkins G, Schneider TG, et al. Imaging interorganelle contacts and local calcium dynamics at the ER-mitochondrial interface. Mol Cell 2010;39:121–32.
39. Cárdenas C, Müller M, McNeal A, Lovy A, Jaña F, Bustos G, et al. Selective vulnerability of cancer cells by inhibition of Ca(2+) transfer from endoplasmic reticulum to mitochondria. Cell Rep 2016;14:2313–24.
40. Dematteis G, Tapella L, Casali C, Talmon M, Tonelli E, Reano S, et al. ER-mitochondria distance is a critical parameter for efficient mitochondrial Ca^{2+} uptake and oxidative metabolism. Commun Biol 2024;7:1294.
41. Bustos G, Ahumada-Castro U, Silva-Pavez E, Puebla A, Lovy A, Cesar Cardenas J, et al. The ER-mitochondria Ca^{2+} signaling in cancer progression: fueling the monster. Int Rev Cell Mol Biol 2021;363: 49–121.
42. Luo Y, Xu W, Li G, Cui W. Weighing in on mTOR complex 2 signaling: the expanding role in cell metabolism. Oxid Med Cell Longev 2018;2018: 7838647.
43. Zeng H, Cohen S, Guy C, Shrestha S, Neale G, Brown SA, et al. mTORC1 and mTORC2 kinase signaling and glucose metabolism drive follicular helper T cell differentiation. Immunity 2016;45:540–54.
44. Lien EC, Vander Heiden MG. A framework for examining how diet impacts tumour metabolism. Nat Rev Cancer 2019;19:651–61.
45 Taylor SR, Falcone JN, Cantley LC, Goncalves MD. Developing dietary interventions as therapy for cancer. Nat Rev Cancer 2022; 22:452–66.
46. Klement RJ, Brehm N, Sweeney RA. Ketogenic diets in medical oncology: a systematic review with focus on clinical outcomes. Med Oncol 2020;37:14.
47. Duraj T, Kalamian M, Zuccoli G, Maroon JC, D'Agostino DP, Scheck AC, et al. Clinical research framework proposal for ketogenic metabolic therapy in glioblastoma. BMC Med 2024;22:578.
48. Miller C, Austin K, Fischer L, Stringer E, Sidhu S. The ketogenic diet: considerations for cancer survivorship. Curr Nutr Rep 2022;11:682–94.
49. Weber DD, Aminzadeh-Gohari S, Tulipan J, Catalano L, Feichtinger RG, Kofler B, et al. Ketogenic diet in the treatment of cancer – where do we stand? Mol Metab 2020;33:102–21.
50. Mukherjee P, Augur ZM, Li M, Hill C, Greenwood B, Domin MA, et al. Therapeutic benefit of combining calorie-restricted ketogenic diet and glutamine targeting in late-stage experimental glioblastoma. Commun Biol 2019;2:200.
51. Evangeliou AE, Spilioti MG, Vassilakou D, Goutsaridou F, Seyfried TN. Restricted ketogenic diet therapy for primary lung cancer with metastasis to the brain: a case report. Cureus 2022;14:e27603.
52. Khodabakhshi A, Akbari ME, Mirzaei HR, Seyfried TN, Kalamian M, Davoodi SH, et al. Effects of ketogenic metabolic therapy on patients with breast cancer: a randomized controlled clinical trial. Clin Nutr 2021;40:751–8.
53. Elsakka AMA, Bary MA, Abdelzaher E, Elnaggar M, Kalamian M, Mukherjee P, et al. Management of glioblastoma multiforme in a patient treated with ketogenic metabolic therapy and modified standard of care: a 24-month follow-up. Front Nutr 2018;5:20.
54. Seyfried TN, Shivane AG, Kalamian M, Maroon JC, Mukherjee P, Zuccoli G, et al. Ketogenic metabolic therapy, without chemo or radiation, for the long-term management of *idh1*-mutant glioblastoma: an 80-month follow-up case report. Front Nutr 2021;8:682243.
55. di Meo NA, Lasorsa F, Rutigliano M, Loizzo D, Ferro M, Stella A, et al. Renal cell carcinoma as a metabolic disease: an update on main pathways, potential biomarkers, and therapeutic targets. Int J Mol Sci 2022;23:14360.
56. Chakraborty S, Balan M, Sabarwal A, Choueiri TK, Pal S. Metabolic reprogramming in renal cancer: events of a metabolic disease. Biochim Biophys Acta Rev Cancer 2021;1876:188559.
57. Seyfried TN, Lee DC, Duraj T, Ta NL, Mukherjee P, Kiebish M, et al. The warburg hypothesis and the emergence of the mitochondrial metabolic theory of cancer. J Bioenerg Biomembr 2025;57:57–83.
58. Mukherjee P, Greenwood B, Henao J, Kiebish MA, Seyfried T. Ketogenic diet as a metabolic vehicle for enhancing the therapeutic efficacy of mebendazole and devimistat in preclinical pediatric glioma. bioRvix 20230609:544252. https://doi.org/10.1101/2023.06.09.544552.
59. Mundi MS, Mohamed Elfadil O, Patel I, Patel J, Hurt RT. Ketogenic diet and cancer: fad or fabulous? JPEN J Parenter Enteral Nutr 2021;45: 26–32.

60. Rieger J, Bähr O, Maurer GD, Hattingen E, Franz K, Brucker D, et al. ERGO: a pilot study of ketogenic diet in recurrent glioblastoma. Int J Oncol 2014;44:1843–52.
61. Cortez NE, Mackenzie GG. Ketogenic diets in pancreatic cancer and associated cachexia: cellular mechanisms and clinical perspectives. Nutrients 2021;13:3202.
62. Kiryttopoulos A, Evangeliou AE, Katsanika I, Boukovinas I, Foroglou N, Zountsas B, et al. Successful application of dietary ketogenic metabolic therapy in patients with glioblastoma: a clinical study. Front Nutr 2025; 11:1489812.
63. Seyfried TN, Arismendi-Morillo G, Zuccoli G, Lee DC, Duraj T, Elsakka AM, et al. Metabolic management of microenvironment acidity in glioblastoma. Front Oncol 2022;12:968351.
64. Potts R. Environmental hypotheses of hominin evolution. Am J Phys Anthropol 1998;107:93–136.
65. Seyfried TN, Mukherjee P. Targeting energy metabolism in brain cancer: review and hypothesis. Nutr Metab 2005;2:30.
66. Li X, Li X, Xiang C, Cao J, Guo J, Zhu S, et al. Starvation-induced phosphorylation activates gasdermin A to initiate pyroptosis. Cell Rep 2024;43:114728.
67. Seyfried TN, Shelton L, Arismendi-Morillo G, Kalamian M, Elsakka A, Maroon J, et al. Provocative question: should ketogenic metabolic therapy become the standard of care for glioblastoma? Neurochem Res 2019;44:2392–404.
68. Seyfried TN, Mukherjee P, Lee DC, Ta L, Nations L. Case report: resolution of malignant canine mast cell tumor using ketogenic metabolic therapy alone. Front Nutr 2023;10:1157517.