International Journal of Biotechnology and Clinical Medicine ISSN 2583-4665
Vol.2, No.3, July - Sep 2023, pp. 01~08

THE METABOLISM OF CANCER CELLS: A PERSPECTIVE FOR THERAPEUTIC TARGETING

L. Konyak[1], Nokenketla[1], M.M. Phukan[1], G. Bupesh[1*]
[1]Department of Forestry, Nagaland University (Central), Lumami, Nagaland - 798627, India

Article Info

Article history:

Received August 5th, 2023
Revised September 12th, 2023
Accepted September 15th, 2023

Keyword:

Cancer metabolism
Therapy resistant
Drug discovery
Computational chemistry
Malignant tumors

ABSTRACT

The Warburg effect refers to a metabolic alteration seen in cancer cells, distinguished by an increased absorption and use of glucose. The sustained stimulation of aerobic glycolysis in cancer cells has been associated with the activation of oncogenes or the loss of tumor suppressors, indicating an accelerated process of cancer development. The suppression of glycolytic ability can potentially contribute to the reduction of carcinogenic properties in malignant cells. The comprehension of the mechanisms behind aerobic glycolysis has the potential to pave the way for novel therapeutic approaches in the treatment of cancer. Inhibition of tumor growth might be achieved by targeting lactate fermentation and other metabolic areas promoting cancer development. This study aims to investigate the dysregulation and reprogramming of cancer metabolism, along with exploring the potential therapeutic significance of metabolic enzymes such as hexokinase, phosphofructokinase, pyruvate kinase M2, lactate dehydrogenase, and pyruvate dehydrogenase kinase. Effectively regulating these metabolic domains may provide therapeutic advantages, enabling the circumvention of chemotherapy or radiation resistance.

Corresponding Author:

Dr. Giridharan Bupesh,
Department of Forestry, Nagaland University (Central), Lumami, Nagaland - 798627, India.
Email: bupeshgiri@nagalanduniversity.ac.in

How to Cite:

Konyak L et al. The metabolism of cancer cells: a perspective for therapeutic targeting. IJBTCM. 2023; Volume 2 (Issue 3): Page 01-08.

1. INTRODUCTION

The occurrence of COVID-19 in the population increased the risk of metabolic diseases and attracted immense scientific research for disclosing different therapeutic effects [1–4]. Cancer cell metabolism directly influences the regulation of intracellular signaling pathways disrupted by mutant oncogenes and tumor-suppressor genes. Mutated oncogenic genes can cause cancer cells to change metabolism [5]. Mutated metabolic enzymes can also aid malignant transformation. Metabolism is an energy-producing mechanism that helps cells maintain cell homeostasis while allowing them to grow and increase [6,7]. Normal cells have sophisticated signaling networks controlled by critical regulatory enzymes that detect environmental inputs and activate metabolic machinery precisely to provide enough energy for survival [8,9]. During cell proliferation, normal cells use metabolic pathways to adapt to the heightened demand for adenosine triphosphate (ATP) required for cell replication. In addition to the metabolic enhancement, by-products generated during aerobic metabolism, such as reactive oxygen species, possess the potential to inflict damage upon cells and induce mutations in DNA [10,11]. As a result, changes in cell metabolism may play a role in cancer development. Mutations in oncogenes and tumor suppressor genes can alter intracellular signaling pathways and, as a result, cell metabolism, making tumorigenesis easier [12]. A shift in signaling pathways allows cells to adapt to tumor cell metabolism, but some metabolic alterations are also essential for malignant transformation [13]. The Warburg effect, also known as aerobic glycolysis, is a metabolic characteristic of tumor metabolism discovered by Otto Warburg in 1926. Unlike normal cells, which create energy largely by pyruvate oxidation in the mitochondria, cancer cells, even under

aerobic conditions, generate energy predominantly through enhanced glycolysis in the cytosol [14]. Most cancer cells use glycolysis as an energy source, regardless of whether in a normoxic or hypoxic environment [15,16].
The link between glycolytic ATP generation and tumor aggressiveness has been documented several times. Initially, it was thought that these metabolic alterations were due to damage to mitochondrial oxidative phosphorylation, meaning that cancer cells could not effectively respire to get enough ATP [17]. However, research has discovered that many cancer cells can synthesize ATP via mitochondrial respiration. Regardless of whether mitochondrial respiration is diminished, cancer cells still have high rates of glycolysis and lactate fermentation, and this glucose reliance might be exploited for therapeutic intervention [9,18]. Studies on mitochondrial function in cancer cells over the last decade have revealed that the Warburg effect is more directly connected to changes in signaling pathways that govern glucose absorption and utilization than mitochondrial abnormalities [19]. Because researchers have begun to re-evaluate the importance of aerobic glycolysis in tumor cells, the Warburg effect has recently resurfaced in cancer research [20]. Oncogenes, tumor suppressors, a hypoxic microenvironment, mtDNA mutations, and other factors contribute to aerobic glycolysis in cancer. Understanding the intricate energy metabolism of cancer will aid in developing innovative ways for early detection and cancer treatment [21]. This review will look at tumor cell metabolism, focusing on changes in enzyme activity in aerobic glycolysis, as well as current cancer treatment strategies that target metabolic pathways.

2. THE WARBURG EFFECT: METABOLIC REPROGRAMMING

Glucose is the main energy source and the major fuel for cellular respiration. Oxidative phosphorylation provides 70% of ATP in normal glucose consumption, whereas glycolysis produces 30% [22]. Because ATP production fluctuates with biological conditions, the glycolysis to oxidative phosphorylation ratio varies in different cells, growth stages, and microenvironments. In hypoxia, for example, increased glycolysis compensates for reduced oxidative phosphorylation to maintain cellular energy balance [23–25]. Despite having a functional oxidative phosphorylation machinery, most solid tumor cells switch to glycolysis rather than respiration, resulting in cancer-specific aerobic glycolysis [26,27]. When the oxidative phosphorylation machinery is hampered for whatever cause (hypoxia, mitochondrial respiration suppression, etc.), alternative routes, such as lactate fermentation, are called upon to provide the cellular energy needed. To multiply, cancer cells demand a large quantity of energy in a short amount of time [28–31]. Muscle cells in hypoxic circumstances and embryo cells during development can adapt to an altered metabolism when the oxygen supply is limited, or the growth rate exceeds the regular energy supply [32–34]. Despite high glucose consumption, these cells convert glucose to lactate to make ATP quickly but inefficiently. Similarly, as the tumor develops, cancer cells modify their metabolism to meet their energy demands, a phenomenon known as the Warburg effect [35]. Even in the presence of properly functioning mitochondria, cancer cells employ aerobic glycolysis instead of mitochondrial respiration for energy generation [14]. Because the former produces fewer ATP molecules per glucose unit, converting glucose to lactate rather than metabolizing it via mitochondrial oxidative phosphorylation is inefficient [36]. A high rate of glucose absorption is required to meet the greater energy needs associated with rapid tumor growth [37]. All of these systems come together to create the Warburg effect.

When glucose uptake and glycolytic activity are greatly increased in transformed cancer cells, the reliance on fermentative metabolism for ATP synthesis implies long-term metabolic reprogramming [38]. Even in normoxia, an acute restrictive signaling cascade imposed on mitochondrial activity is commonly observed [39]. When normal cells become cancer cells, they undergo an irreversible metabolic shift toward glucose transport and consumption and the suppression of mitochondrial respiration [40,41]. If the respiratory system operates correctly, many routes will regulate glycolytic activity to maintain an energy balance [42]. Although Warburg did not mention glutamine, it is a critical bioenergetic and anabolic substrate for various cancer cell types. Aerobic glycolysis is used by cancer cells that employ glutamine as well as glucose as a carbon source [7,43]. By producing intermediates of the tricarboxylic acid (TCA) cycle, glutamine feeds other metabolic pathways as precursors. As a result, cancer cells need glutamine, just as they do with glucose during aerobic glycolysis, to keep the TCA cycle operating [44–46]. Several investigations have found that alterations in glucose metabolism provide additional energy to promote tumor growth. Cell proliferation and tumor formation are both slowed when glycolysis is reduced. Furthermore, blocking glycolysis-related metabolic pathways reduces tumor growth [47,48]. These findings suggest that reducing glycolysis might be a useful strategy for preventing or delaying cancer progression [49,50].

3. ONCOGENIC SIGNALS AND METABOLIC REPROGRAMMING

Mutations that activate oncogenes or inactivate tumor suppressors can significantly influence metabolic enzyme activity, which is important for cancer's aerobic glycolysis [51]. Phosphatidylinositol 30-kinase (PI3K), phosphatase and tensin homolog (PTEN), Myc, and p53 mutations, among other oncogenic alterations, can all

have an impact on cellular metabolism [52,53]. The PI3K pathway is altered in various human cancers and plays a key role in tumor development and survival [54,55]. The PI3K enzyme antagonizes the tumour suppressor PTEN, and the loss of PTEN increases glycolysis by activating AKT and HIF-1. AKT stimulates glycolysis by increasing glucose transporter expression and membrane translocation, as well as phosphorylating glycolytic enzymes such as hexokinase (HK) and phosphofructokinase (PFK) (PFK) [56,57]. HIF-1 also activates pyruvate dehydrogenase kinases (PDKs), preventing pyruvate from entering the TCA cycle by inactivating pyruvate dehydrogenase [58,59]. When pyruvate transport into the mitochondria is inhibited, the rate of oxidative phosphorylation and oxygen consumption is lowered [60]. These modifications result in high levels of glycolysis and glutaminolysis in Myc-induced liver cancer, which are connected to an aggressive tumor phenotype and histology. 30 It's worth mentioning that, in addition to increasing the glycolytic pathway, Myc also improves mitochondrial respiration, all of which contribute to enhanced metabolic activity in cancer cells [61–63].

FH mutations cause fumarate hydratase insufficiency, and it has been associated with uterine and cutaneous leiomyomas and papillary renal cancer [64,65]. The genomic sequencing of cancer patients has shown a relationship between a mutated metabolic enzyme and tumors [66]. IDH1 and IDH2 (nicotinamide adenine dinucleotide IDH1 and IDH2 catalyze the conversion of isocitrate to a-ketoglutarate (aKG) in human cells by producing one molecule of NADPH. IDH1 and IDH2 are homodimeric enzymes in the cytoplasm and mitochondria [67]. Gliomas and acute myeloid leukemia have been shown to contain heterozygous point mutations in many IDH1 residues [68,69]. Importantly, levels of aKG, isocitrate, and several other TCA metabolites are unaffected in cells or tissues with IDH1 mutations. This indicates that alternate metabolic pathways may adapt and maintain normal levels of key metabolites [70,71].

Mutations in the metabolic enzymes SDH, FH, and IDH are associated with an aberrant accumulation of carcinogenic potential compounds [72,73]. The metabolic products of mutant SDH, FH, and IDH obstruct the function of aKG-dependent enzymes (for example, prolyl hydroxylases) [74,75]. Surprisingly, these aKG-dependent enzymes normally seek for and destroy HIF. HIF activation has also been reported in mutant SDH, FH, and IDH [74,75]. For example, oncogenic alterations in cellular metabolism might control non-metabolic pathways that contribute to the oncogenic process, such as altered HIF activity [76,77]. Changes in mitochondrial metabolism may help carcinogenesis. Phosphoglycerate dehydrogenase (PHGDH) and glycine decarboxylase are two enzymes that have similar mutation patterns and might affect mitochondrial metabolism during oncogenesis [78,79]. When overexpressed in estrogen receptor-negative breast tumors, PHGDH catalyses the first step in serine synthesis and is suggested to be an oncogenic enzyme. By transferring glycolytic intermediates into the one-carbon metabolic pathway, PHGDH also regulates nucleotide synthesis [80]. The quantity of aKG, a crucial TCA intermediate, is reduced by PHGDH deficiency, but not the amount of serine. Glycine decarboxylase, an enzyme involved in glycine/serine metabolism and the one-carbon metabolic pathway, is overexpressed in cancer cells [71,81].

4. METABOLIC TARGETING

Metabolic targeting for cancer treatment is now being researched to discover tiny molecules that can specifically interrupt crucial metabolic processes connected to tumor formation [82]. Glycolysis inhibition or attenuation prevents cancer development, implying that glycolysis is essential for cancer proliferation, invasion, and metastasis. It can be stopped by inhibiting the glycolytic enzymes HK, PFK, and pyruvate kinase (PK), all of which control irreversible and rate-limiting steps in glycolysis. Consequently, by blocking the enzymatic activity of these three proteins, cancer cells' increased glycolysis is slowed or completely stopped [83,84]. HK facilitates the early step of glycolysis, where glucose is phosphorylated with the help of ATP. 2-deoxyglucose (2-DG), 3-bromopyruvate (3-BrPA), and lonidamine (LON, 1-[(2,4-chlorophenyl)methyl]-1H-indazole- 3-carboxylic acid) are HK inhibitors that are now in preclinical and early phase clinical trials. 2-DG prevents glucose from reaching the HK enzyme as a competitive inhibitor [85–87]. Because the following glycolytic enzyme, phosphoglucose isomerase, can not recognize or process 2-DG-P, it is taken up by glucose transporters and phosphorylated by HK to 2-DG-P, which is then kept inside the cell. This causes a build-up of 2-DG-P inside the cell and a reduction in cellular ATP generation [88].

However, because 2-DG's efficacy as a single medication is limited, combining it with radiation or chemotherapy boosts tumor-killing effects. Because it affects cancer cell energy metabolism, 3-BrPA is a critical predictor of chemoresistance in various cancer types [89]. ATP depletion caused by 3-BrPA treatment lowers ABC transporter activity and, resulting in drug efflux, enhances drug retention. Consequently, 3-BrPA may improve cancer treatments and overcome chemoresistance [14,90,91]. According to the previous study, increased glycolysis is connected to glucocorticoid resistance, which is linked to treatment failure in children with acute lymphoblastic leukemia, and inhibiting glycolysis with 2-DG, 3-BrPA, or LON increases prednisolone-induced toxicity in leukemia cells [92]. As a combined technique for metabolic targeting of

malignancies, modulation of both transamination and PK has been proposed [93,94]. Transamination-derived metabolites may also regulate the dimer/tetramer configuration of PK. Enzymatic activity necessitates a balanced presence of both PK forms and transamination metabolites, which can alter the dimer/tetramer ratio and harm tumor growth [95,96]. Dichloroacetate, a PDK inhibitor, successfully treats lactic acidosis and mitochondrial diseases and may be useful in treating cancer in multiple studies [97–99].

5. APPLICATION OF CHEMINFORMATICS IN CANCER THERAPEUTICS

In general, developing a medicine to treat cancer takes a long time and is expensive [100–102]. Advances in machine learning approaches will cut drug development time in half shortly, and researchers in this discipline will produce more and more applications that answer well-defined issues [103–105]. Virtual screening is one sector that has benefited considerably from the development of deep learning; however, the essential component of virtual screening is Drug–cancer Target (DTA) prediction, which directly influences its accuracy and efficiency [106]. The potential of a hybrid virtual screening pipeline established in multiple studies rests in its extremely efficient protein-ligand binding prediction algorithms and several stages of screening techniques [107,108], which stresses a progressive change from large-scale efficiency to accuracy in the later stages [109,110]. The hybrid drug screening pipeline dramatically increased the number of inhibitors for possible new cancer treatment targets [111]. Furthermore, the high success rate of the hybrid drug screening pipeline suggests that similar strategies may be used to develop drugs for different targets [112]. The active chemicals discovered thus far and their possible derivatives have the potential to speed up therapeutic development for various cancers [50,113,114]. Understanding the binding mechanism and drug design and improvement is aided by the detailed interaction between those inhibitors and their targets [115,116]. The research involving deep learning-based approaches and MD simulation-related methodologies in large-scale drug lead discovery has a bright future.

6. CONCLUSION

Cancer cells employ aerobic glycolysis, in which glucose is used for energy and glutamine is used to provide biosynthetic precursors to mitochondrial intermediates [117]. Most malignancies, including solid tumors, lymphoma, and leukemia, are expected to retain altered metabolism, which is thought necessary for transforming normal cells into cancer cells [118]. Because each cancer kind has a different tissue origin, malignancies have various characteristics. Cancer cells are deprived of food and oxygen due to the faulty vasculature created during carcinogenesis [119–121]. Cancer cells are more adaptable than normal cells, and it's worth noting. As a result, alterations in tumor cells' metabolic pathways may give a selective advantage to cancer cells in an unfavorable environment for rapid ATP production and appropriate biomolecule synthesis [122]. The metabolic changes in cancer cells are thought to be linked to hypoxia adaptation, which is necessary for tumor survival and development. There is a clear shift in mitochondrial activity from energy generator to biosynthetic intermediate creator, as well as a reduction in oxygen use and rapid energy generation [123,124]. Several metabolite analogs are now being explored as possible therapeutic options to target tumor metabolism [63,125–127]. Further research into the role of mitochondria in cancer cell metabolism might lead to developing a targeted delivery system for hazardous chemicals to cancer cells, boosting efficacy and lowering the toxicity of potentially strong chemotherapeutic treatments. New insights into cancer metabolic characteristics give us hope for developing a new class of cancer treatment drugs. As a result, the appropriate use of metabolic inhibitors might be a therapeutically beneficial treatment approach.

FUNDING

Nil

ETHICAL APPROVAL

Nil

COMPETING INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Mir JM, Maurya RC. Nitric oxide as a therapeutic option for COVID-19 treatment: a concise perspective. New J Chem 2021;45:1774–84.

[2] Work NKFRR, on behalf of the National G, Foundation K. Research Priorities for Kidney-Related Research—An Agenda to Advance Kidney Care: A Position Statement From the National Kidney Foundation. Am J Kidney Dis 2022;79:141–52.

[3] Singh H, Kakkar AK, Chauhan P. Repurposing minocycline for COVID-19 management: mechanisms, opportunities, and challenges. Expert Rev Anti Infect Ther 2020;18:997–1003.
[4] Kumar MP, Sundaram KM, Ramasamy MS. Coronavirus spike (S) glycoprotein (2019-ncov) targeted siddha medicines kabasura kudineer and thonthasura kudineer–in silico evidence for corona viral drug. Asian J Pharm Res Heal Care 2020;12:20–7.
[5] Morrison AJ. Cancer cell metabolism connects epigenetic modifications to transcriptional regulation. FEBS J 2022;289:1302–14.
[6] Ambika S, Manojkumar Y, Arunachalam S, Gowdhami B, Meenakshi Sundaram KK, Solomon RV, et al. Biomolecular interaction, anti-cancer and anti-angiogenic properties of cobalt (III) Schiff base complexes. Sci Rep 2019;9:1–14.
[7] Pavlova NN, Zhu J, Thompson CB. The hallmarks of cancer metabolism: Still emerging. Cell Metab 2022.
[8] Dey P, Kimmelman AC, DePinho RA. Metabolic codependencies in the tumor microenvironment. Cancer Discov 2021;11:1067–81.
[9] Sundararaman, M N, Maruthanayagam V, Meenakshi Sundaram K. Tropical Marine Cyanobacterium Lyngbya sordida Producing Toxic Octacosa–1,27-diene Induces Coagulative Hepatic Necrosis and Progressive Glomerulonephritis in Mus musculus. Encycl. Mar. Biotechnol., vol. 4, John Wiley & Sons Ltd; 2020, p. 2339–64.
[10] Tan J, Ni D, Ribeiro R V, Pinget G V, Macia L. How changes in the nutritional landscape shape gut immunometabolism. Nutrients 2021;13:823.
[11] Saravanan KM, Sundaram KM. Effect of bromocriptine in diabetes mellitus: a review. Uttar Pradesh J Zool 2021:1166–70.
[12] Arfin S, Jha NK, Jha SK, Kesari KK, Ruokolainen J, Roychoudhury S, et al. Oxidative stress in cancer cell metabolism. Antioxidants 2021;10:642.
[13] Martínez-Reyes I, Chandel NS. Cancer metabolism: looking forward. Nat Rev Cancer 2021;21:669–80.
[14] Fan T, Sun G, Sun X, Zhao L, Zhong R, Peng Y. Tumor energy metabolism and potential of 3-bromopyruvate as an inhibitor of aerobic glycolysis: implications in tumor treatment. Cancers (Basel) 2019;11:317.
[15] Hayashi Y, Yokota A, Harada H, Huang G. Hypoxia/pseudohypoxia-mediated activation of hypoxia-inducible factor-1α in cancer. Cancer Sci 2019;110:1510–7.
[16] Subramanian U, Kishorekumar M, Muthuraman S, Munusamy A, Sundaram R. Marine Algal Secondary Metabolites Promising Anti- Angiogenesis Factor against Retinal Neovascularization in CAM Model. Res Rev A J Life Sci 2018:19–25.
[17] Marini C, Cossu V, Bauckneht M, Lanfranchi F, Raffa S, Orengo AM, et al. Metformin and Cancer Glucose Metabolism: At the Bench or at the Bedside? Biomolecules 2021;11:1231.
[18] Seyfried TN, Arismendi-Morillo G, Mukherjee P, Chinopoulos C. On the origin of ATP synthesis in cancer. Iscience 2020;23:101761.
[19] Spencer NY, Stanton RC. The Warburg effect, lactate, and nearly a century of trying to cure cancer. Semin. Nephrol., vol. 39, Elsevier; 2019, p. 380–93.
[20] Hodson LE. Design and Synthesis of Covalent Kinase Inhibitors Utilising Novel Electrophiles 2019.
[21] Valle-Mendiola A, Soto-Cruz I. Energy metabolism in cancer: the roles of STAT3 and STAT5 in the regulation of metabolism-related genes. Cancers (Basel) 2020;12:124.
[22] Bose S, Zhang C, Le A. Glucose metabolism in cancer: The Warburg effect and beyond. Heterog. Cancer Metab., Springer, Cham; 2021, p. 3–15.
[23] Belisario DC, Kopecka J, Pasino M, Akman M, De Smaele E, Donadelli M, et al. Hypoxia dictates metabolic rewiring of tumors: Implications for chemoresistance. Cells 2020;9:2598.
[24] Duraj T, Carrión-Navarro J, Seyfried TN, García-Romero N, Ayuso-Sacido A. Metabolic therapy and bioenergetic analysis: The missing piece of the puzzle. Mol Metab 2021;54:101389.
[25] Balaji RM, Sundaram KM. Studies on antidiabetic activity of indian medicinal plants using alpha-amylase and alpha-glucosidase inhibitory activity-A pathway to antidiabetic drugs. World J Med Sci 2015;12:207–12.
[26] Orang A V, Petersen J, McKinnon RA, Michael MZ. Micromanaging aerobic respiration and glycolysis in cancer cells. Mol Metab 2019;23:98–126.
[27] Al Tameemi W, Dale TP, Al-Jumaily RMK, Forsyth NR. Hypoxia-modified cancer cell metabolism. Front Cell Dev Biol 2019;7:4.
[28] Chinopoulos C, Seyfried TN. Mitochondrial substrate-level phosphorylation as energy source for glioblastoma: review and hypothesis. ASN Neuro 2018;10:1759091418818261.
[29] Brockmueller A, Sameri S, Liskova A, Zhai K, Varghese E, Samuel SM, et al. Resveratrol's anti-cancer effects through the modulation of tumor glucose metabolism. Cancers (Basel) 2021;13:188.
[30] Iessi E, Vona R, Cittadini C, Matarrese P. Targeting the Interplay between Cancer Metabolic Reprogramming and Cell Death Pathways as a Viable Therapeutic Path. Biomedicines 2021;9:1942.
[31] Anand AV, Bharathi V, Bupesh G, Lakshmi NJ, Sundaram KM, Saradhadevi KM. Identification of novel potent pancreatic lipase inhibitors from ficus racemosa. Biomed 2021;41:23–30. https://doi.org/10.51248/.v41i1.528.
[32] Haron A, Ruzal M, Shinder D, Druyan S. Hypoxia during incubation and its effects on broiler's embryonic development. Poult Sci 2021;100:100951.
[33] Reznick J, Park TJ, Lewin GR. A sweet story of metabolic innovation in the naked mole-rat. Extraordinary Biol. Naked Mole-Rat, Springer; 2021, p. 271–86.
[34] Saravanan KM, Selvaraj S. Performance of secondary structure prediction methods on proteins containing

structurally ambivalent sequence fragments. Pept Sci 2013;100:148–53. https://doi.org/https://doi.org/10.1002/bip.22178.
[35] Li Z, Sun C, Qin Z. Metabolic reprogramming of cancer-associated fibroblasts and its effect on cancer cell reprogramming. Theranostics 2021;11:8322.
[36] Lopaschuk GD, Karwi QG, Tian R, Wende AR, Abel ED. Cardiac energy metabolism in heart failure. Circ Res 2021;128:1487–513.
[37] Vaupel P, Schmidberger H, Mayer A. The Warburg effect: essential part of metabolic reprogramming and central contributor to cancer progression. Int J Radiat Biol 2019;95:912–9.
[38] de Alteriis E, Cartenì F, Parascandola P, Serpa J, Mazzoleni S. Revisiting the Crabtree/Warburg effect in a dynamic perspective: a fitness advantage against sugar-induced cell death. Cell Cycle 2018;17:688–701.
[39] Hernansanz-Agustín P, Choya-Foces C, Carregal-Romero S, Ramos E, Oliva T, Villa-Piña T, et al. Na+ controls hypoxic signalling by the mitochondrial respiratory chain. Nature 2020;586:287–91.
[40] Poljsak B, Kovac V, Dahmane R, Levec T, Starc A. Cancer etiology: A metabolic disease originating from life's major evolutionary transition? Oxid Med Cell Longev 2019;2019.
[41] Manivannan C, Sundaram KM, Renganathan R, Sundararaman M. Investigations on Photoinduced Interaction of 9-Aminoacridine with Certain Catechols and Rutin. J Fluoresc 2012;22:1113–25. https://doi.org/10.1007/s10895-012-1050-4.
[42] O'Leary BM, Asao S, Millar AH, Atkin OK. Core principles which explain variation in respiration across biological scales. New Phytol 2019;222:670–86.
[43] Reyes-Castellanos G, Masoud R, Carrier A. Mitochondrial metabolism in PDAC: From better knowledge to new targeting strategies. Biomedicines 2020;8:270.
[44] Chandel NS. Metabolism of proliferating cells. Cold Spring Harb Perspect Biol 2021;13:a040618.
[45] Li T, Le A. Glutamine metabolism in cancer. Heterog Cancer Metab 2018:13–32.
[46] APB B, Bhuvaneswari S, Raj L, Bupesh G, Meenakshisundaram K, KM S. A Review on the Potential Species of the Zingiberaceae Family with Anti-viral Efficacy Towards Enveloped Viruses. J Pure Appl Microbiol 2022;16:796–813. https://doi.org/10.22207/JPAM.16.2.35.
[47] Wang G, Wang J-J, Guan R, Sun Y, Shi F, Gao J, et al. Targeting Strategies for Glucose Metabolic Pathways and T Cells in Colorectal Cancer. Curr Cancer Drug Targets 2019;19:534–50.
[48] Li X, Wenes M, Romero P, Huang SC-C, Fendt S-M, Ho P-C. Navigating metabolic pathways to enhance antitumour immunity and immunotherapy. Nat Rev Clin Oncol 2019;16:425–41.
[49] Siska PJ, Singer K, Evert K, Renner K, Kreutz M. The immunological Warburg effect: Can a metabolic-tumor-stroma score (MeTS) guide cancer immunotherapy? Immunol Rev 2020;295:187–202.
[50] Mutharasu G, Murugesan A, Konda Mani S, Yli-Harja O, Kandhavelu M. Transcriptomic analysis of glioblastoma multiforme providing new insights into GPR17 signaling communication. J Biomol Struct Dyn 2022;40:2586–99. https://doi.org/10.1080/07391102.2020.1841029.
[51] Hosios AM, Manning BD. Cancer Signaling Drives Cancer Metabolism: AKT and the Warburg Effect. Cancer Res 2021;81:4896–8.
[52] Basha R, Ahmad S. Overcoming Drug Resistance in Gynecologic Cancers. Academic Press; 2021.
[53] Xing F, Saidou J, Watabe K. Cancer associated fibroblasts (CAFs) in tumor microenvironment. Front Biosci (Landmark Ed 2010;15:166–79. https://doi.org/10.2741/3613.
[54] Kumari S, Badana AK, Malla R. Reactive oxygen species: a key constituent in cancer survival. Biomark Insights 2018;13:1177271918755391.
[55] Revathidevi S, Munirajan AK. Akt in cancer: mediator and more. Semin. Cancer Biol., vol. 59, Elsevier; 2019, p. 80–91.
[56] Wu Z, Wu J, Zhao Q, Fu S, Jin J. Emerging roles of aerobic glycolysis in breast cancer. Clin Transl Oncol 2020;22:631–46.
[57] O'Brien CM, Mulukutla BC, Mashek DG, Hu W-S. Regulation of metabolic homeostasis in cell culture bioprocesses. Trends Biotechnol 2020;38:1113–27.
[58] Wang X, Shen X, Yan Y, Li H. Pyruvate dehydrogenase kinases (PDKs): an overview toward clinical applications. Biosci Rep 2021;41.
[59] Golias T, Kery M, Radenkovic S, Papandreou I. Microenvironmental control of glucose metabolism in tumors by regulation of pyruvate dehydrogenase. Int J Cancer 2019;144:674–86.
[60] Andersen J V, Jakobsen E, Waagepetersen HS, Aldana BI. Distinct differences in rates of oxygen consumption and ATP synthesis of regionally isolated non-synaptic mouse brain mitochondria. J Neurosci Res 2019;97:961–74.
[61] Matés JM, Di Paola FJ, Campos-Sandoval JA, Mazurek S, Márquez J. Therapeutic targeting of glutaminolysis as an essential strategy to combat cancer. Semin. Cell Dev. Biol., vol. 98, Elsevier; 2020, p. 34–43.
[62] Sun X, Wang M, Wang M, Yu X, Guo J, Sun T, et al. Metabolic reprogramming in triple-negative breast cancer. Front Oncol 2020;10:428.
[63] Afonso J, Santos LL, Longatto-Filho A, Baltazar F. Competitive glucose metabolism as a target to boost bladder cancer immunotherapy. Nat Rev Urol 2020;17:77–106.
[64] Qureshi AS, Ali S. Warburg effect and renal cancer caused by errs in fumarate hydratase encoding gene. Pak J Pharm Sci 2019;32.
[65] Schmidt C, Sciacovelli M, Frezza C. Fumarate hydratase in cancer: A multifaceted tumour suppressor. Semin. Cell Dev. Biol., vol. 98, Elsevier; 2020, p. 15–25.
[66] Ooi A. Advances in hereditary leiomyomatosis and renal cell carcinoma (HLRCC) research. Semin. Cancer Biol.,

vol. 61, Elsevier; 2020, p. 158–66.
[67] Koju N, Qin Z, Sheng R. Reduced nicotinamide adenine dinucleotide phosphate in redox balance and diseases: a friend or foe? Acta Pharmacol Sin 2022:1–16.
[68] Huang LE. Friend or foe—IDH1 mutations in glioma 10 years on. Carcinogenesis 2019;40:1299–307.
[69] Mondesir J, Willekens C, Touat M, de Botton S. IDH1 and IDH2 mutations as novel therapeutic targets: current perspectives. J Blood Med 2016;7:171.
[70] Ruiz CF. Metabolic signatures associated with Mutant KRAS in Non-small cell lung cancer 2019.
[71] Hollinshead KER. Metabolic rewiring in response to genetic and environmental preturbations in cancer 2017.
[72] Montellier E, Gaucher J. Targeting the interplay between metabolism and epigenetics in cancer. Curr Opin Oncol 2019;31:92–9.
[73] Sullivan LB, Gui DY, Heiden MG Vander. Altered metabolite levels in cancer: implications for tumour biology and cancer therapy. Nat Rev Cancer 2016;16:680–93.
[74] Sciacovelli M, Schmidt C, Maher ER, Frezza C. Metabolic drivers in hereditary cancer syndromes. Annu Rev Cancer Biol 2020;4:77–97.
[75] Sciacovelli M, Frezza C. Oncometabolites: Unconventional triggers of oncogenic signalling cascades. Free Radic Biol Med 2016;100:175–81.
[76] Eisenberg L, Eisenberg-Bord M, Eisenberg-Lerner A, Sagi-Eisenberg R. Metabolic alterations in the tumor microenvironment and their role in oncogenesis. Cancer Lett 2020;484:65–71.
[77] Yu X, Li S. Non-metabolic functions of glycolytic enzymes in tumorigenesis. Oncogene 2017;36:2629–36.
[78] De Santis MC, Porporato PE, Martini M, Morandi A. Signaling pathways regulating redox balance in cancer metabolism. Front Oncol 2018;8:126.
[79] Hirschey MD, DeBerardinis RJ, Diehl AME, Drew JE, Frezza C, Green MF, et al. Dysregulated metabolism contributes to oncogenesis. Semin. Cancer Biol., vol. 35, Elsevier; 2015, p. S129–50.
[80] Newman AC, Maddocks ODK. One-carbon metabolism in cancer. Br J Cancer 2017;116:1499–504.
[81] Garcia Bierhals C. a Investigation of glycine transporter GLYT1 in tumour cell proliferation 2018.
[82] Kimmelman AC. Metabolic dependencies in RAS-driven cancers. Clin Cancer Res 2015;21:1828–34.
[83] Xu Y, Guo Y, Chen L, Ni D, Hu P, Shi J. Tumor chemical suffocation therapy by dual respiratory inhibitions. Chem Sci 2021;12:7763–9.
[84] Abdel-Wahab AF, Mahmoud W, Al-Harizy RM. Targeting glucose metabolism to suppress cancer progression: prospective of anti-glycolytic cancer therapy. Pharmacol Res 2019;150:104511.
[85] Sharma LK, Tiwari M, Mishra SK. Mitochondrial alteration: a major player in carcinogenesis. Cell Biol 2015;3:8–16.
[86] Ma J, Lim C, Sacher JR, Van Houten B, Qian W, Wipf P. Mitochondrial targeted β-lapachone induces mitochondrial dysfunction and catastrophic vacuolization in cancer cells. Bioorg Med Chem Lett 2015;25:4828–33.
[87] Chaurasia M, Misra S, Bhatt AN, Das A, Dwarakanath B, Sharma K. Metabolic imbalance associated mitophagy in tumor cells: genesis and implications. J Can Res Updates 2015;4:95–107.
[88] Kuntz EM. An investigation of metabolic vulnerabilities in chronic myeloid leukaemic stem cells 2017.
[89] Grasso C, Jansen G, Giovannetti E. Drug resistance in pancreatic cancer: Impact of altered energy metabolism. Crit Rev Oncol Hematol 2017;114:139–52.
[90] Savic LJ, Chapiro J, Duwe G, Geschwind J-F. Targeting glucose metabolism in cancer: a new class of agents for loco-regional and systemic therapy of liver cancer and beyond? Hepatic Oncol 2016;3:19–28.
[91] Peng J, Cui Y, Xu S, Wu X, Huang Y, Zhou W, et al. Altered glycolysis results in drug-resistant in clinical tumor therapy. Oncol Lett 2021;21:1–14.
[92] Chaudhary MI. Frontiers in Drug Design & Discovery. vol. 7. Bentham Science Publishers; 2016.
[93] Li L, Meng Y, Li Z, Dai W, Xu X, Bi X, et al. Discovery and development of small molecule modulators targeting glutamine metabolism. Eur J Med Chem 2019;163:215–42.
[94] Gill KS, Fernandes P, O'Donovan TR, McKenna SL, Doddakula KK, Power DG, et al. Glycolysis inhibition as a cancer treatment and its role in an anti-tumour immune response. Biochim Biophys Acta (BBA)-Reviews Cancer 2016;1866:87–105.
[95] Edmunds LR. Regulation of metabolism by the oncoprotein C-MYC 2015.
[96] Gyambibi-Barnett P, Mayr M, Xu Q, Zampetaki A. The Role of MiRNAs in Mouse Embryonic Stem Cells: A Proteomics Approach 2018.
[97] Schoonjans CA, Joudiou N, Brusa D, Corbet C, Feron O, Gallez B. Acidosis-induced metabolic reprogramming in tumor cells enhances the anti-proliferative activity of the PDK inhibitor dichloroacetate. Cancer Lett 2020;470:18–28.
[98] Yang Z, Tam KY. Anti-cancer synergy of dichloroacetate and EGFR tyrosine kinase inhibitors in NSCLC cell lines. Eur J Pharmacol 2016;789:458–67.
[99] Kinnaird A, Dromparis P, Saleme B, Gurtu V, Watson K, Paulin R, et al. Metabolic modulation of clear-cell renal cell carcinoma with dichloroacetate, an inhibitor of pyruvate dehydrogenase kinase. Eur Urol 2016;69:734–44.
[100] Saravanan KM, Palanivel S, Yli-Harja O, Kandhavelu M. Identification of novel GPR17-agonists by structural bioinformatics and signaling activation. Int J Biol Macromol 2018;106:901–7. https://doi.org/10.1016/j.ijbiomac.2017.08.088.
[101] Viswanathan A, Zhurina A, Assoah B, Paakkunainen A, Musa A, Kute D, et al. Decane-1,2-diol derivatives as potential antitumor agents for the treatment of glioblastoma. Eur J Pharmacol 2018;837:105–16.

https://doi.org/10.1016/j.ejphar.2018.08.041.
[102] Viswanathan A, Kute D, Musa A, Konda Mani S, Sipilä V, Emmert-Streib F, et al. 2-(2-(2,4-dioxopentan-3-ylidene)hydrazineyl)benzonitrile as novel inhibitor of receptor tyrosine kinase and PI3K/AKT/mTOR signaling pathway in glioblastoma. Eur J Med Chem 2019;166:291–303. https://doi.org/10.1016/j.ejmech.2019.01.021.
[103] Zhang H, Liao L, Saravanan KM, Yin P, Wei Y. DeepBindRG: a deep learning based method for estimating effective protein–ligand affinity. PeerJ 2019;7:e7362. https://doi.org/10.7717/peerj.7362.
[104] Zhang H, Saravanan KM, Lin J, Liao L, Ng JT-Y, Zhou J, et al. DeepBindPoc: a deep learning method to rank ligand binding pockets using molecular vector representation. PeerJ 2020;8:e8864. https://doi.org/10.7717/peerj.8864.
[105] Zhang H, Li J, Saravanan KM, Wu H, Wang Z, Wu D, et al. An Integrated Deep Learning and Molecular Dynamics Simulation-Based Screening Pipeline Identifies Inhibitors of a New Cancer Drug Target TIPE2. Front Pharmacol 2021;12. https://doi.org/10.3389/fphar.2021.772296.
[106] Viswanathan A, Musa A, Murugesan A, Vale JR, Afonso CAM, Konda Mani S, et al. Battling Glioblastoma: A Novel Tyrosine Kinase Inhibitor with Multi-Dimensional Anti-Tumor Effect (Running Title: Cancer Cells Death Signalling Activation). Cells 2019;8. https://doi.org/10.3390/cells8121624.
[107] Nithya P, Jeyaram C, Sundaram KM, Chandrasekar A, Ramasamy MS. Anti-dengue viral compounds from Andrographis paniculata by insilico approach 2014.
[108] Meenakshi Sundaram K, Umadevi S, Manivannan P, Rajakumar S, Muralidharan G, Sundararaman M. In Silico Discovery of Seaweed Molecules against Matrixmetalloproteinase-26. J Adv Bioinforma Appl Res 2015;6:52–61.
[109] Zhang H, Shao X, Peng Y, Teng Y, Saravanan KM, Zhang H, et al. A novel machine learning based approach for iPS progenitor cell identification. PLoS Comput Biol 2019;15. https://doi.org/10.1371/journal.pcbi.1007351.
[110] Zhang H, Yang Y, Li J, Wang M, Saravanan KM, Wei J, et al. A novel virtual screening procedure identifies Pralatrexate as inhibitor of SARS-CoV-2 RdRp and it reduces viral replication in vitro. PLOS Comput Biol 2020;16:e1008489. https://doi.org/10.1371/journal.pcbi.1008489.
[111] Gnanavel M, Murugesan A, Mani SK, Kandhavelu M, Yli-Harja O. Identifying the mirna signature association with aging-related senescence in glioblastoma. Int J Mol Sci 2021;22:1–14. https://doi.org/10.3390/ijms22020517.
[112] Doan P, Nguyen P, Murugesan A, Subramanian K, Konda Mani S, Kalimuthu V, et al. Targeting Orphan G Protein-Coupled Receptor 17 with T0 Ligand Impairs Glioblastoma Growth. Cancers 2021;13. https://doi.org/10.3390/cancers13153773.
[113] Le HTT, Murugesan A, Ramesh T, Yli-Harja O, Konda Mani S, Kandhavelu M. Molecular interaction of HIC, an agonist of P2Y1 receptor, and its role in prostate cancer apoptosis. Int J Biol Macromol 2021;189:142–50. https://doi.org/10.1016/j.ijbiomac.2021.08.103.
[114] Srimathi Devi J, Haripriya D, Arul S, Saravanan KM, Bupesh G. Evaluation of anti-cancer effect of zerumbone and cisplatin on N-nitrosodiethylamine induced hepatic cancer in freshwater fish (Danio rerio). Nat Prod Res 2021:1–5. https://doi.org/10.1080/14786419.2021.2012672.
[115] Saravanan KM, Kannan M, Meera P, Bharathkumar N, Anand T. E3 ligases: a potential multi-drug target for different types of cancers and neurological disorders. Future Med Chem 2022. https://doi.org/10.4155/fmc-2021-0157.
[116] Bharathkumar N, Sunil A, Meera P, Aksah S, Kannan M, Saravanan KM, et al. CRISPR/Cas-Based Modifications for Therapeutic Applications: A Review. Mol Biotechnol 2021;64:355–72. https://doi.org/10.1007/s12033-021-00422-8.
[117] Vincent EE, Sergushichev A, Griss T, Gingras M-C, Samborska B, Ntimbane T, et al. Mitochondrial phosphoenolpyruvate carboxykinase regulates metabolic adaptation and enables glucose-independent tumor growth. Mol Cell 2015;60:195–207.
[118] Boroughs LK, DeBerardinis RJ. Metabolic pathways promoting cancer cell survival and growth. Nat Cell Biol 2015;17:351–9.
[119] Fadaka A, Ajiboye B, Ojo O, Adewale O, Olayide I, Emuowhochere R. Biology of glucose metabolization in cancer cells. J Oncol Sci 2017;3:45–51.
[120] Tahergorabi Z, Khazaei M, Moodi M, Chamani E. From obesity to cancer: a review on proposed mechanisms. Cell Biochem Funct 2016;34:533–45.
[121] Kutova OM, Guryev EL, Sokolova EA, Alzeibak R, Balalaeva I V. Targeted delivery to tumors: multidirectional strategies to improve treatment efficiency. Cancers (Basel) 2019;11:68.
[122] Schiliro C, Firestein BL. Mechanisms of metabolic reprogramming in cancer cells supporting enhanced growth and proliferation. Cells 2021;10:1056.
[123] Mazumdar C, Driggers EM, Turka LA. The untapped opportunity and challenge of immunometabolism: A new paradigm for drug discovery. Cell Metab 2020;31:26–34.
[124] De Vitto H, Palorini R, Votta G, Chiaradonna F. Mitochondria in Focus: Targeting the Cell-Death Mechanism. Apoptosis Beyond Many Ways Cells Die 2018:13–48.
[125] Clemmensen C, Finan B, Müller TD, DiMarchi RD, Tschöp MH, Hofmann SM. Emerging hormonal-based combination pharmacotherapies for the treatment of metabolic diseases. Nat Rev Endocrinol 2019;15:90–104.
[126] Wang Z, Dabrosin C, Yin X, Fuster MM, Arreola A, Rathmell WK, et al. Broad targeting of angiogenesis for cancer prevention and therapy. Semin. Cancer Biol., vol. 35, Elsevier; 2015, p. S224–43.
[127] Choi B-H, Coloff JL. The diverse functions of non-essential amino acids in cancer. Cancers (Basel) 2019;11:675.