The Cancer-Like Metabolism of the Mammalian Retina

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Abstract

The Warburg effect is an explosive area of study within the cancer community in recent years. The expanding knowledge on the molecular basis of the Warburg effect has also led to a greater understanding of mammalian retinal metabolism, and at the same time has also motivated cancer researchers to target the Warburg effect as a novel treatment strategy for cancer. However, the key aspects of the molecular mechanism underlying the Warburg effect are likely conserved between the retina and cancer. Therefore, cancer treatments targeting the Warburg effect may potentially have serious adverse effects on retinal metabolism. Herein, we provide an updated understanding of the Warburg effect in mammalian retina.

Introduction

In the 1920s, Otto Warburg and his team at the Kaiser Wilhelm Institute showed that cancer cells tend to convert glucose to lactate, despite the presence of oxygen. He called this phenomenon "aerobic glycolysis", a term which is now synonymous with the "Warburg effect" (**Fig. 1**). Warburg believed that this phenomenon was abnormal: a breach of the "Pasteur effect" where oxygen inhibits glycolysis, or conversely, hypoxia stimulates glycolysis.[2,3] He further believed that the switch from oxidative phosphorylation (OXPHOS) to glycolysis caused cancer,[1] a concept that was criticized during his lifetime, but that has recently had a resurgence. His team also noted that normal mammalian retinal explants displayed aerobic glycolysis.[4] This finding however did not fit neatly with Warburg's beliefs about cancer pathogenesis and was attributed as an experimental artifact. Several decades thereafter, other researchers confirmed that the mammalian retina indeed displays a strong Warburg effect.[5,6]

In recent years, the Warburg effect has become an explosive area of study within the cancer research community, with many publications in the world's leading scientific journals,[7-10] resulting in a deeper understanding of the Warburg effect at the molecular level. This new knowledge has also led to better comprehension of the presence of the Warburg effect in mammalian retina.[11] However, the fact that the retina also displays the Warburg effect is rarely acknowledged in the cancer literature. For example, the authors of a *Nature Reviews Cancer* publication incorrectly stated that "aerobic glycolysis is uniquely observed in cancer". [12] But the Warburg effect is widely described in other cell types namely embryonic stem cells, human T lymphocytes, neutrophils, dendritic cells and macrophages. [13,14]

With cancer researchers enthusiastically attempting to target the Warburg effect as a therapeutic strategy in cancer treatment, the misconception that it is unique to cancer could potentially lead to treatments that have serious adverse effects on these physiological tissues and cells. In this review we aim to provide an updated understanding of the Warburg effect in the mammalian retina.

Aerobic Glycolysis

Cellular metabolism and the Warburg effect

All life on Earth uses adenosine triphosphate (ATP) to transfer energy. ATP is generated via two related metabolic pathways: OXPHOS and glycolysis.[15] Glycolysis converts a single molecule of glucose into two molecules of pyruvate, generating 2 ATP molecules.[16] The final step requires pyruvate kinase (PK), which exists as several isoforms, notably PKM1 and PKM2.[17] In the presence of oxygen, pyruvate is usually converted to Acetyl CoA, which then enters the Krebs cycle, forming electron donors for OXPHOS, generating approximately 32 net ATP molecules.[18] When oxygen is scarce or falls short of demand, pyruvate is shunted away from OXPHOS and gets converted into lactate by lactate dehydrogenase (LDH) to regenerate nicotinamide adenine dinucleotide (NAD+).[18,19] Each of the steps within the glycolytic pathway is catalysed by a specific enzyme or enzyme complex. [15] Some of these enzymes may have a role in transcription regulation, cell motility and apoptosis regulation.[20-22]

In tumours, proliferating tissue, and the mammalian retina, conversion of pyruvate to lactate occurs despite the presence of oxygen.[1,6,23] This is the so-called Warburg

effect. The biological drive that causes tumours and some other non-neoplastic cells to apparently forsake optimal ATP production remains somewhat speculative. Warburg initially hypothesised that the reliance on the glycolytic metabolism was secondary to development of mitochondrial defects within cancer cells, which impaired OXPHOS.[1] Albeit plausible, this hypothesis was rejected when subsequent studies demonstrated normal functioning mitochondria in most cancer cells.[24,25] A more tenable explanation for the existence of the Warburg effect concerns the biosynthetic requirements of proliferating cells.

The metabolic requirements of tumour and proliferating cells

Vander Heiden *et al*. publishing in *Science*, summarized a widely-accepted explanation for the existence of the Warburg effect in cancer. [10] In proliferating cells, glucose not only produces ATP, but also provides metabolic intermediates for biosynthesis **(Fig. 1)**.[10] Intracellular glucose can also be directed towards biosynthesis: into the pentose phosphate pathway (PPP) to generate nucleotides and NADPH (nicotinamide adenine dinucleotide phosphate, reduced), or to make the amino acids, serine and glycine, branching from glycolysis at phosphoglycerate.[10,26] The enzyme phosphoserine phosphatase (PSPT) is the final step in glucose-serine conversion (**Fig. 1**).[27]

Proliferating cells have the ability to increase glycolytic ATP production under hypoxic conditions, but provided glucose is abundant, in normoxia, they direct metabolic pathways away from OXPHOS towards biomass synthesis. The ability to oscillate between biosynthesis and energy production provides proliferating tissue with a powerful metabolic strategy known as the "metabolic budget system",[28] a

phenomenon which goes hand-in-hand with the Warburg effect **(Fig. 1)**. This strategy can be viewed as the presence of the Warburg effect in a tissue using glucose for biosynthesis.[28] Such a phenomenon, however, has not yet been reported in a non-proliferating tissue, such as the retina.

The metabolic reprogramming

The programming of cellular metabolism involves the interplay of various growth factor signaling pathways.[29,30] Many of these pathways including Jak STAT3,[32] P13K/Akt,[31] mammalian target of rapamycin (mTOR),[32,33] the proto-oncogene and tumor suppressor genes [34,38] have been implicated in the mediation of the Warburg effect. However, the focus has recently converged on pyruvate kinase isoform M2 (PKM2), as well as the hypoxia-inducible factor-1 (HIF-1), as key regulators of the Warburg effect.[35]

HIF-1 is a dimeric transcription factor, comprised of an oxygen regulated alpha subunit (HIF-1α) and a constitutive beta subunit HIF-1b, also known as Arnt), that is essential for driving cellular responses to hypoxia.[36] When oxygen is sufficient, the expression and activity of HIF-1α are inhibited.[37] In hypoxia HIF-1α is stabilised and transcriptionally active; it partners with HIF-1β to transactivate a large set of target genes leading to various changes in cellular processes including the upregulation of glycolysis and the inhibition of OXPHOS. [36,37] Interestingly, HIF-1 has been shown to be active in many cancers, even in normoxia, [37] where it plays a key role in driving the Warburg effect.

Pyruvate kinase (PK) is a glycolytic enzyme which catalyses the conversion of phosphoenolpyruvate (PEP) into pyruvate, generating one molecule of ATP in the rate-limiting final step of glycolysis.[38,39] There are 4 isoforms of pyruvate kinase in mammals: L – liver, R – red blood cell, M1- adult (muscle and brain), M2 – embryonic and tumour.[40] Uniquely, PKM2 has an allosteric pocket not present in the other isoforms, that permits binding to phosphotyrosine peptides and fructose 1,6 biphosphate (FBP).[8,41] This structural configuration renders PKM2 vulnerable to various regulatory inputs. Whilst PKM1 forms a stable, constitutively active tetramer, PKM2 oscillates between the active tetrameric and the inactive dimeric (or monomeric) forms.[28,42] The dimeric form has a low affinity for the substrate PEP, and lower activity than the tetrameric form.[42] When the dimeric form dominates, PEP conversion becomes inefficient, and as a consequence glycolytic intermediates upstream of PEP accumulate and are available for biomass synthesis and cell proliferation.[28] As the glycolytic intermediate, FBP accumulates, the reaction favours conversion of the dimeric form back to the tetrameric form and pyruvate is produced efficiently again. [28,42] These regulations of PKM2, labelled as the "metabolic budget system", are proposed to control the anabolic biosynthesis versus energy production in tumour metabolism.[28] PKM2 activities are also susceptible to other post-translational modifications.[43,44]

Although it was initially assumed that the switch from expression of physiological PKM1 to PKM2 is responsible for the Warburg effect in tumour cells, [8] subsequent experiments demonstrated PKM2 as the predominant pyruvate kinase isoform in both tumour and normal tissues. [4546, 47]. PKM2 was also proposed to act as a co-activator of HIF-1 in the mediation of the Warburg effect in cancer cells, and PKM2 is also a

direct target gene of HIF-1. [9,48]Other experiments have reported non-metabolic functions of PKM2 such as the ability to function as protein kinase, which may confer additional benefits in the promotion of the Warburg effect.[45, 46]

More recent studies however unfolded several sobering findings.[43,49,50] Cortés-Cros *et al* observed that PKM2 knockdown did not affect the growth of established tumour.[49] In addition, the authors highlighted ongoing pyruvate production along with increased serine and glycine biosynthesis in dual PKM1 and PKM2 knockdown tumour cells.[49] One explanation would involve the shunting of accumulated upstream glycolytic intermediates into the serine synthetic pathway, in which serine is produced and subsequently converted into pyruvate.[26] The existence of alternative glycolytic pathways involving not yet characterised enzymes had also been proposed.[51] Israelsen *et al* then reported paradoxical acceleration of tumour growth with the loss of PKM2 in mouse model of breast cancer.[50] Similarly, Anastasiou *et al* demonstrated that high pyruvate kinase activity impedes xenograft tumour growth.[43]

Collectively, these results highlighted two interesting points. Firstly, PKM2 expression is not entirely essential in tumour growth. Secondly, overall high pyruvate kinase activity actually hinders tumour growth. This paradigm in fact fit snugly with the "metabolic budget system", that high pyruvate kinase activity leads to depletion of glycolytic intermediates available for biosynthesis and therefore impairs cellular proliferation and growth. [10, 28,43] Because the activities of PKM2, determined by its conformation in either the highly active tetramer or the inactive dimer, are highly malleable to various regulatory inputs, preferential PKM2 expression confers an

advantageous metabolic flexibility to the differential metabolic needs of proliferating cells and tumours through various proliferative phases.[50]

Mammalian retinal metabolism

Glycolysis in mammalian retina

The retina requires a high level of metabolism even in the resting state, attributable to the continuous energy-demanding processes that are required to maintain the neurons in an excitable state for phototransduction and neurotransmission, in addition to the maintenance of normal cellular function.[52] The initial discovery of the high level of lactate production from explanted retina by Warburg and team sparked the unprecedented impetus for huge interest in the metabolism of mammalian retina.[1] Numerous experiments have subsequently reinforced Warburg's original findings and demonstrated the role and the importance of glycolysis in mammalian retina. [5,52-54]

In year 1951, Noell WK demonstrated the direct dependence of mammalian (rabbits and cats) retina function on glycolysis.[5] The visual functions in these mammals as measured by electroretinogram (ERG), resisted the effect of anoxia but were highly susceptible to iodoacetate inhibition of glycolysis.[5] Iodoacetate is an agent that selectively inhibits glycolysis whilst preserving mitochondrial OXPHOS.[5,53] Loss of electrical activity and selective disappearance of the rod photoreceptor cells were observed following iodoacetate inhibition.[53] In another *in vivo* study, Tornquist and Alm measured the arterio-venous differences in glucose, oxygen and lactate levels for both choroidal and retinal blood in pigs.[55] The data recorded high concentration of

lactate in the venous blood. [55] Additionally, the total amount of oxygen extracted from choroidal and retinal blood flow combined only accounted for complete oxidation of 37% of all the extracted glucose, reflecting the high glycolytic activities. [55] The majority of the glycolytic substrate was derived from the choroidal circulation, indicating greater metabolic activity in the outer retina. [55]

In 1975, Barry Winkler reported the capability of isolated rat retina to support electrical activity in the photoreceptors anaerobically, if significantly high glucose concentrations was provided, a level high enough to sustain maximal lactate production.[56] Of note, the electrical activity was maintained at 80% for 30 minutes of anoxia but inevitably dropped to 40% of the aerobic value when a glucose concentration equivalent to that of rat retina *in vivo* was used.[56] The results clearly showed the reliance of mammalian retina on glycolysis and its high metabolic adaptability whereby it can be driven into "overdrive" glycolytic mode to maintain near normal physiological functions in anoxia, provided that glucose is unlimited. Winkler expanded his experiments in rat retinas to analyse the aerobic versus the anaerobic effect on retinal lactate production, ATP content and electrophysiological recordings.[6] These rat retinas demonstrated an obvious Pasteur effect, whereby increased glycolysis was observed in the anaerobic state, employed to maintain the portion of ATP which is otherwise generated via aerobic OXPHOS.[6] Also perplexing were the findings of disproportionate reduction of lactate production by 50% when glucose concentration was decreased by 80% whilst the ATP level was maintained.[6] Interestingly, both ATP and lactate production plateaued after optimal oxygen and glucose concentrations were reached. [6,57] The paucity in the rise of both ATP and

lactate production might indicate that either the retinal metabolic capacity was exceeded, or the shunting of glucose catabolism into biomass synthesis occurred.

The fact that glycolysis within mammalian retina occurs predominantly in the aerobic setting was substantiated by Wang *et al* which showed the lack of effect from induced hyperoxia in rabbit retina on the lactate production and glucose consumption.[58] In Winkler's elaborate, *in vitro* study of glucose metabolism in both normal and dystrophic rat retinas, 90% of the glucose utilized aerobically was used in glycolysis.[59] Furthermore, an Ames *et al* experiment in isolated rabbit retina documented corresponding changes in the lactate level with neurotransmission, independent of oxygen consumption.[52] The author postulated that neurotransmission through the inner retina was highly dependent on glycolysis. [52]

Higher glycolytic activities in the outer retina

Vast majority of the aerobic glycolysis reportedly takes place in the outer retina, mainly in the photoreceptors.[60-63] Graymore observed a greater than 50% reduction in the glycolytic activities within dystrophic rat retinas lacking photoreceptor cells when compared to normal rat retinas.[60,61] Strong evidence was also described by Wang *et al* who ascertained the glucose consumptions in pig retina *in vivo* by measuring the arteriovenous differences in the glucose concentrations.[62,63] The inner retina metabolised 21% of glucose via glycolysis, and 69% via oxidative metabolism in contrast to the outer retina which metabolised 61% of glucose via glycolysis and only 12% via oxidative metabolism. [62,63] These results are consistent with the differential oxygen consumption reported in mammalian retina. [64-66] The deep inner plexiform

layer, the outer plexiform layer and the inner segments of photoreceptor have much higher oxygen consumptions as opposed to the outer segments of the photoreceptors and the outer nuclear layers in vascularized mammalian retina.[64-66]

Relative contribution of glycolysis versus OXPHOS in relation to retinal functioning

All metabolic evidence for the Warburg effect in the retina comes from experiments on whole retinas, with no discrimination between the different retinal layers. [5,52-54] For these reasons, it has been fairly difficult to correlate the retinal metabolism to the cellular processes, and the exact contribution of glycolysis versus OXPHOS in retinal functioning remains estimative. Variations also exist across different mammalian species and with different experimental designs. [52,54,62,67] Reported contributions of aerobic glycolysis to retinal glucose metabolism range from 40-80% in rabbit,[52,54] 60% in pig, [65] 90% in rat,[59] to 99% in cultured human retinal Müller cells.[71]

The highly glycolytic mammalian retina also confers protection against short-term anoxia, through upregulation of glycolysis, provided that glucose is abundant.[5,6,53,56] Noell demonstrated that retinal ganglion cells (RGCs) are susceptible to hypoxia and are the "weakest link in the chain" of visual perception when oxygen is scarce.[68] The neuroprotective effect of glucose was supported by our previous research which indicated that an elevated vitreal glucose level at the time of acute[69] or chronic retinal ischaemia[70] or experimental glaucoma[71] provides robust protection to the RGCs. We recently demonstrated that, *in vitro*, this is predominantly due to glycolytic ATP production.[72] The protective effect is abolished if the vitreous glucose is elevated post ischaemia.[73] These results suggest that the RGCs can upregulate glycolysis during ischaemia to generate ATP (the Pasteur effect). Winkler *et al*. attempted to determine

whether cultured RGCs displayed the Pasteur effect,[74] but unfortunately their methodology was flawed because they used an RGC-5 cell line, which was later recognized to be of photoreceptor origin.[75,76] Hence, information about the Pasteur effect in RGCs remains incomplete.

Nevertheless, experimental evidences have indicated that neither OXPHOS nor glycolysis are dispensable for optimal retinal metabolism and functioning.[6,52] The essentiality of mitochondrial OXPHOS in mammalian retina functioning is seen in retinitis pigmentosa model.[77] The *IDH3B* gene encodes for the B-subunit of NAD-specific isocitrate dehydrogenase (NAD-IDH) which is required to catalyse the oxidation of isocitrate to alpha-ketoglutarate in the citric acid cycle of mitochondrial OXPHOS. *IDH3B* mutations in familial retinitis pigmentosa result in the impairment of mitochondrial OXPHOS. This may, in part, contribute to progressive rod and cone photoreceptor degeneration, characteristic of the disease.[77] The notion of mitochondrial dysfunction and associated oxidative stress in retinitis pigmentosa is also supported by other experiments.[78-80]

Explanation for the Warburg effect in mammalian retina

We have recently published a teleological explanation for the presence of the Warburg effect in the mammalian retina: Even though the adult mammalian retina is non-proliferative, it shares similar biosynthesis requirements to neoplastic tissue due to the prodigious turnover of the opsin protein in the disc membranes of the photoreceptor outer segments.[11] Each mammalian rod outer segment (ROS) consists of a stack of ~1500 distinct discs enclosed by the plasma membrane.[81,82] Approximately 60% of the dry weight of the disc membrane is protein, and opsin

comprises 90% of the protein content.[83] Hence, rhodopsin forms a large structural component of the rod disc membrane. Rhodopsin, retinal-bound opsin, is a G protein-coupled receptor comprising 348 amino acids, with a rich glycine and serine component.[84]

In a landmark experiment using radioactively labelled methionine and radioautography tracing, Richard Young showed that rhodopsin was constantly renewed as the disc membranes moved in a sclerad direction along the ROS towards the retinal pigment epithelium in mouse, rat and frog retinas. [85] The rhodopsin turnover rate as measured by the position of radioactive band displacement, was notably faster in rats than in frogs. [85] Thus, the reason that the Warburg effect has evolved in the mammalian retina is simply because it has similar metabolic requirements to a proliferating tissue, owing to the constant rhodopsin turnover. The rhodopsin turnover rate parallels the degree of aerobic glycolysis found in different species.[85] Furthermore, the relatively low rate of photoreceptor turnover in lower vertebrates is temperature dependent, increasing at higher temperatures,[85] reflecting the temperature-dependent Warburg effect. [4]

Also in accordance to this postulation, was the observation by Agathocleus *et al* which reported facultative aerobic glycolytic nature of developing *Xenopus laevis* frog and zebrafish retinas, to match the biosynthetic requirements.[86] Glycolysis inhibition resulted in cellular apoptosis but OXPHOS interference had no deleterious consequence.[86] Nevertheless, a switch to greater reliance of OXPHOS was noted in mature retina.[86]

An alternate hypothesis to the high glycolytic process in the photoreceptors may involve the highly compartmentalized cellular configurations, with the confinement of mitochondria to the inner segment, while absent from the outer segment. [82,87] The dense aggregation of mitochondria in the ellipsoid region of the inner segment reflects the considerable reliance of this portion on oxidative energy.[87-89] Supporting this was the finding of high concentration of malate dehydrogenase (an enzyme involved in OXPHOS) in the monkey photoreceptor inner segment, 30 times higher than that in the outer segment.[90] On the contrary, measured LDH was significantly lower in the inner segment as compared to the outer segment. [90] The exclusion of mitochondria from the photoreceptor outer segment possibly necessitates its reliance on glycolysis for cellular energy.[90]

Aerobic glycolysis and lactate from Müller Cells

In addition to the biosynthetic requirements of the photoreceptors, aerobic glycolysis and lactate production from Müller cell cultures has also been described. [67] The Müller cells are the predominant glial cells of the retina, and have been proposed as the primary storage sites for glycogen.[91] The human Müller cells (HMC) metabolize glucose primarily via aerobic glycolysis, accounting for 99% of total glucose metabolism and the remaining 1% undergoes mitochondrial OXPHOS.[67] This observation is consistent with the so-called astrocyte neuronal lactate shuttle hypothesis (ANLSH) in the brain.[92] The ANLSH asserts that brain neurones use astrocyte-derived lactate as a primary energy source and that the delivery of lactate is calibrated by neuronal activity.[92] There is evidence for and against this hypothesis and the matter remains highly controversial.[93] Conceivably, a similar phenomenon exists in the retina with the Müller cells taking the place of the astrocytes.

Experimental findings also unveiled the multipotent differentiative capability of the adult HMC, whereby it can undergo differentiation into retinal neurons, astrocytes, oligodendrocytes[94] and also rod photoreceptors.[95] Reportedly, the differentiation into rod photoreceptors is six-fold faster than conventional pluripotent stem cells. [95] The unique capability of adult HMC to proliferate and differentiate likely explains its inherent metabolic preference for aerobic glycolysis, which is better suited for this role. Recent evidence indicates that Müller cell ablation in a transgenic model causes photoreceptor degeneration related to loss of neurotrophic support.[96] Whether the mechanisms driving lactate production in Müller cell cultures also involve PKM2 is completely unknown.

Lactate dehydrogenase in cancer and the retina

Lactate dehydrogenase (LDH) is a tetrameric enzyme comprising two major subunits A and/or B, (encoded by the *Ldh-A* and *Ldh-B* genes) resulting in five isoenzymes (A4, A3B1, A2B2, A1B3, and B4) that catalyse the forward and backward conversion of pyruvate to lactate. LDHA (LDH-5, M-LDH, or A4), which is the predominant form in skeletal muscle, kinetically favours the conversion of pyruvate to lactate.[97,98] LDHB (LDH-1, H-LDH, or B4), which is found in heart muscle, converts lactate to pyruvate that is further oxidized in mitochondria.[97,98] Cancers also utilize the LDHA form, (even when oxygen is abundant); hence, the quantification of LDHA in cancer has become a routine surrogate marker of the Warburg effect, providing diagnostic and prognostic clinical information.[99]

The mammalian retina also expresses relatively high levels of LDHA, typical of a tumour.[100-102] *Saavedra et al* reported the exceptionally high amount of LDH_k (synonymous with LDH-5) activity in rat, mouse, guinea pig retina, equivalent to the level measured in human cancer cells.[101,102] Lower vertebrates such as turtle, toad and frog that do not display the Warburg effect, have correspondingly much lower LDH-5 activities.[102] Graymore, publishing in *Nature* in 1964, noted that the expression of the LDHA isoenzyme in the retina was reduced in rats with inherited "retinitis pigmentosa", characterized pathologically by loss of the photoreceptors.[100] This observation indicated that the photoreceptors were principally responsible for the retinal lactate production and also supported evidence that the photoreceptors were particularly susceptible to glycolytic inhibition.[5]

PKM2 and HIF-1α in mammalian retina

We have recently found an evidence for the presence of PKM2 and constitutive expression of low level HIF-1α in the rat retina (unpublished data). *Hughes et al* have earlier reported the presence of stabilized HIF-1α in normal physiological human and rat retinas.[103]. The presence of PKM2 in mouse retina was demonstrated by Morohoshi *et al* using purified IgG specific for the M2 isoform from individuals with age-related macular degeneration (ARMD).[104] The authors proposed that PKM2 may correlate with the severity and progression of ARMD.[104] Conceivably, the presence of PKM2 antibodies in ARMD has a causal relation but, to our knowledge, remains untested. These important findings of the coexpression of PKM2 and HIF-1α in normal mammalian retina suggest that these molecular factors likely play a role in driving the Warburg effect in this tissue in a similar manner to how they do in cancer.

Anti cancer therapy targeting glycolysis and the Warburg effect

Advances in the understanding of the molecular mechanism of the Warburg effect in cancer have motivated countless efforts to develop targeted therapies as novel cancer treatment.[105-113] Variable successes have been reported with PKM2 modulation *in vitro* and *in vivo* animal studies. [43,50,111-113] Besides targeting PKM2, many other drugs that target different stages of glycolysis are also under preclinical development. [105-110] However, the extent of toxicities of these drugs towards normal, metabolically active tissues utilizing glycolysis in humans is largely unknown.

The obligatory reliance of mammalian retinal metabolism and functioning on glycolysis as highlighted in this review raises a huge concern on the potential toxicities of these therapies towards the retina, especially the photoreceptors. Any disruption to the key metabolic pathway essential for physiological maintenance of continuous photoreceptor renewal, energy production, phototransduction and neurotransmission will likely result in significant cellular disturbance or irreversible cell death within the retina. Also, the key aspects of the molecular mechanism underlying the Warburg effect are likely conserved between the retina and cancer.[114]

Ongoing research endeavours are therefore vital to continue to fill the gaps in our knowledge and guide us towards a better understanding of retina biology and metabolism. Such progresses may hopefully lead to breakthrough findings in the treatment of various retinal diseases and also aid clinicians to predict the potential adverse effects to the retina of cancer treatments targeting the Warburg effect. At the

same time, the notion of targeting the Warburg effect and PKM2 as a therapeutic strategy for cancer should proceed cautiously.

Figure 1

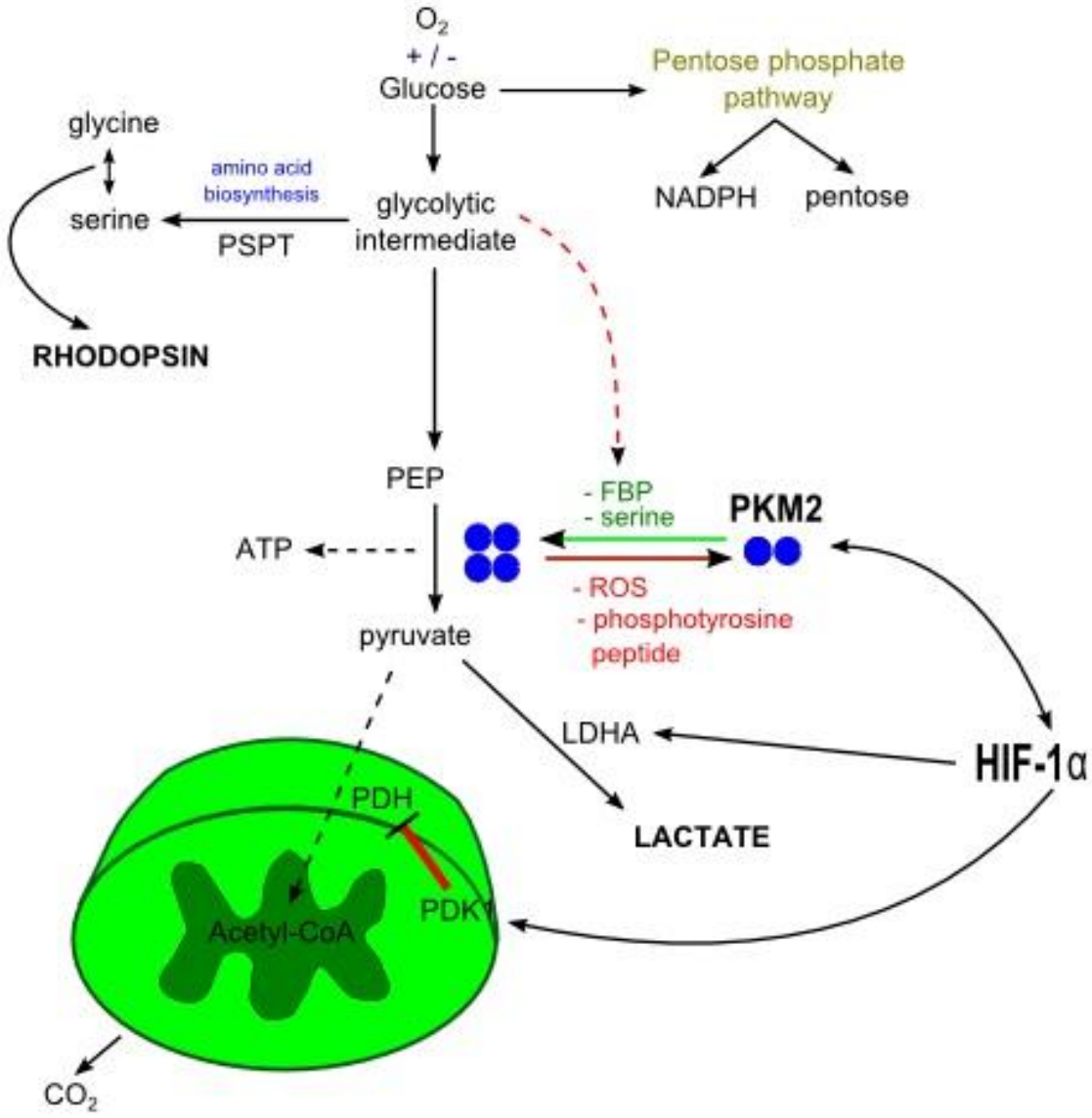

Fig. 1 Metabolic budget system and the Warburg effect. PKM2 exists as an active tetrameric form and an inactive dimeric form. Its transition is found to be regulated by fructose 1,6 biphosphate, serine, reactive oxygen species and phosphotyrosine peptide. PKM2 is also a co-activator and a target gene of HIF-1α. We propose that glucose-derived amino acids are required for rhodopsin synthesis, and that the Warburg effect is HIF-dependent.
PPP = pentose phosphate pathway; PEP = phosphoenolpyruvate
PKM2 = pyruvate kinase M2; HIF-1α = hypoxia-inducible factor-1alpha; LDHA = lactate dehydrogenase A; PDH = pyruvate dehydrogenase; PDK1 = pyruvate dehydrogenase kinase 1; PSPT = phosphoserine phosphatase; FBP = fructose 1,6 biphosphate; ROS = reactive oxygen species.

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