Short Conceptual Overview

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Adaptive regulation of glucose transport, glycolysis and respiration for cell proliferation

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Abstract: The cell must utilise nutrients to generate energy as a means of sustaining its life. As the environment is not necessarily abundant in nutrients and oxygen, the cell must be able to regulate energy metabolism to adapt to changes in extracellular and intracellular conditions. Recently, several key regulators of energy metabolism have been reported. This review describes the recent advances in molecular regulation of energy metabolism, focusing mainly on glycolysis and its shunt pathways. Human diseases, such as cancer and neurodegenerative disorders, are also discussed in relation to failure of energy metabolism regulation.

Keywords: cancer; energy metabolism; glucose; glycolysis; mitochondria; neurodegenerative disorder.

Introduction

Living organisms must continuously generate energy from food for maintenance of their life and to allow proliferation. We can utilise glucose, fatty acids and amino acids to generate adenosine triphosphate (ATP). Glucose is the primary source of energy and carbon for most eukaryotes, including humans. Due to its polar nature, glucose cannot pass through the lipid bilayer of the plasma membrane. Therefore, glucose must be transported into the cell via the glucose transporter on the plasma membrane. Following its uptake, glucose is phosphorylated by hexokinase to produce glucose 6-phosphate, whose negative charge prevents diffusion of glucose out of the cell. Glucose 6-phosphate is processed by a chain of glycolytic enzymes to generate pyruvate as the major product (1). In an aerobic environment, pyruvate is then metabolised into acetyl coenzyme A that enters the tricarboxylic acid (TCA) cycle occurring in the mitochondrial matrix. In the TCA cycle, a set of enzymes generates the reduced form of nicotinamide adenine dinucleotide (NADH), protons (H^+), and CO_2. NADH, H^+ and O_2 are then used by the mitochondrial respiration complexes (Complex I – IV) to generate a proton gradient across the mitochondrial inner membrane. ATP synthase (Complex V) generates ATP from ADP and inorganic phosphate by utilising this proton gradient. In this way, the cell uses glucose as an efficient energy source, with a theoretical yield of up to 38 ATP molecules per glucose molecule. As energy metabolism is critical for cellular functions and survival, its activity is regulated by multiple pathways to accommodate environmental changes (e.g. extracellular glucose and oxygen levels) (2). In addition, glycolysis has several branch pathways to synthesise nucleic acids, amino acids and polysaccharides, which are used as building blocks or for energy storage for mother and daughter cells (1). Thus, glucose metabolism plays a critical role in cellular functions and survival. This article presents a review of recent studies on energy metabolism with a focus on regulation of glucose metabolism, and its relationship with human diseases, such as diabetes, cancer and neurodegeneration. Based on recent studies, we argue that understanding and controlling glucose metabolism will represent unique avenues to alleviate or prevent some human diseases.

Regulation of glucose transport

Glucose transport across the plasma membrane is the most upstream and one of the most important processes in cellular glucose metabolism. The glucose transporter facilitates movement of glucose across the membrane (3), and thus glucose flux is controlled by regulation of glucose transporters. Our recent study using the fission yeast *Schizosaccharomyces pombe* as a model demonstrated

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that two evolutionarily conserved intracellular signalling pathways, the CaMKK (Ca^{2+}/calmodulin-dependent kinase kinase) and the TORC2 (target of rapamycin kinase complex 2) pathways, play central roles in regulation of glucose/hexose transporters in response to changes in extracellular glucose concentrations (Figure 1) (4).

Cell culture in higher-than-normal glucose media or changing the glucose level of culture media would be a straightforward approach to study cellular responses and the molecular mechanisms of hyperglycaemia. When wild-type fission yeast cells are transferred from high-glucose medium containing 2% (111 mM) glucose, in which they are normally cultivated in laboratories, to low-glucose medium containing 0.08% (4.4 mM) glucose, which is equivalent to the normal glucose level in human blood, the abundance and distribution of glucose transporters on the cell membrane show marked changes (Figure 1). The CaMKK and TORC2 pathways regulate the transcription of glucose transporter genes and the trafficking of their gene products to the cell membrane, respectively. These distinct phosphorylation-mediated signalling pathways are known to play critical roles in supporting proliferation of fission yeast cells in low-glucose environments (4–6); the CaMKK and the Sds23 protein, a negative regulator of type 2A-like protein phosphatases, function synergistically to enable vigorous cell proliferation under low-glucose conditions, while TORC2 is required for control of cell size upon reduction of extracellular glucose levels. Among eight putative glucose/hexose transporters (Ght1–Ght8) (7, 8), we found that Ght5, a high-affinity hexose transporter, was necessary and sufficient for proliferation in low-glucose media. Although Ght5 was already expressed at high levels under high-glucose conditions, its expression level was further increased by shifting the cells to the low-glucose medium, ensuring sufficient glucose uptake in glucose-limited environments. Interestingly, Sds23, Ssp1 (a fission yeast CaMKK) and Tor1 (the catalytic subunit of TORC2) were found to play critical roles in regulating Ght5 protein expression and localisation. When the concentration of glucose in medium is reduced, a transcriptional repressor, Scr1, which represses *ght5*$^+$ transcription under high-glucose conditions, is translocated from the nucleus to the cytoplasm in a manner dependent on Ssp1/CaMKK and Sds23, so that expression of the *ght5*$^+$ gene is derepressed (Figure 1). Proper localisation of the newly synthesised Ght5 transporter to the cell membrane requires the functional TORC2 signalling pathway consisting of Tor1, Ste20/Rictor, Gad8/Akt and Ksg1/PDK1 (phosphoinositide-dependent kinase 1) (9–13); Ght5 was accumulated in the cytoplasm in mutant cells defective in each of these proteins. The primary discoveries of the article (4) are that large-scale remodelling occurs in the control of glucose transport, metabolism and cell division in response to changes in the environmental glucose concentrations, and that such remodelling is governed by calcium-, phosphatase- and TOR kinase-mediated signalling cascades. Proteomic and metabolomic studies of fission yeast cells under low-glucose conditions may provide further insights into cellular remodelling for adaptation to glucose restriction.

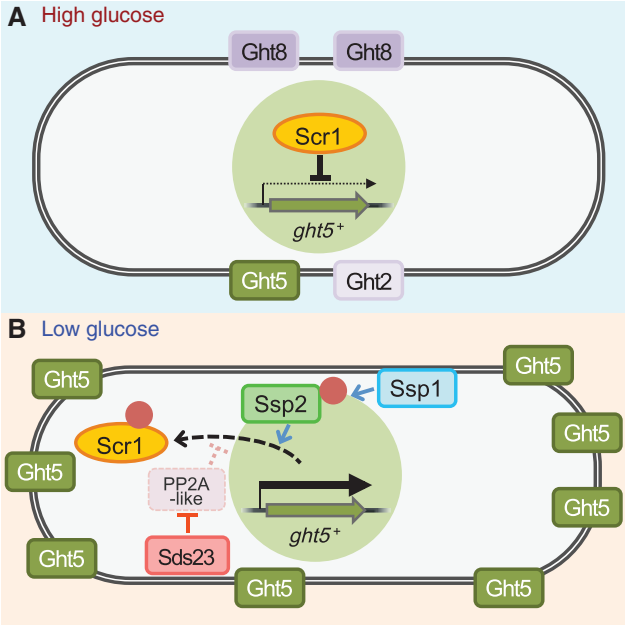

Figure 1: Model of the mechanism underlying regulation of glucose transporter Ght5.
Schematic illustrations of the proposed mechanisms underlying regulation of expression of the fission yeast glucose transporter Ght5. (A) Under high-glucose conditions, transcription of the *ght5*$^+$ gene is repressed by Scr1. Ght5, Ght2 and Ght8 transporters are targeted to the middle of the cell. (B) In a glucose-limited environment, Scr1 is sequestered from the nucleus to the cytoplasm in a manner dependent on Ssp1/CaMKK and Ssp2/AMPK-related kinases. Type 2A protein phosphatase (PP2A) and Sds23 regulate translocation of Scr1. Transcription of *ght5*$^+$ is then derepressed. Ght5 protein shows distinct localisation to the cell tip under glucose-limited conditions. See main text and the reference (4) for details.

It should be noted that there is an interesting similarity between fission yeast and humans in regulation of the hexose transporter function in response to extracellular glucose levels. Expression and localisation of the GLUT4/SLC2A4 hexose transporter on the plasma membrane in mammalian skeletal muscle cells are regulated by insulin-dependent and -independent pathways (14, 15). In these cells, upon insulin stimulation, cytoplasmic vesicles containing GLUT4 are transported to the plasma membrane by exocytosis, mediated by Akt, TORC2 and PDK1

kinases (16–19). Independent of insulin, contractile activity upregulates GLUT4 transcription by the Ca^{2+} signalling pathway, which may involve CaMKK, CaMK and adenosine monophosphate-activated protein kinase (AMPK) (20–22). As mentioned above, these molecules also regulate the Ght5 transporter in fission yeast and are required for proliferation in low-glucose medium (4–6), with glucose level comparable to that in human blood. Thus, although fission yeast does not produce insulin (23), we propose that fission yeast is an attractive model system in which to study the molecular mechanisms involved in responding to changes in glucose levels in cellular environments.

Regulations of glycolytic enzymes and their alterations in cancer

Enhanced glycolysis, referred to as the Warburg effect (24), and cellular immortalisation are hallmarks of cancer (25–27). Previously, Kondoh and colleagues identified the glycolytic enzyme phosphoglycerate mutase (PGM), which converts 3-phosphoglycerate to 2-phosphoglycerate, in an unbiased screen for genes that can immortalise mouse embryonic fibroblasts (MEFs) (27). Twofold enhancement of PGM expression made the MEFs immortal, like MEFs transfected with the p53 dominant-negative transgene. The protein level and activity of PGM were found to be negatively regulated by p53. Consistent with these observations, glycolysis enhancement by the dominant negative p53 and PGM transgenes protected the cells from oxidative stress and premature senescence induced by the *ras* oncogene. Taken together, these findings indicated that PGM is the key glycolytic enzyme that can determine the glycolytic activity and cell fate, i.e. senescence or immortalisation (27). Consistent with this indication, PGM was recently found to stimulate tumour formation by decreasing 3-phosphoglycerate, which inhibited biosynthesis via a glycolytic shunt of the pentose phosphate pathway (PPP) (28). Uncovering a mechanism regulating PGM abundance may, therefore, provide insight into the Warburg effect and tumour formation.

A recent study on the relationship of glycolysis regulation and tumour formation revealed the molecular mechanisms of PGM stability as well as its effect on cancerous transformation (29). In this study, p21 (Cdc42/Rac1)-activated kinase 1 (Pak1) was demonstrated to phosphorylate Ser118 of PGM, and this phosphorylation, in turn, was shown to promote polyubiquitination of PGM by the ubiquitin protein ligase (E3) Mdm2 for degradation by the 26S proteasome in MEF cells. Mdm2 functions downstream of p53 and destabilises p53 by polyubiquitination, forming a negative feedback loop (30). Activation of p53 during senescence promoted Mdm2-mediated degradation of PGM, and consequently downregulated glycolytic flux. Taken together, these findings suggest that Mdm2 and p53 may suppress tumorigenesis by downregulation of glycolysis via promotion of the ubiquitin/proteasome-mediated degradation of PGM, a key regulator of cell fate and glucose metabolism (29).

Consistent with the above suggestion, the tumour suppressor p53 was reported to have additional roles in glucose metabolism, as well as the established roles in DNA damage response, apoptosis and cell cycle regulation (31); under conditions of stress, activated p53 induces the expression of an evolutionarily conserved gene, TIGAR (TP53-induced glycolysis and apoptosis regulator) in wild type p53-expressing cell lines such as U2OS and RKO (32). TIGAR, which possesses fructose-2,6-bisphosphatase activity, functions through the PPP shunt to lower fructose-2,6-bisphosphate levels in cells, and consequently to decrease the levels of cellular reactive oxygen species (ROS), which generate proapoptotic stress. p53 was also suggested to reduce the expression level of the GLUT3/SLC2A3 glucose transporter and glucose consumption under aerobic conditions to prevent transformation of MEF cells (33). In summary, p53 controls the glucose metabolism pathways via modulating the stability of the glycolytic enzyme, PGM and expression of the fructose-2,6-bisphosphatase TIGAR and the GLUT3 transporter (29, 32, 33). Considering a wide range of functions of p53 in cellular processes, it is reasonable that more than half of all malignant cancers show a defect in p53 (34, 35).

It should be noted that enhanced aerobic glycolysis is observed also in normal, non-cancerous, cells involved in the immune system, such as monocytes, macrophages and T-helper 17 cells (36, 37). In human primary monocytes exposed to β-glucan, which induces trained innate immune memory, expression of glycolytic enzymes increases in a manner dependent on the mTOR and HIF-1α signalling pathway (36). A metabolic shift towards aerobic glycolysis is supposedly important for rapid cell proliferation (1).

Role of Parkinson's disease-associated DJ-1 in metabolism

Alterations in metabolism are associated with many of common diseases, including diabetes and cancer. A number of long-term studies indicated better prognosis

of cancer patients taking metformin, a medication for diabetes that inhibits mitochondrial Complex I (38–41). Neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, have also been suggested to be associated with alterations in metabolism (42, 43). It is known that patients with some types of cancer have reduced incidence rates of Parkinson's disease (44, 45). Similarly, an inverse relation between cancer and Alzheimer's disease was reported, showing a 33% lower risk of developing Alzheimer's disease among survivors of cancer (46). Therefore, defects or alterations in metabolism accompanying these neurodegenerative diseases and cancer may somehow antagonise each other. The relationship between energy metabolism and Parkinson's disease is discussed below.

Parkinson's disease is caused by a decline of dopaminergic neurons from the *substantia nigra*, a region deep within the brain (47). Difficulties in motion, including tremor, slow movement and rigidity, are the major symptoms of Parkinson's disease. Parkinson's-associated genes (PARK loci) have been found by genetic studies of relatively rare familial Parkinson's disease as well as large-scale studies (47). Surprisingly, a number of these genes are linked to mitochondrial activity, the centres for energy production through aerobic glucose catabolism (48); these genes include PTEN-induced putative kinase (PINK1/PARK6), an E3 ubiquitin ligase Parkin/PARK2 (49–51), LRRK2/PARK8 kinase controlling mitochondrial dynamics (52) and DJ-1/PARK7. Deficiency in DJ-1/PARK7, which causes early-onset Parkinson's disease, was reported to lead to abnormal mitochondrial morphology and dynamics, increased sensitivity to oxidative stress and impaired mitochondrial function (53–57). Functions of DJ-1 are further described below, as this protein can be viewed as a unique coordinator of glucose metabolism, mitochondrial function and Parkinson's disease.

DJ-1 is a relatively small protein (189 amino acids) that is evolutionarily conserved from bacteria to mammals (53, 58, 59), and was originally identified as an oncogene that markedly increased transformation ability of the *ras* oncogene in mouse NIH3T3 cells (60). Several studies have indicated that DJ-1 antagonises the tumour suppressor PTEN (Phosphatase and Tensin Homologue Deleted from Chromosome 10), and activates the phosphatidylinositol-3′ kinase (PI3K) signalling cascade that promotes cell growth and cell cycle progression (61–64). DJ-1 is upregulated under conditions of stress, such as oxidative stress, low oxygen, hyperglycaemia and aging, to support cell survival (64–68). In addition to the proliferation-stimulating functions, DJ-1 was recently reported to have glyoxalase activity (Figure 2) (69). In glycolysis, aldolase catalyses

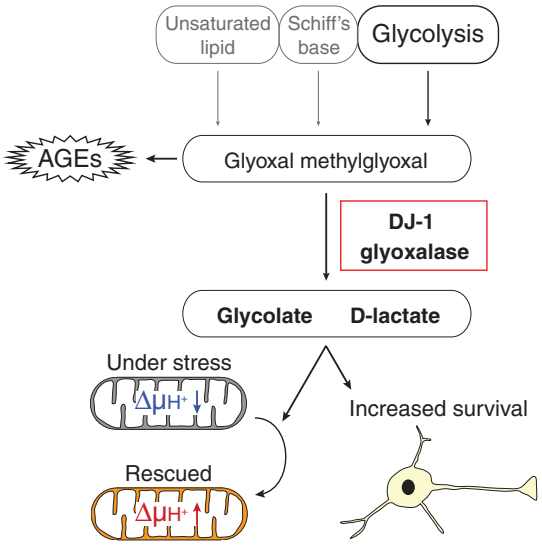

Figure 2: Novel role of glycolic acid and D-lactic acid produced by the DJ-1 glyoxalase.
A schematic illustration of production and effects of glycolic acid (GA) and D-lactic acid (DL) produced by the DJ-1 glyoxalase is shown. Aggressive aldehydes, glyoxal and methylglyoxal, generated by a glycolytic shunt and peroxidation of lipids, covalently bind to biomolecules to produce advanced glycation end-products (AGEs) implicated in a wide range of diseases. GA and DL produced from these aldehydes by the DJ-1 glyoxalase restore the reduced mitochondrial membrane potential caused by downregulation of DJ-1 and PINK1 and environmental stress such as paraquat. GA and DL also increase *in vitro* survival of mouse primary dopaminergic neurons. See main text and the reference (75) for details.

production of dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3-phosphate (GAP) from one molecule of fructose-2,6-bisphosphate. While most GAP is further metabolised rapidly, presumably because of the high level of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) expression (70), a small fraction (~0.1%–1%) of triose phosphate is converted to methylglyoxal (71, 72). Methylglyoxal and glyoxal, the aggressive 2-oxoaldehyde species, can bind covalently to proteins, nucleic acids and lipids, forming advanced glycation end-products (AGEs) that have been implicated in a wide range of human diseases, including cancer, diabetes and neurodegenerative disorders (73, 74). DJ-1 was found to function as GLO III class of glyoxalase (69, 75), which converts these reactive molecules into safer molecules, D-lactic acid (DL) and glycolic acid (GA) without the need for a cofactor (Figure 2) (76). Although DL and GA have been considered as physiologically inactive substances produced during detoxification of glyoxal and methylglyoxal, these molecules were found to play important roles in maintenance of mitochondrial fitness and viability of dopaminergic neurons (77).

In the study reported by Toyoda et al. (2014), a defect in DJ-1 glyoxalase was shown to decrease mitochondrial membrane potential in *Caenorhabditis elegans* larvae as well as cultured human cells. Notably, the decreased mitochondrial membrane potential due to DJ-1 deficiency was restored by the addition of DL and GA, but not by L-lactate (LL) (77). Mitochondrial defects caused by knockdown of the PINK1 gene (78) or treatment with Paraquat (*N*,*N*′-dimethyl-4,4′-bipyridinium dichloride, PQ^{2+}), which was used as a pesticide and impairs mitochondrial respiration (79–81), were also restored by DL and GA, but not by LL, in HeLa cells. Furthermore, GA and DL, but not LL, were shown to increase *in vitro* viability of primary dopaminergic neurons isolated from both wild-type and DJ-1 mutant mouse embryos, and their resistance against low-level administration of PQ^{2+} (Figure 2) (77). Taken together, these findings demonstrate unexpected roles of DL and GA, the products of DJ-1 and glyoxalases, in protection of mitochondrial function and the dopaminergic neurons from genetic and environmental stresses (Figure 2) (77). Importantly, DL is naturally produced at a branch pathway from glycolysis (see Figure 2) (72). Therefore, the Parkinson's disease-related DJ-1 functionally connects glucose metabolism and mitochondrial activities. A decline in mitochondrial activity, represented by mitochondrial membrane potential, is associated with many diseases, including Parkinson's disease and Alzheimer's disease (82). While it remains to be clarified how GA and DL affect mitochondria, these substances that occur naturally (e.g. DL in yoghurt) may have a general role in protecting cells from decline.

Conclusion

In this article we have reviewed cellular strategies to adapt to changes in environmental levels and/or cellular requirements for glucose. The rates of glucose metabolism appear to be tightly regulated via evolutionarily conserved signalling cascades, including calcium- and phosphorylation-mediated pathways, to produce appropriate levels of ATP and glycolytic metabolites. Failure in this regulation may cause a wide range of human diseases, such as diabetes, cancer and Parkinson's disease. While the large number of proteins involved in the complicated circuits of glucose/energy metabolism are well known, the molecular mechanisms regulating the activities of these proteins remain largely unclear. Systematic studies are necessary to identify more regulators of energy metabolism. Determination of the metabolic functions of disease-associated genes as well as a better understanding of the molecular mechanisms of energy metabolism will provide insights to control metabolism-related diseases.

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List of abbreviations

AGEs	advanced glycation end-products
AMPK	adenosine monophosphate-activated protein kinase
CaMKK	Ca^{2+}/calmodulin-dependent kinase kinase
DHAP	dihydroxyacetone phosphate
GAP	glyceraldehyde 3-phosphate
GAPDH	GAP dehydrogenase
MEF	mouse embryonic fibroblast
TIGAR	TP53-induced glycolysis and apoptosis regulator
PDK1	phosphoinositide-dependent kinase
PGM	phosphoglycerate mutase
PP2A	type 2A protein phosphatase
PPP	pentose phosphate pathway
PQ^{2+}	paraquat / *N*,*N*′-dimethyl-4,4′-bipyridinium dichloride
TORC2	target of rapamycin kinase complex 2
PINK1	PTEN-induced putative kinase
PTEN	phosphatase and tensin homolog deleted from chromosome 10
DL	D-lactate
LL	L-lactate
GA	glycolic acid

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