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Metabolic and non-metabolic roles of pyruvate kinase M2 isoform in retinal rod photoreceptor cells

Glucose is the main source of fuel for every living cell. Normal cells take up glucose and burn it in the mitochondria (oxidative phosphorylation) for energy production (ATP synthesis). Rapidly dividing cells, such as cancer cells, and fetal tissues redirect glucose to make (synthesize) biomolecules, such as protein, lipid, RNA, and DNA. The use of energy to build molecules is called an "anabolic process" and is needed for cell growth. Interestingly, retinal photoreceptors (cells that respond to light) do not divide, yet use large amounts of glucose for anabolic processes. Normally, in the presence of oxygen, more than 85 percent of glucose is converted to pyruvate (aerobic glycolysis) and enters the mitochondria for oxidative phosphorylation. The net result is ATP (energy) production. In the absence of oxygen, glucose is converted to lactic acid (anaerobic glycolysis) (Fig. 1).

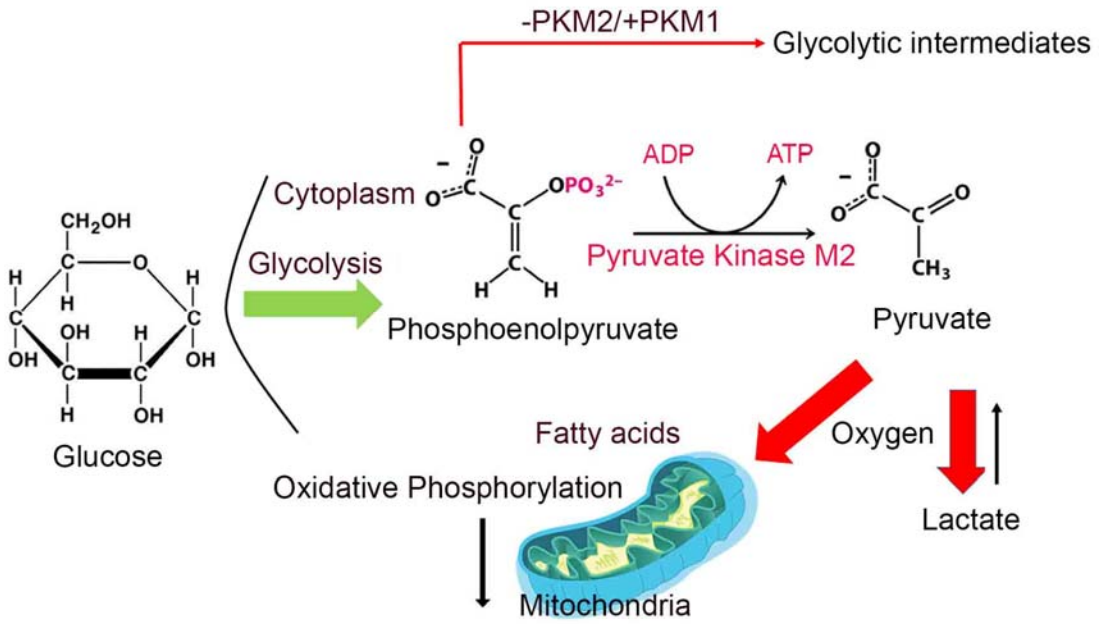

Fig. 1. Pyruvate kinase M2 isoform regulates photoreceptor structure and function and viability. Photoreceptor cells exhibit the Warburg effect. The absence of PKM2 resulted in the accumulation of glycolytic intermediates. Lack of PKM2 leads to slow cell death, with a significant loss of function. Our study showed that PKM1 is unable to fully complement PKM2 and fatty acid β-oxidation might be involved in providing energy to photoreceptors to meet the demand in the absence of glucose utilization.

However, both tumor cells and retinal cells convert glucose to lactic acid in the presence of oxygen. A German scientist, Otto Heinrich Warburg, observed this effect. Thus, the phenomenon is called the "Warburg effect". Vertebrate photoreceptors, like cancer cells and cells in other tissues that rely on active growth, use a specific isoform of pyruvate kinase, PKM2, which promotes the Warburg effect (Fig. 1). Cells also express PKM1, which does not support the Warburg effect. PKM2

suppresses the expression of PKM1 gene transcription (making a copy of a gene sequence). We and others believe that retinal photoreceptors require the Warburg effect for anabolic processes to support photoreceptor structure and function. Loss of photoreceptor structure and function is a hallmark of retinal degenerative diseases. Furthermore, the Warburg effect increases glycolytic intermediates (substances created when glucose is broken down) needed for anabolic processes. In rapidly growing tumors, replacing PKM2 with PKM1 reverses cancer progression. Retinal photoreceptor cells express PKM2 as the major enzyme; deletion of this enzyme from photoreceptor cells produces a marked increase in PKM1 protein. However, increased PKM1 does not promote glycolysis in photoreceptors in the absence of PKM2, a unique finding that differs from tumor cells.

Photoreceptor cells [first-order neurons (nerve cells)] are the primary cells involved in the absorption of photons and convert these rays into a neurological signal that coordinates with second-order neurons and transmits the signal to the brain centers for visual perception. Our study shows that rod photoreceptor cells lacking PKM2 have defects in transmitting the light signal to the brain. PKM2 acts as a transcriptional co-regulator (protein that interacts with factors to encourage/discourage synthesis of other proteins) in cGMP-phosphodiesterase 6-beta (PDE6β) expression PDE6β is a protein that is part of a complex ion channel in the plasma membrane that shields photoreceptor discs. Mutations in PDE6β leads to retinal degeneration. In the absence of PKM2, PDE6β expression is reduced, explaining the defects we have observed in the function of rod photoreceptor cells. We have found that building up of glycolytic intermediates and increasing NADPH (a small molecule necessary for cell survival) levels is not enough to increase anabolic activity and cell survival. Our findings are evidence that there are other important reasons why PKM2 is so highly expressed in cells requiring highly active anabolic activity. The literature suggests that an increase in glycolytic intermediates would make cells more anabolic and proliferative, but in photoreceptors, increased glycolytic intermediates cannot prevent cell death. In photoreceptors, we found increased NADPH in PKM2-deleted rods, but this failed to increase lipid synthesis, indicating that the highly conserved specific expression of PKM2 in photoreceptors has additional important functions. Our studies show that PKM1 cannot fully complement the functions of PKM2, suggesting that there may be another source of acetate for mitochondrial production of ATP, perhaps through the oxidation of fatty acids. The current study opens up a new area of investigation to examine the role of lipids in the absence of glucose, both in cancer and photoreceptor fields.

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