Cancer Cell Metabolism

The internet is a wonderful thing, information really becomes available at our fingertips. Like everything, with the good comes the bad and, when we speak of cancer, a lot of bad information is unfortunately published. Everybody seems to have his/her own interpretation of the Warburg theory. In this document I'll try to clarify what this theory is and what we know about cancer cell metabolism.

The Warburg Effect

In 1931 Otto Heinrich Warburg was attributed the Nobel price in Physiology and Medicine mainly for his investigation of the metabolism of tumours and the respiration of cells, and more particularly for his discovery of the nature and mode of action of respiratory enzymes. He edited and has much of his original work published in *The Metabolism of Tumours* (tr. 1931) and wrote *New Methods of Cell Physiology* (1962).

Otto Warburg observed that cancer cells' metabolism is different than the one of normal adult cells. Normal adult cells use a small energy plant located inside them to produce most of their energy needs from oxygen, this is an aerobic process. In contrast, cancer cells rely mainly on the first part of the energy production process dependant on glucose (sugar), this is an anaerobic process. The anaerobic process is called *glycolysis*.

The paradox is that cancer cells rely on glycolysis even if oxygen is available. This phenomenon is called ***aerobic glycolysis*** or the ***Warburg effect***.

Many decades later, this observation was exploited by clinicians to better visualize tumours using PET (positron emission technology) imaging. But it has not been known exactly how tumour cells perform this alternate metabolic feat, nor was it known if this process was essential for tumour growth. Now, two papers appearing in the March 13 (2008) issue of the journal Nature help answer these questions. Led by researchers at Beth Israel Deaconess Medical Centre (BIDMC) and Harvard Medical School, the papers find that the metabolic process that has come to be known as the Warburg effect is essential for tumours' rapid growth, and identifies the M2 form of pyruvate kinase (PKM2), an enzyme involved in sugar metabolism, as an important mechanism behind this process.

The "Warburg Effect" is a unique property of most cancers. The phenomenon is characterized by increased glucose uptake and reliance on glycolysis for ATP production despite available oxygen source.

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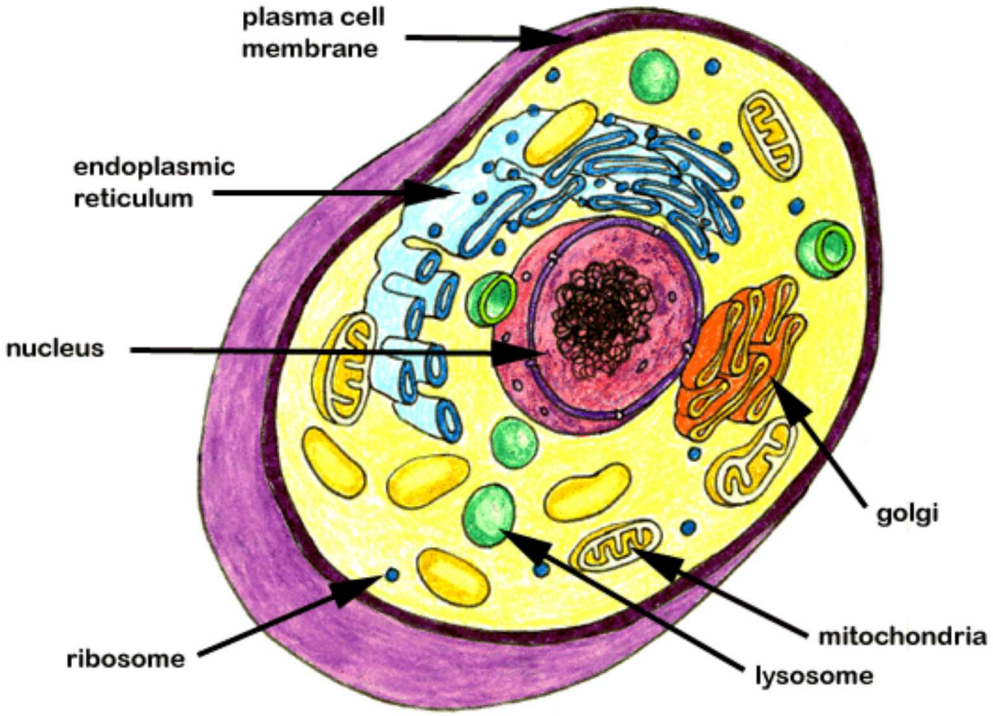
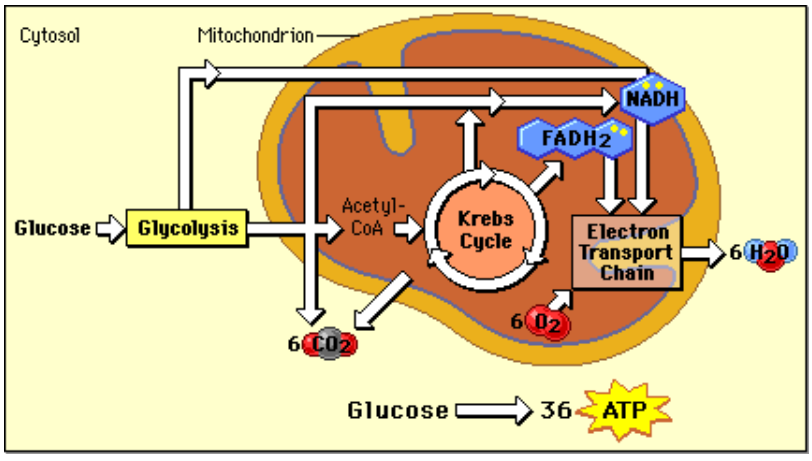


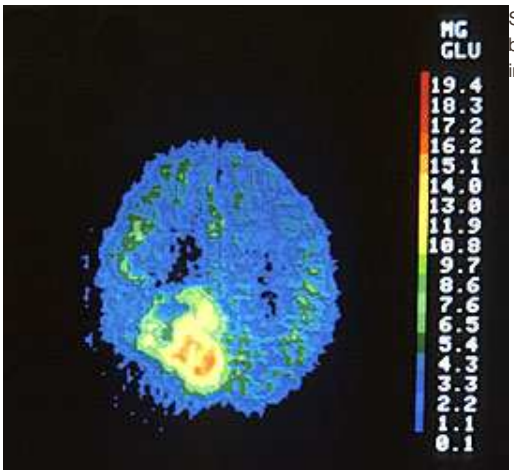
In the above figure, the yellow coloured part is named cytosol, this is where the energy production process starts. At first, glucose molecules are percolating into the cell through the cell membrane by diffusion. You can imagine the glucose molecule in the yellow part of the cell: the cytosol. It doesn't stay free very long, it becomes engaged in a biochemical process to produce what the cells like the best (their favourite food), **ATP**. This process occurring in the cytosol is named **glycolysis**. It is not very efficient, only two servings (2 molecules) of ATP are available for all cell metabolism needs. Usually, to satisfy the huge appetite of normal cells, little power plants also nicknamed Mitochondria take a by-product of glycolysis, ***pyruvate***, and convert it into 36 servings!! To accomplish such miracle, mitochondria use oxygen.



What Otto Warburg discovered is that most cancer cells rely only on the first part of the energy process: glycolysis. They use glucose to produce their cell food (ATP). Their mitochondria are not involved in the cell food production process. Because they rely on glycolysis which is a less efficient mean of production (only 2 servings of ATP), they need more glucose to satisfy their enormous appetite.

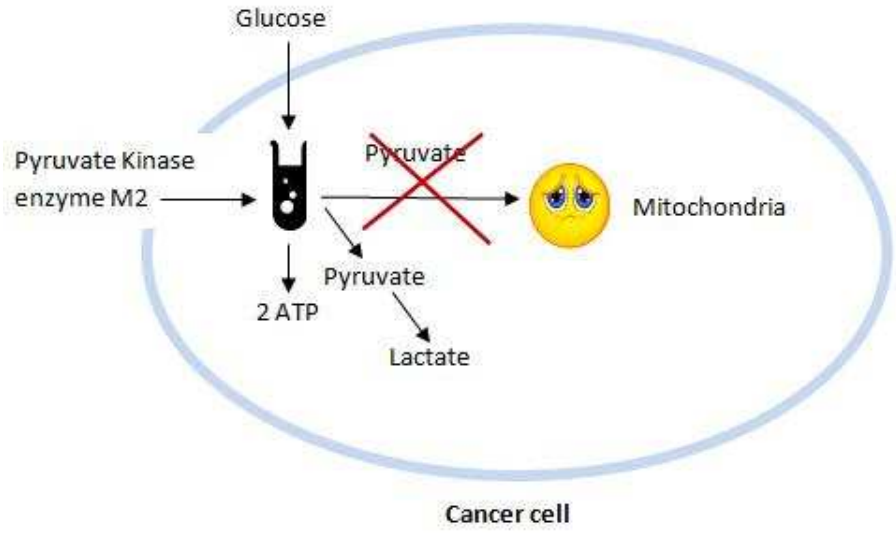
Compared to normal cells which can, from a single molecule of glucose, produce 36 to 38 servings of ATP, cancer cells will need 19 molecules of glucose to produce an equivalent quantity (38 ATP = 2 ATP X 19 glucose). From these numbers we can see that cancer cells will BE huge consumers of glucose to satisfy their sugar crave. This is why some medical imaging techniques can help us locate tumours when they reach a certain size. Radio-active glucose is injected in patients. The Positron Emission Tomography (PET) scan tool is sensible to radio-active material. Since cancer cell will consume 18 to 19

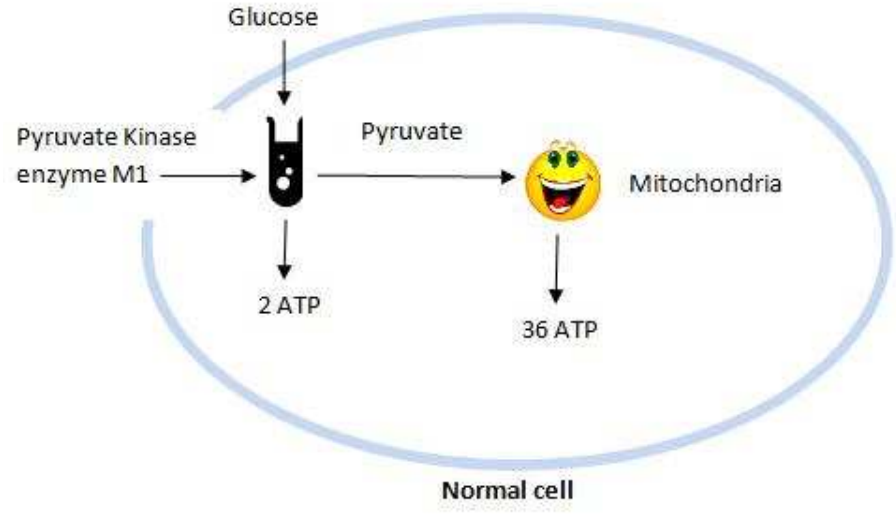
times more glucose than normal cells, they will accumulate more radio-active material as illustrated in the picture below.



Shown in the left is a Positron Emission Tomography (PET) scan of a 62 year old man with a brain tumour. The irregular bright yellow and orange area in the lower left portion of the brain indicates the location of the tumour, which metabolizes glucose faster than normal cells.

The Role of Enzymes in Glycolysis





The aerobic glycolysis or the Warburg effect, is thought to be due to the reprogramming of metabolic genes to allow cancer cells to function more like fetal cells and to enable a greater fraction of glucose metabolites to be incorporated into macromolecules synthesis rather than burned to CO2. In other words, glucose is used more for replication than for normal cell metabolism.

Recent research demonstrated that one enzyme makes the whole difference: ***Pyruvate Kinase***. It is an enzyme involved in the last step of the glycolysis process.

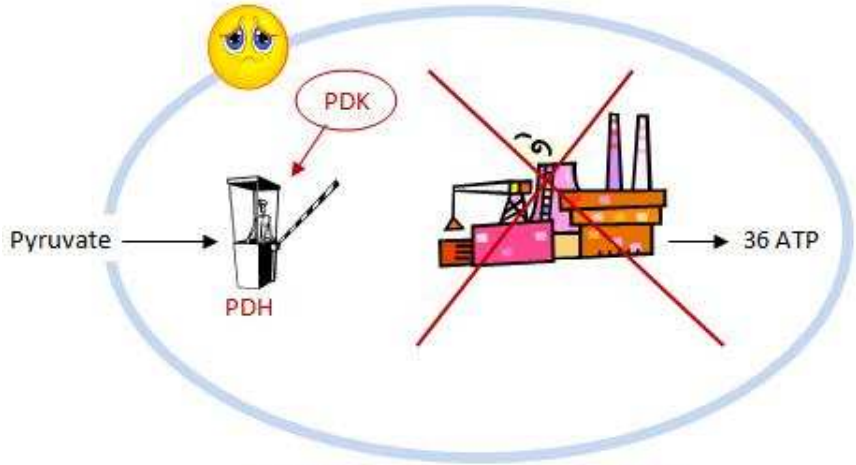
Pyruvate kinase exists in two different versions: M1 and M2. The M1 isoform is expressed in most adult tissues; and the M2 isoform is a slice variant of M1 expressed during embryonic development(1).

It has been reported that tumour tissues exclusively express the embryonic M2 isoform of pyruvate kinase(2,3,4).

Given that pyruvate kinase M2 is expressed during embryonic development and in many non-transformed cell lines, M2 expression alone is unlikely to be a transforming event Rather, the presence of of PKM2, may contribute to a metabolism environment that is amenable to cell proliferation.

At the end of the glycolysis process, the enzyme pyruvate kinase help in the final production of two molecules of ATP and one molecule of pyruvate. The pyruvate molecule is then passed to the mitochondria to be transformed into 36 molecules of ATP.

A gatekeeper stands at the front of the mitochondria, it is a mitochondrial enzyme, the **pyruvate dehydrogenase** (PDH). Without the latter, the pyruvate produced by the glycolysis cannot gets into the highly efficient mitochondria power plant.



Inside the Mitochondria of a cancer cell

Writing Notes: I need to review the document to edit and most probably add new content. I should get more info on DCA. There is a growing evidence that DCA is very potent for several cancer cases. I saw more and more well documented remission reports in the last months. I should add more content about why glycolysis can contribute to cancer cell proliferation and why some molecules like DCA bring back the natural life cycle. I also need to add several sections about the different stages of tumourigenesis. Barry said that I need to add some content on why active mitochondria lead to apoptosis because this is the DCA active pathway. I think he is right.

references

(1) Jurica M.S et al. The allosteric regulation of pyruvate kinase by fructose-1,6-bisphosphate, Structure 6, 195-210 (1998)

(2) KHeather R. Christofk et al. The M2 slice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. Nature vol. 452|13 March 2008.

(3) Mazurek et al. Pyruvate kinase type M2 and its role in tumour growth and spreading. Semin. Cancer biol. 15, 300-308 (2005)

(4) Dombrauckas et al. Structural basis for tumor pyruvate kinase M2 allosteric regulation and catalysis. Biochemistry 44, 9417-9429 (2005).