

Current Findings in Cancer Cell Metabolism

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Otto Warburg is a pioneer in the research and study of respiration. He made the observation that even in the presence of oxygen cancer cells metabolize significantly more lactic acid from glucose than a normal cell, this is called the Warburg effect (Koppenol et al. 2011) . This discovery by Warburg was made in the 1920s, and since then new research and observations have been made on cancer cell metabolism. Current research shows other cellular components can contribute to tumorigenesis. Understanding how cancer cells metabolize and what process actually led to tumorigenesis will allow for new treatment and cancer therapy. This microreview will focus on and discuss the new findings on cancer cell metabolism. The research discussed will demonstrate that the Warburg effect alone is not enough for cancer progression.

Introduction

Otto Warburg believed the fact that cancer cells have reduced mitochondrial oxidative phosphorylation and produce large amounts of lactic acid from glucose even in the presence of oxygen, led to tumorigenesis. The environment of a tumor contributes to the type of metabolism used by the cells. Stated by Hsu et.al (2008) “The oxygen levels within a tumor vary both spatially and temporally, and the resulting rounds of fluctuating oxygen levels potentially select for tumors that constitutively upregulate glycolysis.” This fluctuation in oxygen is due to the incomplete lessening of the hypoxic state of the tumor. The tumor becomes hypoxic when it grows, and becomes too large for its local blood supply. HIF, hypoxia-inducible transcription factor, is responsible for relieving the stress from hypoxia, but as stated before it is unable to fully do so (Hsu et al. 2008). Fumarate hydratase (FH) and succinate dehydrogenase (SDH) are metabolic enzymes that have oncogenic mutations. When mutated, these enzymes are produced in excess and inhibit the enzymes that are responsible for the modifications and degradation of HIF. When HIF is not regulated, it is produced even if the levels of oxygen are normal, which triggers tumorigenesis. The production of HIF in oxygen sufficient conditions stimulates the Warburg effect (Koppenol et al. 2011).

Recent Progress

Recent studies have shown that aerobic glycolysis in the cancer cell is not due to a defect in mitochondrial respiration, but a defect in the regulation of glycolysis. One gene set that is overexpressed in cancer are glycolytic genes. The glycolytic gene, pyruvate kinase, is found in higher levels in tumors (Christofk et al. 2008). Pyruvate kinase is responsible for regulating the rate-limiting step in glycolysis. There are four isoforms of pyruvate kinase that are found in mammals, and one of which, M2, is found in tumor tissues. The M1 isoform is found in adult tissues, while the spliced variant of M1, M2, expressed in embryonic development as well as in tumor cells (Christofk et al. 2008). Christofk et al. (2008) found that M2 cells were able to multiply in 0.5% oxygen, while M1 cell proliferation was significantly decreased in this low level of oxygen. It is suggested that M2 cells are less dependent of oxidative phosphorylation than M1 cells, which would be why tumor cells switch to express the M2 isoform rather than the M1 isoform. Christofk et al. (2008) performed an experiment on mice to determine if M2 expression is related to tumor growth. They injected one set of mice with M1 cells, and another set with M2 cells. The results they incurred were the mice that were injected with the M1 cells showed fewer and slower development of tumors as compared to the group injected with M2 cells. Also, the tumors that did grow in the mice injected with M1 cells were smaller in size and mass than the tumors developed in the M2 mice.

Cancer cells have to support a high rate of reproduction, and in order to do so they must consume extra nutrients and the must redirect them in to macromolecular synthesis pathways. In order for this to occur the metabolic pathways must produce an adequate amount of ATP to support cell growth. Through the findings of Warburg and his co-workers, Koppenol et al. (2011) determined that there is a 10% increase in ATP production by cancer cells when compared to normal cells. Part of this excess ATP is produced when glucose molecules are converted into lactic acid (in normoxic conditions 1 ATP per lactic acid). When lactate dehydrogenase is inhibited, it forces cancer cell to use oxidative phosphorylation to produce ATP. When this occurs, tumor growth is tapered, which suggests that aerobic glycolysis could be crucial for cancer progression.

Cells are made up of complex material which is too intricate for the increase conversion of glucose to lactate alone to promote cell replication. Cell replication requires nucleotides, proteins, membrane lipids, fatty acids, and ATP. The cytosolic acetyl coenzyme A is the antecedent for many lipid types. When ATP citrate lyase, the enzyme that converts citrate into cytosolic acetyl coenzyme A, is inhibited tumor growth and proliferation are stunted. Additionally, fatty acid synthase is increased in cancer cells (Hsu et al. (2008). The citric acid cycle also plays a role in cell replication. Glutamine contributes to anabolic carbons and other elements of a growing cell. The intermediates in the citric acid cycle are hybrids of glucose and glutamine carbons. Glutamine enters the citric acid cycle and then through processes is converted into alpha-ketoglutarate (Koppenol et al. 2011). To carry on proficient replication, cancer cells must also be able to eradicate waste and toxic by-products.

Koppenol et al. (2011) suggest cancer cell progression may also result from mutations with no direct effect on glucose metabolism. Mitochondrial DNA (mtDNA) mutations have been found in many cancers. Mutations in mtDNA are found in normal cell tissues, but in cancer cell tissues they are found in a much larger abundance. These mutations interfere with respiration and lead to high levels of oxyradicals. These oxyradicals lead to an unstable genome that would give cancer cells the advantage to progress.

Discussion

The information provided by Warburg and his colleagues has greatly contributed to current perceptions of cancer metabolism. While there have been several additions to Warburg's discovery it gave a starting point for investigation of cancer metabolism, and was a largely significant discovery. The Warburg effect was thought to occur in place of mitochondrial respiration, but it is now known that this is not the case. Cancer cells are seen to

have damage to the regulation of glycolysis not damage to respiration (Koppenol et al. 2011).

Research has shown how the environment of a tumor cell can cause the Warburg effect. When a tumor grows it is no longer supplied with sufficient oxygen, and the cell must find ways to counter-act this hypoxic environment. When mutations evolve and the cell produces enzymes for a hypoxic environment in a non-hypoxic environment tumorigenesis occurs. Pyruvate kinase, an enzyme in glycolysis, has been identified as a factor in proliferation of cancer cells. Its isoform normally seen in embryonic development has been identified in cancer cells. This M2 isoform contributes to the rate and size of tumor growth.

Cancer cells are complex and are largely made of proteins and ribonucleic acid. They are too complex to be regulated by aerobic glycolysis alone. It is a mixture of lipid, fatty acids, proteins, ATP, and nucleotides that allow for cell replication and growth. There have also been discoveries outside of glucose metabolism that can give some explanation to cancer cell proliferation.

By understanding the metabolism of cancer cells new medications and therapies can be introduced to target these processes. The more we understand the better we can treat patients. Some untested, but provocative ideas include lactate as paracrine signal. Hsu et al. stated "The interconversion of lactate and pyruvate might alter the NAD⁺/NADH ratio in cells, and lactate exchange may serve to coordinate the metabolism of group cells." Also it may be that cancer cells use other fuel sources other than ATP for energy (Hsu et al. 2008). The metabolism of the normal human genome is still not completely understood, which makes it much harder to understand the metabolism of cancer cells. There has been lots of progression in the study of cancer cell metabolism but there is still much more to discover.

References

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