

Association between shortage of energy supply and nuclear gene mutations leading to carcinomatous transformation (Review)

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Abstract. Anaerobic bacteria use glycolysis, an oxygen-independent metabolic pathway, whereas energy metabolism in the evolved eukaryotic cell is performed via oxidative phosphorylation, with all eukaryotic cell activities depending upon high energy consumption. However, in cancer cells evolving from eukaryotic cells, the energy metabolism switches from oxidative phosphorylation to glycolysis. The shortage of energy supply induces cancer cells to acquire specific characteristics. Base pair renewal is the most energy-consuming process in the cell, and shortage of energy supply may lead to errors in this process; the more prominent the shortage in energy supply, the more errors are likely to occur in base pair renewal, resulting in gene mutations and expression of cancer cell characteristics. Thus, shortage of energy supply is associated with carcinomatous transformation.

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1. Introduction

Metastasis occurs when cancer cells disseminate from the primary tumor and form secondary tumors at distant sites in the body. This is a crucial characteristic that distinguishes the cancer cell from the normal parent cell; all types of cancer cells differ from their normal parent cells to various degrees. Investigating the underlying mechanism may help identify

more effective ways to treat cancer patients. The commonly accepted theory is that genes determine cell characteristics, and there is a hypothesis that mitochondrial oncogenesis is the trigger of gene mutations leading to the formation of cancer cells from normal cells (1). As the cancer cell is considered to evolve from the eukaryote, the answer may lie with the process of eukaryotic cell evolution and normal somatic cell oncogenesis.

2. Endosymbiotic theory and gene alterations

The endosymbiotic theory was proposed by Lynn Margulis in the 1960s and suggested that aerobic bacteria (ancient mitochondria) were ingested by anaerobic bacteria (ancient prokaryotic cells) and transferred most of their DNA to the nucleus of the anaerobic bacteria; in this manner, they both had a survival advantage for as long as they continued their 'partnership'. The aerobic bacteria utilized the oxygen, which is toxic for anaerobic bacteria, whereas the anaerobic bacteria ingested nutrients and protected the aerobic 'symbiote' (2,3). This theory provided a satisfactory explanation for the evolution of eukaryotic cells. With continued aerobic metabolism, a reasonable conclusion may be drawn that the ancient genes regulating pathway signaling in glycolysis were obliged to mutate (alter themselves) to survive under the conditions of oxidative phosphorylation. The result was that the genes of the eukaryotic cell (wild-type genes) were also available in another status (mutant genes) if the eukaryotic cell was under atavistic conditions. As eukaryotic cells degenerate prokaryotic cells the related genes for prokaryotic cells would be expressed.

3. Prokaryote hypothesis and the Warburg effect

In light of the endosymbiotic theory and the hypothesis that the replicative ability of cancer cells is similar to the proliferation of prokaryotic cells, Klaus Grossgebauer first proposed the prokaryote hypothesis of oncogenesis, suggesting that a re-evolution from eukaryotic to prokaryotic cells leads to cancer development (4,5). This theory supported that, under special conditions, such as oncogenesis, eukaryotic cells may express certain prokaryotic cell characteristics. The Warburg effect is a typical example of this re-evolution, which is reflected in the metabolism.

Under physiological conditions, the majority of normal eukaryotic cells use the more energy-efficient oxidative

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phosphorylation as the main route to generate ATP. However, Warburg observed that cancer cells performed energy metabolism in a manner that was different from normal adult cells; cancer cells obtained energy through glycolysis rather than oxidative phosphorylation. Therefore, Warburg formulated the hypothesis that the cause of cancer was primarily the defect in energy metabolism (6,7). A number of cancer cells have been proven to actively use the glycolytic pathway for ATP generation, even in the presence of oxygen (aerobic glycolysis). It may be concluded that energy metabolism determines the development of cancer, in the sense that chain reactions directed to eukaryotic cells are initiated if oxidative phosphorylation plays a dominant role; likewise, chain reactions directed to cancer cells are initiated if glycolysis plays a dominant role. However, the mechanism underlying the induction of these alterations has not been fully elucidated.

4. Energy metabolism determines gene status

As mentioned above, our hypothesis was based on the assumption that the base pairs of genes are continually renewed during the life cycle of cells, maintaining a dynamic balance between reproduction and extinction; it is also based on the fact that each cell characteristic is affected by multiple genes and the majority of the genes determines the characteristics of the cells.

The process leading to genes expressing characteristics of eukaryotic cells is based on adequate energy supply. With eukaryotic cell evolution, a single eukaryotic cell gives rise to multiple eukaryotic cells, with the daughter cells maintaining the same shape as the mother cell. With multi-eukaryotic cell evolution, an advanced differentiation occurs (development of advanced organisms), meaning that certain advanced genes evolve to regulate the structure of evolved eukaryotic cells (the process during which ancient genes evolve to advanced genes is identical to the one during which the base pairs of chromosomes are repermuted and recombined). It may be hypothesized that this progression occurs under appropriate conditions of oxidative phosphorylation, and that the genes expressing the characteristics of eukaryotic cells are transformed into the dominant genes based on adequate energy supply (normal expressions of eukaryotic cell characteristics depend upon the genes of eukaryotic cells, which include the base pairs encoding the normal eukaryotic cell characteristics and require a high energy supply). It has been proven that a high ATP level is required for DNA synthesis (8) and DNA stabilization, which maintains the characteristics of eukaryotic cells.

Shortage of energy supply alters the base pairs of genes. As soon as malignant transformation of eukaryotic cells occurs, cancer cells have to obtain energy through glycolysis rather than oxidative phosphorylation. The total energy supply is rapidly reduced, as the total energy yield of glycolysis is different. The glycolytic pathway for ATP generation is unable to produce sufficient energy for the normal renewal of the base pairs of eukaryotic cell genes. At this time, normal base pairs

are replaced by abnormal base pairs, resulting in gene mutations, DNA methylation, overexpression and no or reduced expression (9-12). Different chromosomes exhibit different abilities to tolerate the shortage of energy, with some chromosomes being more vulnerable compared with others. For this reason, the proteins of cancer cells depend upon the changes in the quantity of base pairs, which determine the degree of gene changes in the chromosomes.

Abnormal genes express characteristics of cancer cells. It has been proven that a cell characteristic depends upon a number of proteins, which are encoded by a set of genes. The abnormal gene is unable to produce a protein identical to that encoded by the primary normal gene. Therefore, the more genes change, the more cancer cell proteins deviate from parent-cell proteins and the more characteristics of cancer cells resemble those of ancient prokaryotic cells.

5. Conclusion

Following malignant transformation of eukaryotic cells, the cancer cells cannot obtain sufficient energy from glycolysis to maintain normal chromosome base pair renewal. Abnormal base pairs replace normal base pairs, inducing gene mutations. The more genes change, the more abnormal proteins are produced, which cause the characteristics of cancer cell to resemble those of ancient prokaryotic cells.

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