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CANCER AS A METABOLIC DISORDER

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ABSTRACT

Traditionally, oncogenes and tumor suppressor genes have been thought to be the main genetic causes of cancer. Nonetheless, mounting data points to a key role for dysregulated cellular metabolism in the initiation and spread of cancer. The Warburg effect, which shows that even in the presence of enough oxygen, cancer cells preferentially choose aerobic glycolysis over oxidative phosphorylation, is an example of this paradigm shift. Elevated glutamine metabolism, changed fatty acid synthesis, and enhanced glucose absorption and fermentation to lactate are important metabolic changes in cancer cells. Mutations in tumor suppressors like p53 and oncogenes like c-Myc and KRAS, which converge on signaling pathways like PI3K/Akt and HIF-1α, are frequently the cause of these alterations. The idea that cancer is a metabolic disease has significant ramifications for both diagnosis and treatment. The increased glucose consumption in tumors is used by metabolic imaging methods, such as PET scans using radio labelled glucose analogs, to detect them. Additionally, focusing on metabolic pathways presents innovative treatment approaches. Ketogenic diets, for example, try to stop cancer cells from getting glucose, which may limit the growth of tumors. Clinical evidence for these therapies is still developing, though.

1. INTRODUCTION

Numerous temporal and spatial changes in cellular physiology, which ultimately lead to the development of malignant tumors, are characteristics of cancer, a complex disease. Neoplasia, or aberrant cell growth, is the biological result of this illness. For most cancer patients, the main cause of morbidity and death is the invasion of tumor cells into nearby tissues and distant organs. For many years, the biomedical sciences have conducted in- depth research on the conversion of healthy cells into cancerous ones. However, even after much research, effective

treatments or long-term management plans for metastatic cancer are still as elusive as they were when President Richard Nixon launched a nationwide cancer campaign forty years ago.[1,2]

Cancer's etiology is unknown. Paradoxes and contradictions have plagued the field.[3-6] It becomes difficult to develop a clear plan for effective management of cancer if the causes are not fully understood. Although a variety of unspecific causes, including radiation, chemicals, viruses, inflammation, etc., can initiate the disease, malignant transformation is induced by very specific pathways. Indeed, long-term exposure to almost any environmental trigger appears to have the capacity to cause cancer.[7,8] This is what Szent Gyorgyi called "the oncogenic paradox," according to which a highly specialized process can be initiated in a highly nonspecific manner.[8] Most parts of this puzzle remain unsolved.[7] In a groundbreaking analysis, Hanahan and Weinberg suggested that six basic alterations in cell physiology could be the root cause of malignant cell growth.[6] These six traits were claimed to be present in nearly all cancers: 1) self-sufficiency in growth signals; 2) insensitivity to growth inhibitory (antigrowth) signals; 3) apoptosis, or the avoidance of programmed cell death; 4) infinite potential for reproduction; 5) angiogenesis, or prolonged vascularity; and 6) tissue invasion and metastasis. It was believed that the primary enabling element for humans displaying the six traits was increased mutability brought on by genomic instability.[6] However, since most genes have a low rate of mutation, it is unlikely that the numerous detrimental alterations found in cancer cells would occasionally occur throughout the course of a normal human life span.[7]

2. Living cell Energy and The role of mitochondria in cancer cells

For cells to remain viable and carry out their genetically preprogrammed tasks, they must produce useful energy. Known as the free energy of ATP hydrolysis, this energy is mostly held in adenosine triphosphate (ATP) and is liberated when the terminal phosphate link hydrolyzes. ΔG'ATP, the standard energy of ATP hydrolysis under physiological conditions, is strictly controlled in all cells and normally ranges from -53 to -60 kJ/mol. Ionic membrane pumps are powered by a sizable amount of this energy. Most of the energy in cells with functional mitochondria is generated by oxidative phosphorylation, which accounts for about 88% of total cellular energy, or roughly 28 out of 32 total ATP molecules.

2.1 Role of mitochondria in cancer cells

The function of the mitochondria in cancer cells has been the subject of intense discussion. Britton Chance and Sidney Weinhouse played a crucial role in igniting this debate by critically

examining the Warburg theory and mitochondrial participation. Weinhouse proposed that even in the presence of increased glycolysis, cancer cells may continue to transport carbon and electrons in a quantitatively and qualitatively normal manner. He proposed that CO2 production and oxygen consumption served as markers of linked respiration. On the other hand, excessive Donnan active material (ATP) synthesis would result from linked respiration and increased glycolysis.

3. Cancer cell mitochondrial Dysfunction and The connection between mitochondrial Dysfunction and Genomic instability

Tumor mitochondria are physically and functionally aberrant and unable to produce normal amounts of energy, according to a number of studies.[10,60,61,68-74] Additionally, recent data indicates that the electron transport chain's function and the lipid content of mitochondrial membranes are modified by the in vitro growth environment.[75] Furthermore, the lipid abnormalities observed in malignant tissue and tumors formed in vivo differ from the mitochondrial lipid abnormalities caused by the in vitro growth environment. It seems that the in vitro growth environment blurs the lines between the Crabtree and Warburg effects and decreases Complex I activity. High glucose levels can reduce respiration in the Crabtree effect,[76,77] while defective oxidative phosphorylation can decrease respiration in the Warburg effect.

4. Genomic instability, Retrograde Reaction and Similarities between Yeast and Mammalian cells in relation to compromised respiration

An alternative explanation for the origin of somatic mutations to the genome guardian hypothesis is that a prolonged retrograde reaction could be a factor in the genomic instability and mutability seen in tumor cells. Cellular responses to changes in mitochondrial function are included in the retrograde (RTG) response, which is a term used to describe mitochondrial signaling. Although yeast has been the subject of the majority of studies on the RTG response, mammalian cells also have a similar mitochondrial stress signaling pathway. The expression of several nuclear genes that control energy metabolism is markedly altered after disturbances in mitochondrial energy balance. Abnormalities in mitochondrial DNA (mtDNA), the tricarboxylic acid cycle (TCA), the electron transport chain, or the proton motive force ($\Delta\Psi m$) across the inner membrane are some of the causes that can cause mitochondrial dysfunction.

5. The mutator phenotype, Mitochondrial Malfunction and Mitochondrial dysfunction after viral infection

Increased rates of mutation, notable chromosomal rearrangements, and changes in chromosome numbers are characteristics of genomic instability seen in the majority of human cancer cells. The mutator phenotype seen in tumor cells may be attributed to mitochondrial malfunction, which is mostly mediated by the RTG response (a signaling pathway for mitochondrial stress), according to recent studies by the Singh and Jazwinski groups. Compared to human cells with normal mitochondrial DNA (mtDNA), those with reduced mtDNA exhibit noticeably greater levels of chromosomal instability, gene mutation expression, and carcinogenic traits. Furthermore, apurinic/apyrimidinic endonuclease APE1, a redox- sensitive multifunctional enzyme essential to DNA transcription and repair, can be down- regulated as a result of mitochondrial malfunction.

6. Invasion, Metastasis and Linking the dots

One of the main causes of cancer-related morbidity and death is metastasis, which is the process by which cancer cells spread from the primary tumor to nearby tissues and distant organs. There are several complex and related phases involved in this phenomena. Cancer cells must separate from the original tumor, enter the bloodstream and lymphatic system, avoid immune responses, leave the circulation at a distant capillary location, and then invade and multiply within distant organs in order for metastasis to be successful. Additionally, the milieu that metastatic cells produce encourages angiogenesis and proliferation, which results in the development of obvious malignant secondary tumors.

7. The hypothesis's implications for managing Cancer and Addressing glucose

If, as this review discusses, cancer is essentially a problem of energy metabolism, then medicines that target energy metabolism specifically may be useful for managing cancer. Although mitochondrial replacement therapy may help tumor cells return to a more normal energy metabolism and differentiated state, it is unlikely that this treatment will be available anytime soon. However, a number of studies show that dietary energy restriction acts as a broad metabolic therapy that naturally lowers blood glucose levels and dramatically slows the growth and spread of a variety of tumor types, such as brain, colon, breast, pancreatic, lung, and prostate cancers.

For example, energy restriction effectively inhibits the growth of U87 human gliomas when implanted in the brains of immunodeficient SCID mice, but it has no effect when the tumor is grown outside the brain in non-obese diabetic SCID mice. The effect of energy restriction on tumor growth can vary depending on the host's background and the location of the tumor.

8. Targeting the microenvironment & Implications of the hypothesis to cancer prevention

Some cancers have traits in common with wounds that don't heal. Fibroblasts and macrophages, which are normally involved in the wound healing process, generate growth factors and cytokines that can unintentionally cause persistent inflammation and accelerate the growth of tumors. Angiogenesis is encouraged and the extracellular matrix is broken down as part of the wound healing process, both of which aid in the growth of tumors. It has been demonstrated that dietary energy restriction affects the signaling pathways that promote tumor angiogenesis as well as inflammation. Actually, Calorie restriction is known to be a simple and successful method of addressing inflammation and tumor angiogenesis. Restricting calories or dietary energy can be a useful strategy for decreasing the growth of tumors since it works as a systemic therapy that impacts the surrounding tumor microenvironment as well as the tumor cells.

9. CONCLUSION

The primary hypothesis that energy metabolism abnormalities are the root cause of cancer is substantially supported by the evidence analyzed. Impaired mitochondrial function can be connected to the main characteristics of cancer. Tumor cells use glucose and glutamine as their main energy sources and progressively shift towards substrate-level phosphorylation to ensure their survival. Although germline mutations that cause cancer are uncommon, the secondary effects of mitochondrial malfunction are responsible for the high frequency of somatic genomic abnormalities in the majority of malignancies. Once somatic genetic instability has been established, tumor cells may experience additional mitochondrial impairments and metabolic stiffness.

Because myeloid-derived cells naturally have the ability to move between different tissues, the long-term damage done to their mitochondria is likely to result in the formation of systemic metastasis. According to this theory, limiting energy intake may cause some tumors to regress, and enforcing such dietary restrictions may stop the emergence of numerous malignancies. Therefore, a logical approach to the continued treatment and prevention of various malignancies is to combine energy-restricted diets with drugs that target glucose and glutamine.

Changes in cellular metabolism characterize cancer, a complex and multidimensional disease. The diagnosis, treatment, and prevention of cancer are all significantly impacted by the notion that cancer is a metabolic disease. To fully understand the processes, more research is needed.

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