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Opinion

Cell Energy: A New Hypothesis in Decoding Cancer Evolution

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Abstract

The present study deviates from previous approaches as it focuses on the concept of energy to illuminate cancer-related issues. Energy is a prerequisite for any function; cellular function is no exception, and thus, reduced energy in human cells can impair their performance. This hypothesis provides a novel view of cancer formation. It shows that a normal cell transforms into its cancerous counterpart in response to cellular adenosine triphosphate (ATP) depletion. Moreover, it presents a new definition for the origin of cancer stem cells and how they can regenerate cancer. This article regards a distinct aspect of cancer that helps to differentiate various phases of its progression and shed light on some of the uncharted zones of its pathway for the first time that needs further confirmation by empirical studies.

Keywords: ATP, Cancer biology, Cancer genomics, Cancer stem cell

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Background

Avicenna (Ibn Sina) (ca. 980–1037) believed that all human diseases have a common origin—the loss of energy (recognized by the thinker as power). He designated disease as "dysfunction"; if healthy cells (for any reason) fail to function normally, disease occurs.[1] More recent scientific efforts have introduced numerous mechanisms by which cancer occurs. Warburg, for example, proposed that irreversible mitochondrial dysfunction is the main predisposing factor for cancer, with such dysfunction driving cells to rely on glycolysis for energy production (aerobic glycolysis).[2] Crabtree claimed that increased glucose uptake shifts the metabolism of cancer cells to glycolysis and exerts depressive effects on oxygen uptake.[3] No general agreement has been achieved regarding the pathway of cancer cells (from formation to progression). To fill this void, we formulated a novel hypothesis regarding the association between cancer cell evolution and cell energy level.

The Hypothesis

This hypothesis considers cellular adenosine triphosphate (ATP) depletion as the basis of DNA instability which in turn serves as the milestone for cancer cell formation. In response to DNA instability, many changes occur in cancer cell metabolism that drive it to a complex pathway.

Cellular Energy Depletion: The Primary Insult to DNA Instability

With reference to cancer risk factors (e.g. aging, sedentary lifestyle, and oxidative cellular damage), we constructed a model in which a decrease in cellular energy triggers cellular remodeling (secondary to DNA instability) and initiates the development of cancer cells (Figure 1). Throughout our lives, we are exposed to many factors that can change the amount of cellular energy in our bodies (e.g. diet, aging, exercise, tobacco). Some of them decrease cellular energy, whereas others make it goes up. Oftentimes, booster factors neutralize the effects of depressors, but their absence decreases cellular energy. On the other hand, each human cell is exposed to 10 000–20 000 DNA mutation per day. These mutations can cause the transformation of a normal cell to its cancerous counterpart. Therefore, the efficiency of DNA repair system is vital. The first step in the repair of double-strand breaks is unfolding DNA to allow access to repair complexes.[4] This ATP-dependent process is known as chromatin remodeling. There are many proteins that take part in chromatin remodeling. These proteins are classified into four families, INO80, CHD, SWI/SNF, and ISWI.[5] Therefore, it may be concluded that cellular DNA requires ATP to preserve its structure and repair the mutations. The various stages of cancer cell formation are described below (Figure 1).

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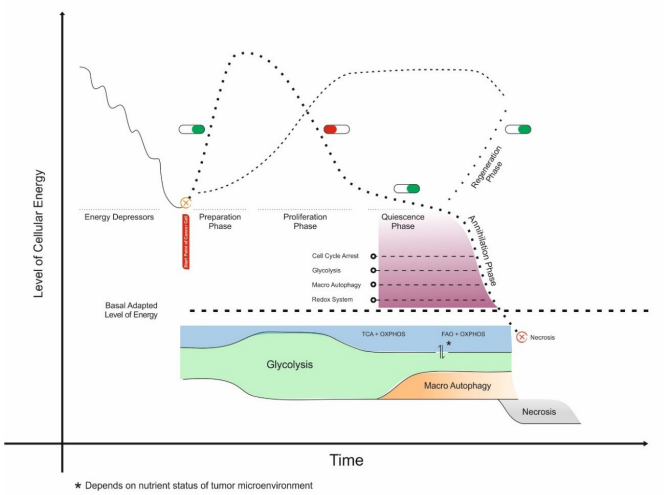

Figure 1. This figure depicts the trends of cellular energy (dotted line) and cellular proliferation (broken lines). As a result of energy depressors, cellular energy falls to a level that impairs ATP-dependent DNA repair molecules (i.e., INO80, CHD, SWI/SNF, and ISWI) and induces DNA instability. This is the starting point of cancer cell formation. In the initial step **(preparation phase),** cancer cells run a bioenergetic process by acquiring a bulk of nutrients and activating TCA + OXPHOS to accumulate intracellular ATP and NADPH, thereby supporting further proliferation. In the next step **(proliferation phase),** the cells consume available ATP molecules and run biosynthetic processes to support proliferation and use NADPHs to detoxify released reactive oxygen species. Put differently, this phase is glycolysis-dominant, thus providing building blocks (e.g., fatty acids, cholesterol, nucleotides, and non-essential amino acids) for cellular proliferation. In this phase, after ATP consumption and cellular proliferation, the relative cellular energy declines. This step continues to a level wherein some of the cancer cells transform into a special type of cells that develop the ability to survive in low-energy situations. In the **quiescence phase**, the cancer cells provide themselves with some defensive mechanisms against the immune system and various treatments (e.g., chemotherapy and radiotherapy). Known defensive barriers include cell cycle arrest, glycolysis dependency, macroautophagy, activation of efficient redox systems, and creation of tumor microenvironments. The downslope energy trend of this phase is due to the progressive shortage of nutrients after tumor growth. Quiescent cancer cells remain in this situation until favorable conditions (i.e., availability of nutrients or weakening of the immune system) emerge. DNA stability is energy-dependent; in concert with energy depletion, undifferentiation and changes in molecular markers occur. Therefore, it can restart the regeneration phase in other cellular features. On the other hand, if cancer cells cannot derive an energy source, their energy decreases to a level that is lower than the basal adapted level of energy, thus causing necrosis **(annihilation phase)**. All these steps are stringently regulated by certain mediators, including adenosine monophosphate–activated protein kinase (AMPK), P53, and high mobility group box protein 1 (HMGB1). The expression of AMPK, as a cellular ATP detector, is denoted in red (off) or green (on) lights (***Source:*** Authors' compilation).

The Preparation Phase

Once the cancer cell develops (secondary to DNA instability), it acquires certain abilities to independently secure nutrients for sustained proliferation. These processes are run by aberrantly activated oncogenes and/or loss of tumor suppressors; they are also independent of circulating growth factors. This phenomenon means that cancer cells turn to autonomous components.[6] In what we call the "preparation phase," cancer cells operate bioenergetic processes and produce bulks of ATP and nicotinamide adenine dinucleotide phosphate (NADPH) molecules, thereby supporting further proliferation.

The Proliferation Phase

In this glycolysis-dependent step, the cancer cell consumes ATPs, thus producing the components necessary for proliferation (e.g. amino acids, fatty acids).[6] ATP consumption, along with concurrent proliferation, decreases relative cellular ATP levels.

The Quiescence Phase

In line with the gradual decline in cellular ATP, some tumoral cells can survive and enter a phase that enables them to withstand low ATP status by developing certain defensive barriers. We call this phase "the quiescence phase". Cancer cells in the quiescence phase suppress their cell cycle and shift their metabolism to glycolysis in order to withstand the harsh situation of acidotic and low-nutrient tumor microenvironment (TME). By arresting the cell cycle, they can also protect themselves against the noxious effects of radiotherapy/chemotherapy. Cancer cells remain in this phase until the TME situation become safe to make repopulation possible (described in the regeneration phase section). The metabolic barriers of the quiescence phase are including cell cycle arrest, glycolysis dependency, macro autophagy, enhanced Redox system, and immunosuppression.

Regeneration Phase

In vitro studies have found that cell cycle arrest is irreversible; they have noted that this process is regulated by some oncogenes and mediated by P53; hence the term "oncogene-induced senescence".[7] However, other studies have shown that cancer cells can bypass this state and restart the course of proliferation.[8] Accordingly, we used the term "quiescence" instead of "senescence". This process may be mediated by an increase in intracellular ATP and further deactivation of P53.[9] In some situations, quiescent cancer cells may access nutrients and enhance their intracellular ATP levels. For instance, they may access microvasculature

via secretion of matrix metalloproteinases and vascular endothelial growth factor.[6] This condition may also happen secondary to metastasis to a nutrient-rich nidus. With access to nutrients and a rise in ATP level, P53 and DNA dissociate and cancer cells re-enter the preparation phase. In concert with this process, access to nutrients (including oxygen) deactivates the hypoxia-inducible factor. As a result, metabolism shifts from glycolysis to tricarboxylic acid cycle + oxidative phosphorylation (TCA + OXPHOS).[10] In summary, harsh situations drive cancer cells to deactivate themselves into the quiescence state, and nutrient availability prompts them to activate preliminary steps of proliferation. We call these special cells "initiating quiescent" (IQ) cells. Based on the cellular behavior, we hypothesize that IQ cells are the cancer stem cells.

The Annihilation Phase

If IQ cells cannot access a nutrient source, their energy decreases to a level that stalls the activation of defensive barriers and causes necrosis. In other words, following nutrient deprivation, natural selection occurs and mediates the necrosis of cancer cells that cannot maintain their energy levels. This process can be mediated by loss of function mutations in related main regulators as a response to gradual ATP loss.

The Consequence of the Hypothesis and Discussion

This article introduced the cell energy hypothesis to explain the entire pathway of cancer development. The hypothesis submits that maintaining cell energy prevents and counteracts sporadic cancer development. In other words, it proposed that depletion of cell energy plays a key role in cytogenetic instability and is the primary insult for cancer formation. Furthermore, the novel definition of the origin of cancer stem cells (named IQ cells in this article) can provide effective targets to eradicate such resistant cells and inhibit further tumor recurrence. This hypothesis is a starting point for further studies on more practical ways of dealing with cancer.

Authors' Contribution

HA provided the main concept of hypothesis. FTH designed and performed the research and wrote the manuscript. YH and MB revised the manuscript. All authors read and approved the final manuscript.

Conflict of Interest Disclosures

The authors declare no conflict of interest.

Consent for Publication

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Not applicable.

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