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HYPOTHESIS

Metabolic Conditions, Hypothermia, and Hypoxia Induced by Continuous Stress Are More Often Associated with Carcinogenesis than Known Carcinogens

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Abstract. Many investigators believe that carcinogenesis occurs in cells as genetic mutational events induced by carcinogens such as ultraviolet rays, food additives, nuclear radiation, and air pollution. However, in cancer clinics it is typically difficulty to determine whether such carcinogens actually cause cancer in patients. On the other hand, cumulative evidence has revealed that cancer cells produce energy mainly through glycolysis, and such cells contain few mitochondria. There is a question as to how genetic mutations, carcinogens, and glycolysis in cancer cells are associated with each other. To address this question, we propose a new concept on carcinogenesis, namely, the concept of "adaptive response of glycolysis to adverse internal conditions induced by stress". When humans and animals are exposed to severe stress, they can undergo hypothermia, hypoxia, and hyperglycemia. Related factors in these processes include catecholamines induced by sympathetic activation, and glucocorticoids secreted by adrenal glands. This internal environment is beneficial for the anaerobic glycolysis pathway. However, if stress continues unabated, this environment suppresses oxidative phosphorylation in mitochondria. Among normally dividing cells with fewer mitochondria, adaptive responses occur gradually. After multi-step genetic mutations, some cells are able to change their genetic properties to overcome hypothermia and hypoxia. These are typically cancer cells. The concept proposed here may provide some explanation as to how external environmental factors interplay with endogenous cellular metabolism to promote carcinogenesis.

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1. Introduction

We had previously characterized the *in vivo* conditions of stress in mice. When mice were exposed to restraint stress, they simultaneously exhibited hypothermia (39.0—35.0°C), hypoxia, and hyperglycemia [1,2]. If adrenaline or a glucocorticoid was administered to the mice, the same conditions (i.e., hypothermia, hypoxia, and hyperglycemia) were observed. In parallel with these animal experiments, we had conducted a study on the internal physiological conditions of patients with early and advanced cancer [3,4]. Irrespective of the stage, many patients exhibited hypothermia (<36.0°C), hypoxia, and hyperglycemia. This environment in humans resembled the stress-induced internal conditions in animals. In light of these findings, the cancer patients were reevaluated and queried. Almost all patients told of their stressful life-style before the onset of cancer. The sources of such stress included overwork, lack of sleep, mental stress, and obesity [3]. It was speculated that these lifestyle issues may be responsible for the activation of sympathetic nerves and the hypothalamic-pituitary-adrenal axis.

If the stressful conditions are not prolonged too long, it is possible that hypothermia, hypoxia, and hyperglycemia may be quite important for recovery [5]. This type of internal environment may cause the activation of the glycolysis pathway in the body. Energy produced by anaerobic glycolysis is known to be readily used by white muscle fibers [6]. As a result, an individual facing impending danger is able to physically escape from the harmful situation, also known as "fight-or-flight". However, if the stress continues and is prolonged, these internal conditions suppress oxidative phosphorylation in mitochondria. Thus, energy that is required by red muscle fibers is diminished (general fatigue in a patient). Energy for protein synthesis is also dependent on oxidative phosphorylation. As a result, a patient can become emaciated due to lack of protein synthesis and energy depletion.

2. Hypothesis

Stress-associated conditions can induce hypothermia, hypoxia, and hyperglycemia. If this type of internal environment is prolonged, one can envision that an adaptive response is initiated in the body. Consider that the process of cell division is dependent on the number and metabolic output of mitochondria [3]. For example, dividing cells such as sperm cells, skin epidermal cells, and intestinal epithelia, which have few mitochondria, mainly depend on glycolysis for their energy production. In contrast, non-dividing cells, such as cardiac muscle cells, red fiber muscles, and neurons, which have many mitochondria, are dependent on oxidative phosphorylation for their energy production.

When the conditions of hypothermia and hypoxia are prolonged and potentiated even furthermore, some adaptive responses are possibly required by dividing cells to overcome adverse internal conditions, which require a multi-step genetic mutation process. These adaptive cells, which carry few mitochondria and depend on glycolysis for energy production, are cancer cells. It was reported that anemia and hypoxia are essential for the progression of tumor growth in cancer patients [7-10]. Namely, carcinogenesis might be an adaptive response in the animal body. It is unlikely that genetic disruption induced by carcinogens is the main cause of cancer [11-15]. Even if such cases of genetic alterations are present, they are rare. There is no reasonable explanation why known carcinogens induce the metabolic changes which cause normal dividing cells to become cancer cells.

It has been postulated that the primordial ancestor of eukaryotic cells originated through an association between cells with exclusive glycolytic metabolism and mitochondria; a process which is believed to have occurred approximately 2 billion years ago [16,17]. Glycolytic cells were thought to be rapidly-dividing bacteria under anaerobic conditions

and produced acetate from glucose metabolism. Mitochondria are thought to have been parasitic on these glycolytic cells, but failed initially due to their paucity within their resident cells. The survival of mitochondria within cells necessitated that glycolytic cell division had to be suppressed for successful parasitism of mitochondria. It is speculated that the origin of cell proliferation genes (oncogenes) might be from glycolytic cells, and the origin of proliferation-suppressor genes (tumor suppressor genes) might be from mitochondria.

Considering the history of eukaryotes, it is reasonable to see how we humans have two different energy production systems, namely, the anaerobic glycolysis pathway and the aerobic mitochondrial pathway. Energy produced by glycolysis is used for the "fight-or-flight" response and cell division, whereas energy produced by mitochondria is used for sustained physical output and suppression of cell division [6]. Moreover, the optimal body temperature is different, at 32 to 33°C for glycolysis and >37°C for mitochondria [3].

Otto Warburg reported that cancer cells contained few mitochondria and produced energy mainly by glycolysis [18]. Recent cumulative evidence also supports this earlier observation [19,20]. It is speculated that cancer cells are highly adaptive to hypothermia and hypoxia. It seems reasonable to consider that carcinogenesis itself (i.e., cross-return to living beings with glycolysis at 2 billion years ago by successful genetic mutation) is an adaptive response to overcome a stress-associated environment. Although the environment for the onset of cancer is produced by stress, the maintenance conditions for the growth of cancer cells might be produced by certain cytokines produced by macrophages and cancer cells themselves. For example, TNFα and TGFβ are known to induce hypothermia and hypoxia [21,22]. In other words, the mechanisms underlying the induction of hypothermia and hypoxia can affect different stages of cancer.

2. **Evaluation of Hypothesis**

In our recent study, many cancer patients could live and thrive without further tumor enlargement when they were exposed to mild hyperthermia (i.e., the maximum rectal temperature was 38.0°C for 15–30 min) [4]. In some cases, tumor regression resulted from mild hyperthermia. At this time, the pH, PO_2, PCO_2 values and other factors improved. Immunosuppression and anemia seen in the cancer patients were also alleviated. These results suggest that a slight shift in glucose metabolism from the glycolysis pathway to the mitochondrial pathway might be important in the treatment of malignant cancers. Locally administered, strong hyperthermia (e.g., 42°C) was not effective, and instead acted as a severe stress in cancer patients. Therefore, the systemic improvement of the internal environment is critical to cure cancer malignancy. Important considerations for spontaneous regression of cancer are as follows: change in harmful lifestyles (e.g., overwork), the use of a hot-water bottle at sleeping time, taking deep breaths several times a day, dietary considerations and the control of fear.

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