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The Dysfunction of Metabolic Controlling of Cell Hydration Precedes Warburg Phenomenon in Carcinogenesis

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At present, cancer is one of the major causes of death worldwide. However, the detailed mechanism of carcinogenesis is not clear yet.

More than 80 years ago Nobel Prize laureate Warburg pointed out that in cancerous cell the loss of oxidative capacity of mitochondria and the glycolytic metabolism shift relative to oxidative phosphorylation as O_2 could not reach to mitochondria [1]. However, the nature of the primary mechanism leading to generation of Warburg phenomenon has not been elucidated yet.

In 1971 the second revolutionary discovery was made in cancer research by Raymond Damadian, who elucidated that cancerous cell is markedly overhydrated and can be much as 90% water while in norm it can be 70-73%. "Magnetic Resonance" method [2] of detection of cell over hydration suggested by him which serves as an early tumor detection diagnostic method at present has a worldwide clinical usage. It is established that cell swelling triggers its proliferation, while cell shrinkage promotes its apoptosis [3-6]. Cell hydration causes not only the promotion of cell division and oncogene expression but also inactivates genes inducing cell apoptosis [7]. On the basis of these data cell over hydration was suggested as a primary messenger in carcinogenesis [3,7]. However, the nature of metabolic mechanism the dysfunction of which causes over hydration in cancer cells as well as the link between cell over hydration and Warburg phenomenon are also not elucidated yet. Therefore, it is suggested that the discovery of intracellular signaling pathway through which the correlation between cell hydration and mitochondrial function is realized could be one of the key problems of modern cancer research.

The cell membrane is highly permeable for water because of the existence of special water channels (aqua pores) [8] which makes cell hydration a dynamic and fundamental cell parameter determining its functional activity. Regulatory role of cell hydration is realized a) by changing the hydration of intracellular macromolecules (folding-unfolding mechanisms) [9] and b) by changing the number of surface-dependent functionally active protein molecules in membrane having receptors [10], enzymatic [11] and channel forming [12] properties.

It is known that Na^+/K^+ pump has a crucial role in regulation of cell hydration [3-5,13] and its dysfunction is a common consequence of any pathology including cancer [14]. Na^+/K^+ATP-ase (working molecules of Na^+/K^+ pump) has 4 catalytic subunits having different functional activities and sensitivities to cardiac glycoside: α_1 (low), α_2 (middle), α_3 and α_4 (high) [15], the latter is identified only in testis [14]. From these isoforms α_1 (fully) and α_2 (partly) have ion transporting function [15,16], while α_3 isoform mainly performs intracellular signaling function [17-19]. However, the individual role of these isoforms in cell volume regulation is not identified.

In healthy animals only the excitable cells (neurons and muscle) have all three isoforms, while in non-excitable cells only α_1 is expressed. Several studies have revealed a highly expressed α_3 isoform in cancer cells, which allows to suggest it to be one of the early hallmarks for carcinogenesis [20-22]. However, by our recent data it has been shown that the 3 isoforms are present both in tumor tissues and in non-excitable tissues of sarcoma tumor carrying mice, and these tissues are more hydrated compared to healthy mice tissues [23]. It was also shown that the number of these three isoforms in cell membrane increases by cell swelling and decreases by cell shrinkage [11]. Nevertheless, surface–dependent changes were more pronounced for α_3 receptors than for low affinity ones. Cell swelling and the increase of the number of α_3 receptors take place in response of stimulation of factor-induced increase of membrane permeability [11,24,25]. As α_3 receptors serve as an extra-sensitive and universal sensor for different chemical and physical factors [26,27] it is predicted that its abnormal activation could bring to over hydration which in its turn will lead to higher activation of mitochondrial function producing more CO_2 and H_2O in intracellular medium. As CO_2 solubility in aqua medium is more than 20 times higher than O_2 solubility [28], oxygen could not reach to mitochondria and would lead to generation of Warburg phenomenon. Therefore, prevention of generation of Warburg phenomenon can be achieved by both cell dehydration and the decrease of CO_2 solubility in cytoplasm. Previous our study has shown that static magnetic field which has dehydration effect on cells, including cancer [24,25] has also depressing effect on CO_2 solubility [29,30]. Therefore, magnetotheraphy could serve as one of the powerful tools for cancer prevention

The next pathway for cancer prevention could be the activation of bicarbonate transport (HCO_3) from the cells. There are different modes of bicarbonate transport: Na^+/HCO_3, Na driven CI/HCO_3 and K^+/HCO_3 [31]. It is suggested that the first two modes leading to the increase of intracellular Na^+ and intracellular CI respectively, have activation effect on mitochondrial function, while K^+/HCO_3 doesn't have such effect. Therefore, K^+/HCO_3 transporter protein could be considered as an effective therapeutic target for cancer prevention and the detailed study of the role of this protein in restoring the intracellular pH could serve as one of the modern problems in cancer prevention research.

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