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Mechanism of Changes Balance Anaerobic Processes and Aerobic Processes in Cancer Metabolism Causing Warburg Effect Mechanism

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Abstract

Changes balance catabolic anaerobic exergonic processes of oxidative phosphorylation and catabolic aerobic exergonic processes of respiratory oxidation induce violation interaction between mitochondrial oxidative processes and nuclear proliferative function. Just the changes balance catabolic anaerobic processes and catabolic aerobic processes cause transition Pasteur Effect "incompatible glycolysis and aerobic oxidation" in norm into Warburg effect "aerobic glycolysis" of cancer metabolism. Normal Stationary State of balance anabolic endergonic processes and catabolic exergonic processes is mutated into Quasi-stationary pathologic State due to the shift balance anabolic processes and catabolic processes into excessive anabolic processes with partial suppression catabolic processes in cancer tissue. Considering Krebs tricarboxylic citric acids cycle as the link between anaerobic catabolic processes and aerobic catabolic processes, it was explained the mechanism destruction of this link in cancer tissue metabolism. Thus the partial suppression of catabolic anaerobic exergonic processes leads to misbalance between catabolic anaerobic exergonic processes of oxidative phosphorylation and catabolic aerobic exergonic processes of respiratory oxidation in cancer tissue. This misbalance is induced by the expressed excessive anabolic processes in cancer tissue. These processes promote survival cancer cells as Apoptosis Resistance and display "aerobic glycolysis" which characterizes Warburg effect mechanism. Taking into account role of Citric acids cycle in the mechanism of the misbalance between catabolic anaerobic processes and catabolic aerobic exergonic processes in cancer tissue, it was offered the method prevention supplementary new metastasis by up-to-date methods of cytotoxic chemotherapy.

Keywords: Pasteur effect; Warburg effect; Anabolic endergonic processes; Glycolysis; Krebs tricarboxylic acids cycle [TCA]; Cellular capacitors; Reactive Oxygen Species (ROS); Fenton reaction

Introduction

The shift normal balance anabolic endergonic processes and catabolic exergonic processes into excessive anabolic processes causes partial suppression catabolic processes due to consumption great quantity Acetyl-CoA and energy by huge anabolic processes that leads to misbalance between anabolic processes and catabolic processes in cancer metabolism. Misbalance between anabolic processes and catabolic processes induce change mutual interactions between mitochondrial oxidative processes and nuclear proliferative function that causes increase production superoxide (O^{*}) and ROS/H_2O_2/Free radicals. These cancerous processes lead to mechanism irrepressible cancer tumors growth, metastasis and then to general violation metabolism of an organism, i.e., Quasi-stationary pathologic State of an organism. Also these cancerous processes violate stability of an organism's Internal Energy (U) [1,2]. Thus Stationary State of open non-equilibrium non-linear thermodynamic system of an able-bodied organism is characterized by stable balance catabolic exergonic processes & anabolic endergonic processes [3-6]. Quasi-stationary pathologic State of open non-equilibrium non-linear thermodynamic system of an organism is characterized by shift of balance catabolic processes & anabolic processes into excessive anabolic endergonic processes causing Warburg effect mechanism of cancer disease [3,4]. Quasi-stationary pathologic State of open non-equilibrium non-linear thermodynamic system of an organism is characterized by shift balance catabolic processes and anabolic processes into excessive catabolic exergonic processes in inflammatory processes [3,4].

The Mechanism Misbalance of Catabolic Anaerobic Processes and Catabolic Aerobic Processes in Warburg Effect Mechanism

Excessive anabolic processes in cancer tissue metabolism cause the excessive consumption energy and Acetyl–CoA for anabolic (biosynthetic) processes that lead to the overload of "nodal point bifurcation anabolic and catabolic processes [NPBac] in Acetyl-CoA". The overload of NPBac causes partial suppression catabolic processes because of the remained lack of Acetyl–CoA for catabolic anaerobic exergonic processes of oxidative phosphorylation (Figure 1) [3].

However some catabolic anaerobic processes remain for cancer cells survival. Besides the increase of lactic acids production is the necessary endergonic mechanism of accumulation energy for huge anabolic endergonic processes in condition of intensive Glycolysis metabolism and AKT expression [3]. Thus Warburg effect mechanism is formed in cancer tissue exhibiting combination Aerobic Oxidation with Glycolysis versus Pasteur Effect [Incompatibility Glycolysis with Aerobic Oxidation] in normal tissue (Figure 1) [3].

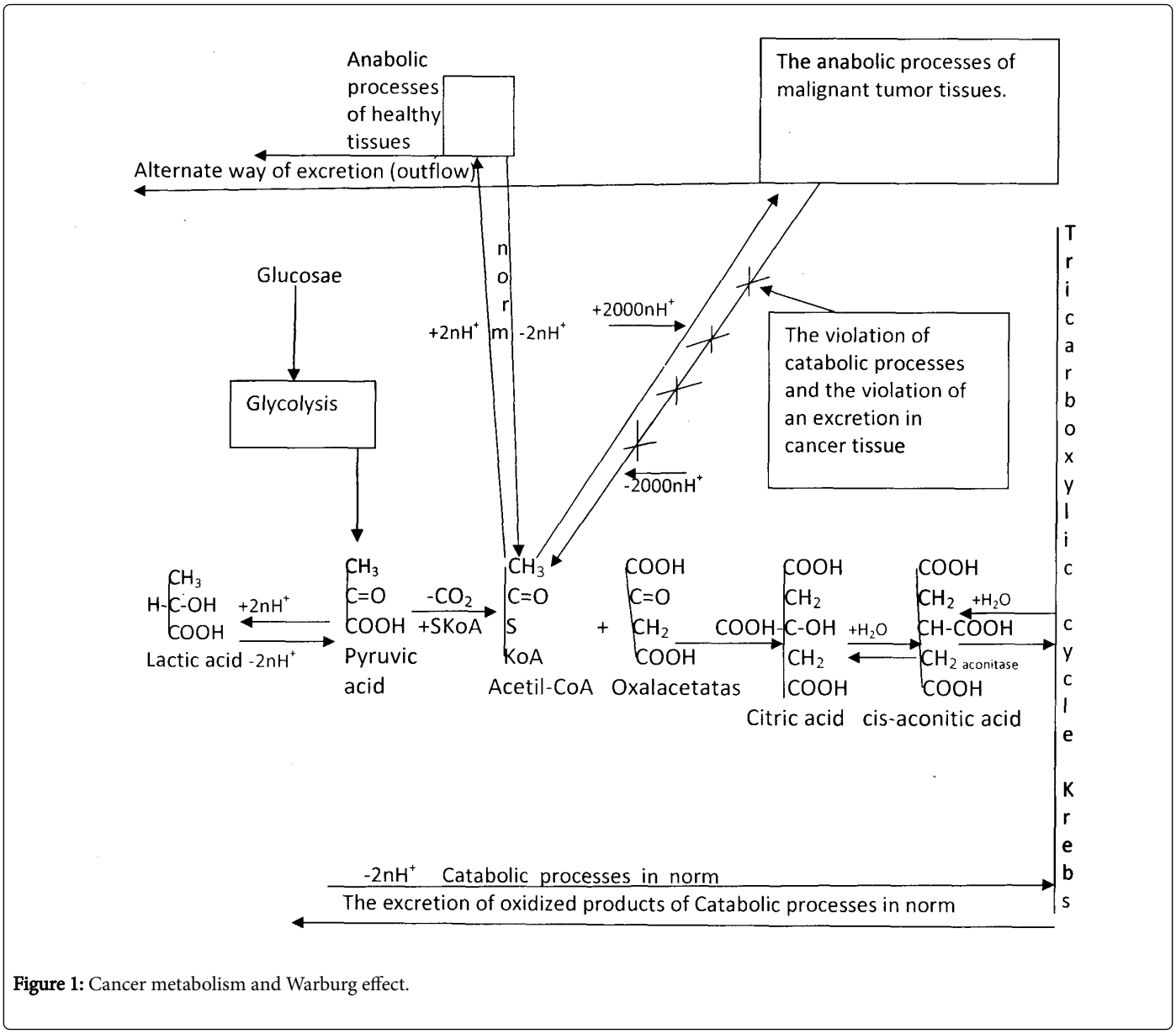

Figure 1: Cancer metabolism and Warburg effect.

Just the mechanism of Warburg effect leads to forming metastasis and unhealed cancer wounds in following mode: The overload of "nodal point bifurcation anabolic and catabolic processes" [NPBac] causes partial suppression catabolic anaerobic processes due to lack Acetyl-CoA. Partial suppression catabolic anaerobic exergonic oxidative phosphorylation impedes oxidative decomposing synthesized high-molecular substances leading to excretion these high-molecular substances within separated cancer cells. These separated cancer cells with high-molecular substances in them move to healthy tissue without overload of "nodal point bifurcation anabolic and catabolic processes" [NPBac] forming metastasis. Besides some cancer cells with the high-molecular substances in them fall out into environment that forms cancerous unhealed wound. Moreover partial suppression of catabolic anaerobic processes leads to prevalence aerobic oxidation over anaerobic oxidative phosphorylation. Thereby these two catabolic pathways develop separately displaying "aerobic glycolysis" in Warburg effect mechanism of cancer metabolism. As concern to Pasteur Effect of able-bodied metabolism, it occurs the suppression glycolysis and aerobic oxidation one another due to the identical catabolic pathways of aerobic oxidation and glycolysis anaerobic oxidative phosphorylation, exhibiting "incompatible glycolysis and aerobic oxidation in norm" [3] (Figure 1). Just mitochondrial aerobic oxidative function produces stable quantity Oxygen ions [O^{-2}] via operation of cytochrome system [cytochrome C, cytochrome-c-oxidase, cytochrome P450 etc.] in cancer cells because of delivering stable quantity Oxygen (O_2) by Hemoglobin system in blood corresponding to stable Respiratory Index [CO_2/O_2=0.8-1.0] in an organism. The shift balance Aerobic oxidative processes and anaerobic processes of oxidative phosphorylation into prevailing Aerobic oxidative processes in mitochondria of cancer cells causes increase of Reactive Oxygen Species (ROS). Increase of Reactive Oxygen Species (ROS) induces increased quantity mitochondrial superoxide [O_2^{*}] because supplementary oxygen [O_2] adds electron and is transformed into superoxide [O_2^{*-}] (Figure 2).

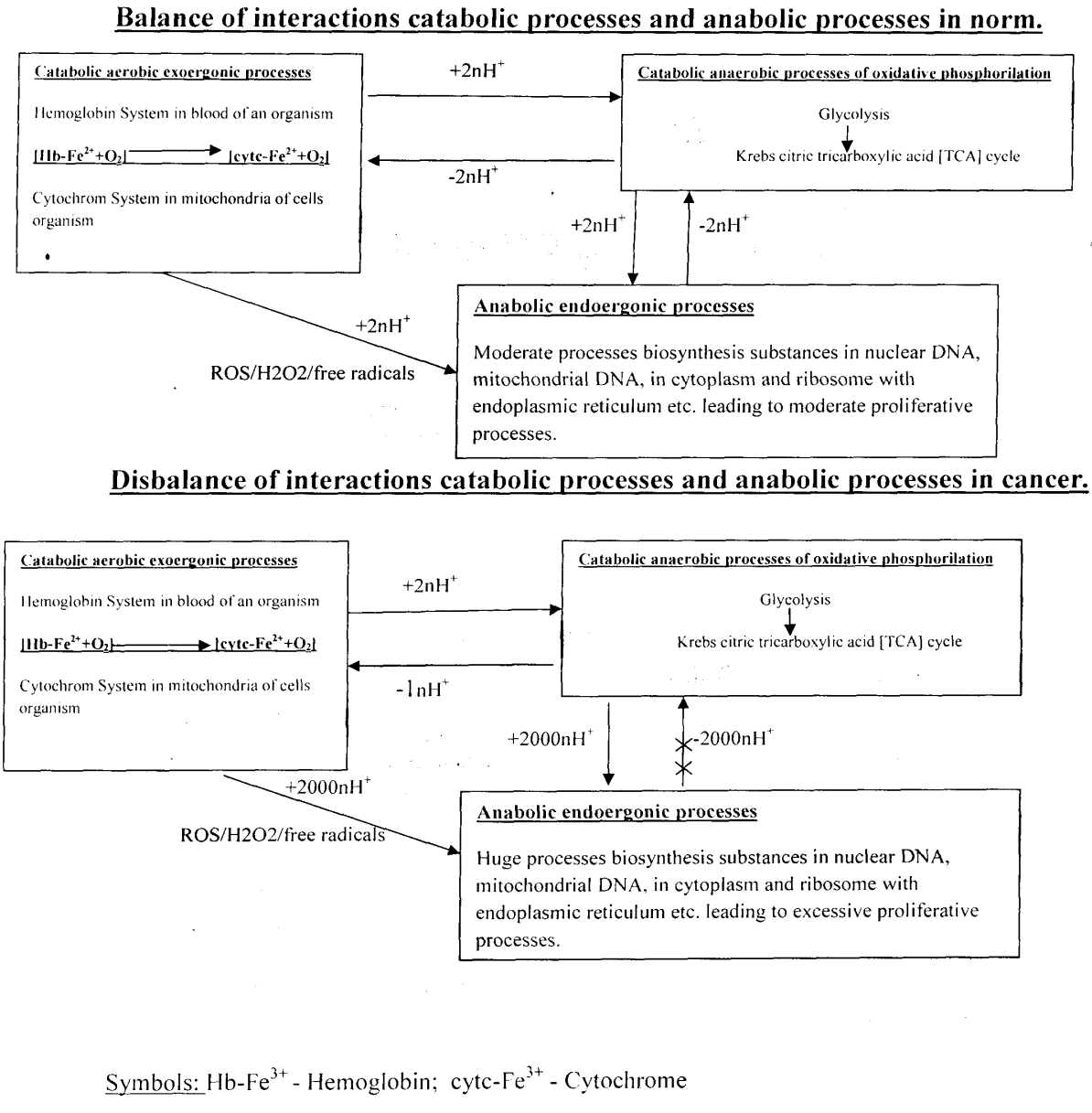

Figure 2: Interaction catabolic and anabolic processes.

The increased quantity of mitochondrial superoxide [O_2^{*}] does not support processes of suppressed anaerobic oxidative phosphorylation and does not lead to final products CO_2 and H_2O. The superoxide [O_2^{*-}] reduces Ferric iron [Fe^{3+}] into Ferrous iron [Fe^{2+}] and forms supplementary oxygen:

$$O_2 + e^- \rightarrow O_2^{*-} \quad (1)$$

$$O_2^{*-} + Fe^{3+} \rightarrow Fe^{2+} + O_2 \quad (2)$$

Then superoxide anion is subjected to dismutation by manganese superoxide dismutase (MnSOD) and copper-zinc superoxide dismutase (Cu, ZnSOD) converting into hydrogen peroxide:

$$2O_2^{*-} + 2H^+ = H_2O_2 + O_2 \quad (3)$$

The normal steady concentration of superoxide [O_2^{*}] is higher in mitochondrial matrix than in cytoplasm and nucleus. Thus it happen Haber-Weiss reaction of catalyzed iron production via superoxide transformations which pass into Fenton reaction with forming free radicals [7-9]:

$$Fe^{3+} + O_2^{*-} \rightarrow Fe^{2+} + O_2$$

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + -OH + {}^{*}OH$$

$$O_2^{*-} + H_2O_2 \rightarrow {}^{-}OH + {}^{*}OH + O_2 + Fe^3 \quad (4)$$

The formed complex ROS/H_2O_2 with free radicals (*OH) passes through mitochondrial membranes and cytoplasm into nucleus. Free radicals (*OH) react on nuclear DNA [nDNA] and induce process replication via realizing of 2nDNA [8]:

$^*OH + H_2$-nDNA-DNA –-> $H_2O + H^\bullet$-nDNA-DNA

$O^* + 2H_2O$ –-> $2H^\bullet + 2OH^-$

$2H^\bullet$-nDNA-DNA + $2H^\bullet$ –-> 2nDNA-$H^\bullet$ + 2nDNA-$H^\bullet$

2nDNA-$H^\bullet$ + 2^*OH –-> 2nDNA + H_2O (5)

Thus the free radicals (*OH and $H^\bullet$) induce nDNA replication in G2 phase cellular cycle, and also the free radicals (*OH and $H^\bullet$) are neutralized in final G2 phase of nDNA replication as in cancer cells as well as in normal cells [7-13]. Then it occurs M phase of cellular cycle, i.e., Mitosis in cell division.

The Role of Misbalance Energy Flows in Transmutation Pasteur Effect Mechanism of Able-Bodied Metabolism into Warburg Effect Mechanism of Cancer Metabolism

Just mutual exchanges of equal quantity positive and negative energy as between Catabolic processes and Anabolic processes as well as between Catabolic aerobic processes and Catabolic anaerobic processes contribute to both balance Catabolic processes and Anabolic processes and balance Catabolic anaerobic processes and Catabolic aerobic processes as in an organism as well as in cells of an organism in norm (Figure 2). Balance catabolic processes and anabolic processes and balance catabolic anaerobic processes and catabolic aerobic processes in cells of an organism determine stable Internal Energy of cell (U_{cell}) in norm. Just stable Internal Energy of cell (U_{cell}) shows stable cellular chemical potential (μ_{cell}) due to basophilic coloration cytoplasm via staining of cell. Stable chemical potential of cytoplasm ($\mu_{cytoplasm}$) induces the charges in internal cellular membrane of cellular wall and in external membranes of both mitochondrial shells and nuclear shells. The operations of nucleus and mitochondria determine as nuclear chemical potential ($\mu_{nucleus}$) as well as mitochondria chemical potentials ($\mu_{mitochondria}$) which induce the charges as in the internal nuclear membrane of nuclear shell as well as in the internal mitochondrial membranes of mitochondrial shells. The chemical potential of cells' external medium (μ_{medium}) induces the charge in external cellular membrane of cellular wall. Thus these charges in nuclear membranes, in mitochondrial membranes and in cellular membranes create nuclear capacitors, mitochondrial capacitors and cellular capacitors. The operations of cellular capacitors promote via cells' relative resonance waves maintenance stability Internal Energy of an organism (U) [Stable temperature 36.6C-36.9C by which all enzymes operate, and the other indices]. Also dynamic interactions between nucleus capacitor and mitochondria capacitors determine the stable cytoplasm Internal Energy (cytoplasm) showing stable cytoplasm basophilic chemical potential ($\mu_{cytoplasm}$) [14,15]. Shift balance Aerobic oxidative respiratory processes and anaerobic processes of oxidative phosphorylation into increase of Aerobic oxidative processes in cancer tissue leads to misbalance between dynamic interactions nucleus capacitor and mitochondria capacitors in cancer cells. It makes cellular chemical potential of cancer cells ($\mu_{cancer\ cell}$) unrelated to cellular chemical potentials of an organism's cells (μ_{cell}). Misbalance between cellular chemical potential of cancer cells ($\mu_{cancer\ cell}$) and cellular chemical potentials of an organism's cells (μ_{cell}) results in forming excessive Reactive Oxygen Species (ROS) and Free radicals leading to production of excessive quantity superoxide [O^*] because of surplus delivery of Oxygen ion in cancer cells' mitochondria (see above part 3) (Figure 2). So production of excessive quantity Free radicals exerts irrepressible proliferative processes of cancer cells via excessive realizing of 2nDNA replications [10-15].

The Role Changes Basic Metabolism of Glycolysis and Krebs Tricarboxylic Acids Cycle (TCA) in Causing Transmutation Pasteur Effect Mechanism of Able-Bodied Metabolism into Warburg Effect Mechanism of Cancer Metabolism

Glycolysis and Krebs Tricarboxylic Acids Cycle (TCA) create catabolic anaerobic oxidative phosphorylation in three mediums: In cytoplasm, in mitochondria, in extracellular medium of an organism's tissue (Figures 3 and 4). Catabolic aerobic respiratory processes in lung exert oxidative respiration which transfers oxygen [O_2] into system of Hemoglobin in blood forming balance catabolic anaerobic processes and catabolic aerobic processes in tissue of extracellular medium. Besides oxygen [O_2] is transferred from Hemoglobin in blood into cytochrome systems [especially cytochrome C] in cellular mitochondria forming balance catabolic anaerobic processes and catabolic aerobic processes both in cytoplasm and in mitochondria (Figures 3 and 4). Krebs Tricarboxylic Acids Cycle (TCA) carries out role of main driving mechanism of production supplementary superoxide (O_2^*) in such mode: Produced in Krebs TCA Hydrogen ions (H^+) react with Oxygen (O_2) and form Water (H_2O) that must eliminate Oxygen from liquids of an organism and cells of an organism (Figure 3). However the supplementary Oxygen (O_2) does not find sufficiently Hydrogen ion (H^+) to react with Oxygen (O_2) and does not produce supplementary Water (H_2O). Therefore this supplementary Oxygen (O_2) adds electron due to Reactive Oxygen Species (ROS) operation and is transformed into superoxide (O_2^*) which generates free radicals.

Free radicals exert DNA replications in G2 phase of cellular cycle via inducing reaction 2nDNA replication in norm. Partial suppression catabolic processes of Krebs tricarboxylic acids cycle (TCA) increases insufficient Hydrogen ions (H^+) production in cancer metabolism. The great insufficiency of Hydrogen ions (H^+) production causes abundance superoxide (O_2^*) inducing excessive quantity of ROS/H_2O_2/free radicals which exert accelerative DNA replications via inducing accelerative reaction 2nDNA reactions in cancer cells. Thus moderate cellular replication occurs in norm due to production moderate quantity ROS/H_2O_2/free radicals in able-bodied cells, and irrepressible excessive cellular replication occurs in cancer cells' nuclei due to production excessive quantity of ROS/H_2O_2/free radicals in cancer cells [8,14].

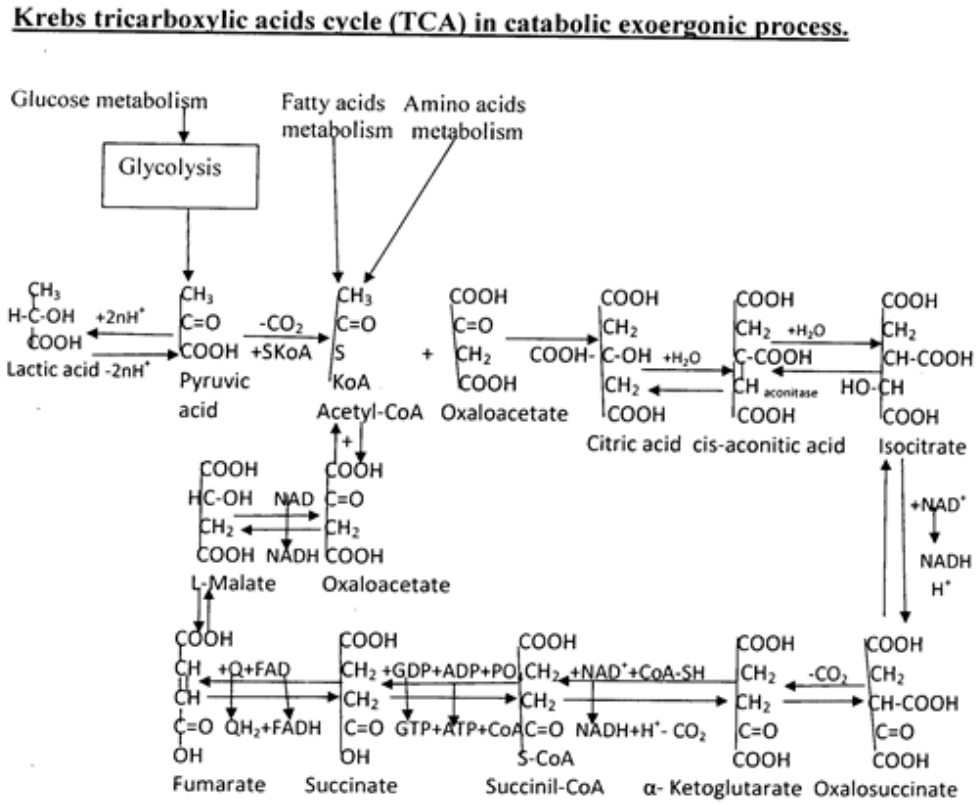

Figure 3: Krebs tricarboxylic acids cycle.

Interactions between catabolic processes in mitochondria, cytoplasm, extracellular medium and anabolic processes in nucleus and extracellular medium induce different charges on Internal and External Membranes of cellular capacitors, nuclear capacitors, mitochondrial capacitors and the other organelles' capacitors. Operations of all these capacitors contribute to maintenance stability Internal Energy of all cells due to relative resonance waives between them in norm [4,12]. The interactions between oxidative processes in mitochondria, proliferative processes in nucleus and operation all cellular capacitors promote maintenance stability balance anabolic endergonic processes & catabolic exergonic processes causing stability Internal Energy both in an able-bodied organism and in cells of an organism in norm.

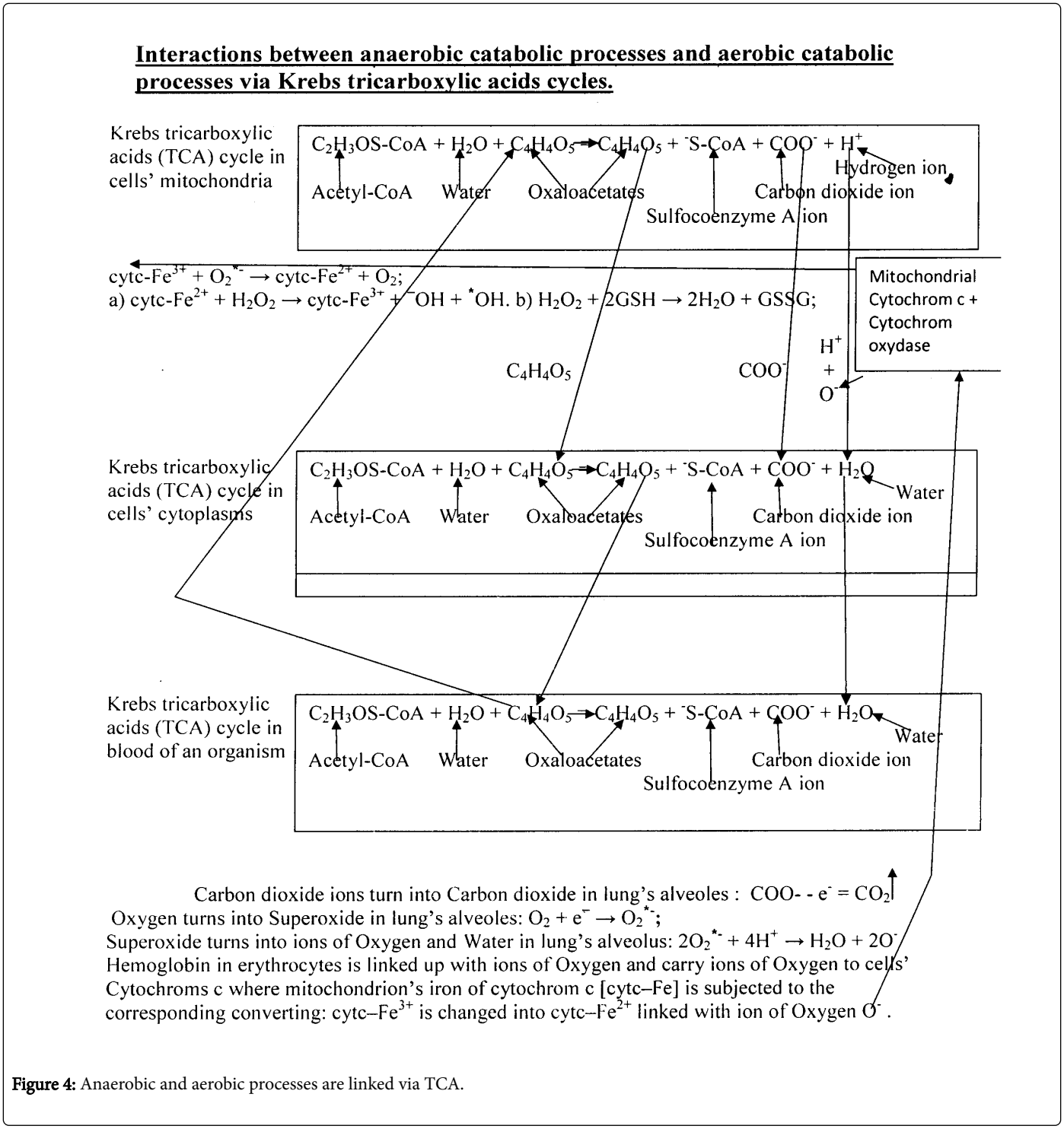

Figure 4: Anaerobic and aerobic processes are linked via TCA.

Besides balance anabolic processes and catabolic anaerobic processes and balance catabolic anaerobic processes and catabolic aerobic processes depend on each other. Thus common balance catabolic anaerobic processes and catabolic aerobic processes and anabolic processes [Common Balance [anaerobic, aerobic, and anabolic] is the joint mechanism which creates as biochemical maintenance stability Internal Energy as well as biophysical maintenance stability Internal Energy of an organism and cells of an organism [3,15]. Excessive anabolic processes of cancer metabolism causes misbalance of anabolic processes and catabolic processes which induce misbalance catabolic anaerobic processes & catabolic aerobic processes via partial suppression catabolic anaerobic processes in Krebs tricarboxylic citric acid cycle [TCA] due to prevalence aerobic processes over anaerobic processes. Partial suppression catabolic anaerobic processes in link Glycolysis-Krebs tricarboxylic citric acid cycle [TCA] occurs in extracellular medium of cancer tissue, in cancer cells' cytoplasm and in cancer cells' mitochondria inducing misbalance of operations system cytochromes in mitochondria and nuclear

functions. Thus the violation common balance stability of anabolic processes and catabolic anaerobic processes and catabolic aerobic processes occurs in nucleus, in cytoplasm and in mitochondria of the oncogene affected cell. The violation common balance stability anabolic processes and catabolic anaerobic processes and catabolic aerobic processes of the oncogene affected cell results in transmutation normal cell into cancer cell via increasing quantity Lactic acids, as the main marker of glycolysis, reflecting transmutation Pasteur effect [incompatibility glycolysis and aerobic oxidation] into Warburg effect [aerobic glycolysis], i.e., increasing glycolysis with great expression of aerobic oxidation. As matter of fact Common Balance stability [anaerobic, aerobic, and anabolic] makes even distribution of glycolysis' production-Lactic acids between anaerobic, aerobic and anabolic pathways that impedes either increase quantity Lactic acids by expression aerobic oxidation or expression aerobic oxidation by increase quantity Lactic acids, i.e., displays "incompatibility glycolysis and aerobic oxidation in norm" according Pasteur effect. The violation common balance stability anabolic processes and catabolic anaerobic processes and catabolic aerobic processes via shift into excessive anabolic processes uses huge quantity Lactic acids for accumulation huge quantity energy needing for excessive anabolic processes in cancer metabolism. Thus huge quantity Lactic acids due to excessive anabolic processes with expression aerobic processes result in "glycolysis oxidation in cancer metabolism" according Warburg effect. The advanced cancer process via irrepressible cancer tumor growth and metastasis leads to transition Stationary State of an organism into Quasi-stationary pathologic State of an organism. However cancer cells don't exhibit strange chemical potentials ($\mu_{can.cells}$) to chemical potential of an organism ($\mu_{org.}$) although chemical potentials of cancer cells ($\mu_{can.cells}$) are unrelated to chemical potentials of an organism ($\mu_{org.}$) and chemical potentials of an organism's cells ($\mu_{org.cells}$). Thus cancer cells are unrelated to an organism and an organism's cells. Hence cancer cellular capacitors don't create cohesive resonance waves joining cancer cells with an organism. Thereby cancer cells are not subjected to regulating influences of an organism showing autonomous development of cancer cells [11,14]. Cancer cells display considerably accelerated cellular cycle due to production of excessive ROS/H_2O_2/Free radicals in mitochondria being caused by oncogene affected DNA operations which are induced by misbalance between nuclear capacitors operations and mitochondria capacitors operations. Accelerative cancer cellular cycle being induced by accelerated v-oncogene cycle causes excessive proliferative processes via realizing excessive 2nDNA process replication.

Highlight of Warburg effect mechanism: As outcome of oncogenes operation the huge anabolic processes cause huge consumption of energy and Acetyl-CoA and partial suppress catabolic anaerobic processes in cancer tissue due to lack Acetyl-CoA for catabolic anaerobic processes in cancer metabolism. Just Lactic acids accumulate energy for excessive anabolic processes in condition glycolysis metabolism in cancer tissue. Partial suppression catabolic anaerobic oxidative phosphorylation of link Glycolysis-Krebs tricarboxylic citric acids cycle causes shift balance Aerobic oxidative respiratory processes and anaerobic processes of oxidative phosphorylation into prevalence of Aerobic oxidative processes. Partial suppression of Anaerobic processes of oxidative phosphorylation of cancer cells induces forming excessive quantity of ROS/H_2O_2/Free radicals in mitochondria which exert excessive accelerating replications in G2 phase cellular cycle via realizing of excessive 2nDNA replication process causing cancer cells' irrepressible proliferative processes and cancer tumor growth (Figure 2).

States of Common Mechanisms Maintenance Stability Internal Energy of an Organism and Cells of an Organism in Norm and in Cancer Pathology

Studying human organism as an open thermodynamic system, it was considered energy flow causing mechanism maintenance stability Internal Energy of an organism. The stable balance of catabolic exergonic processes and anabolic endergonic processes determines stability Internal Energy of Stationary State healthy human organism according first law of thermodynamics. The pathologic Internal Energy of an organism is formed due to shift balance catabolic exergonic processes and anabolic endergonic processes into excessive anabolic processes showing Quasi-stationary pathologic State of cancer disease. Otherwise the pathologic Internal Energy of an organism is formed due to shift balance catabolic exergonic processes and anabolic endergonic processes into excessive catabolic processes showing Quasi-stationary pathologic State of inflammation disease. The interdependence between balance catabolic processes and anabolic processes and balance catabolic anaerobic processes and catabolic aerobic processes causes mechanism maintenance stability of common balance catabolic aerobic processes and catabolic anaerobic processes and anabolic processes [Common Balance [anaerobic, aerobic, and anabolic]]. Common Balance [anaerobic, aerobic, and anabolic] determines stability Stationary State of a healthy human organism and cells of an organism. The mechanism maintenance stability of Common Balance [anaerobic, aerobic, and anabolic] includes catabolic processes of aerobic respiratory oxidation in lung, system of Hemoglobin in blood, system cytochrome in mitochondria, catabolic anaerobic processes of oxidative phosphorylation [link Glycolysis–Krebs tricarboxylic acids cycle] and anabolic processes in nucleus, in cytoplasm, in extracellular medium of tissue. The joint mechanism of nuclear capacitors operation, mitochondrial capacitors operations, and cellular capacitors operation causes mechanism stability Internal Energy of a healthy human organism and cells of an organism. Just the mechanism stability of Common Balance [anaerobic, aerobic, and anabolic] is subjected to the joint mechanism of all cellular capacitors operation in norm. The mechanism transitions Stationary States of a healthy metabolism into Quasi-stationary pathologic State of cancer disease metabolism occurs due to destruction Common Balance [anaerobic, aerobic, and anabolic] because of expression abundance anabolic processes and prevalence catabolic aerobic processes over partial suppressed anaerobic processes in cancer tissue metabolism. These changes create misbalance between catabolic aerobic processes, catabolic anaerobic processes and anabolic processes causing Warburg effect mechanism of cancer metabolism. Mechanism of Warburg effect displays also biochemical and biophysical mechanisms of development cancer cells via irrepressible proliferative processes inducing cancer tumor irrepressible growth and cancer metastasis. Such development cancer cells leads to pathological Quasi-stationary State of an organism [3].

Critical Reviews of Mechanism Metastasis and Role Mechanisms Exertion Krebs Tricarboxylic Citric Acids Cycle in Cancer Metabolism as Well as in the Mechanism Prevention Supplementary Metastasis in Processes of Up-To-Date Chemotherapy

The some theories explain mechanism of cancer metastasis based on the low expression of K^+ in the Kv channel of malignant tumors [16-18] and also the role of mitochondrial frataxin protein in

mechanism of cancer metastasis [3,19]. The above explained mechanism of Warburg effect gives possibility to explain the mechanism metastasis in following mode [3]: The huge anabolic processes block excretion from cancer tissue of synthesized high-molecular substances via oxidative destruction them because of overload "Nodal point bifurcation anabolic and catabolic processes [NPBac]" and lack of Acetyl-CoA for oxidative processes (Figure 1). Therefore the excretion of synthesized high-molecular substances occurs within cancer cells which move to healthy tissue without overloaded "Nodal point bifurcation anabolic and catabolic processes [NPBac]" and having sufficiency of Acetyl-CoA. These cancer cells are carried by lymph or blood causing cancer metastasis. Really expression of mitochondrial frataxin occurs due to overload "Nodal point bifurcation anabolic and catabolic processes [NPBac]" and lack Acetyl-CoA which promotes partial suppression anaerobic oxidative phosphorylation and causes prevalence aerobic oxidative processes over anaerobic oxidative phosphorylation in mitochondria. Just the overload NPBac and lack Acetyl-CoA leads to expression of mitochondrial frataxin because of overload NPBac and prevalence aerobic oxidative processes over anaerobic oxidative phosphorylation in mitochondria [3,19]. Besides the low expression of K^+ in the Kv channel of malignant tumors is induced by overload "Nodal point bifurcation anabolic and catabolic processes [NPBac]" and lack Acetyl CoA, which is the carrier of K^+ ions in Kv channel. Thus the mechanism of cancer metabolism promotes the low expression of K^+ in the Kv channel [16-18]. The partial suppression catabolic processes due to overload "Nodal point bifurcation anabolic and catabolic processes [NPBac]" and lack Acetyl-CoA in cancer tissue touches on Krebs tricarboxylic citric acids cycle [TCA] via partial suppression mechanism transferring Oxaloacetates from cancer tissue TCA to cancer cells' TCA (Figure 4). The partial suppressed mechanism transferring Oxaloacetates from cancer tissue TCA to cancer cells' TCA violates link between cancer tissue TCA and both cancer cells' mitochondrial TCA and cancer cells' mitochondrial cytochrome system. Thus overload NPBac with partial suppressed mechanism transferring Oxaloacetates from cancer tissue TCA to cancer cells' TCA results in expression mechanism metastasis due to blocking oxidative destruction of synthesized high-molecular substances in cancer tissue (Figure 4). Also operations of cancer cells' cellular capacitors via related resonance waves promote movement cancer cells with the synthesized high-molecular substances within them to healthy tissue without overload "Nodal point bifurcation anabolic and catabolic processes [NPBac]" and lack of Acetyl-CoA and cause metastases. The use citric acids from citric juice, in which the enzymes for Citric Acids cycle are preserved, exerts expression Krebs tricarboxylic citric acids cycle (TCA) and increases Acetyl-CoA eliminating overload "Nodal point bifurcation anabolic and catabolic processes [NPBac]" and partial suppression catabolic anaerobic processes. Elimination overload NPBac with partial suppression catabolic anaerobic processes contributes to prevention additional metastasis in processes of up-to-date chemotherapy. Really excessive quantity of citric acids with appropriate enzymes increases quantity Acetyl-CoA due to mechanism maintenance stable index of Equilibrium Constant reaction in Krebs tricarboxylic acids cycle (1): Acetyl-CoA^+ Oxaloacetate ↔ Citric acid (Figure 3 and 4). This reaction in Krebs tricarboxylic acids cycle [TCA] moves right saving stable Equilibrium Constant of the reaction Acetyl-CoA^+ Oxaloacetate → Citric acid. However this reaction moves left via increase Acetyl-CoA in condition increased quantity citric acid for saving stable Equilibrium Constant of the reaction Acetyl-CoA^+ Oxaloacetate ← Citric acid. Increased quantity of Acetyl-CoA eliminates overload "Nodal point bifurcation anabolic and catabolic processes [NPBac]" and partial suppression catabolic anaerobic processes that contributes to prevention additional metastasis in processes of up-to-date chemotherapy. Beside increased quantity citric acids exert Citric Acids cycle causing expression of catabolic anaerobic processes that stimulates also catabolic aerobic processes via mitochondrial frataxin protein operation with cytochrome c inhibiting cancer metabolism and preventing supplementary cancer metastasis in processes of up-to-date chemotherapy. There are the clinical observations: I have treated the sick man whom was found the multiple metastases in visceral peritoneum. The sick man has refused himself from the offered alternative therapy of "Prolonged medical starvation during 45 days with small dosage cytotoxic remedy" [20-23] and has chosen up-to-date chemotherapy with Fluorouracil and Erbitux immunotherapy. Taking into account the above described mechanisms of the role citric acids in Citric acids cycle, I have recommended him to use citric juice from the squeezed two citrons by day which should be diluted in 1 liter water for prevention intestine irritation due to great concentration of citric acids. This method must be used simultaneously with chemotherapy as the supplementary method for prevention new metastasis. The patient has drunk the citric juice prepared in such mode during two months. Then patient has drunk the citric juice from the squeezed one citron daily which was diluted in 1 liter water. The weekly examinations showed that there were not found new metastasis by the patient during the period of two years. The state of the patient is satisfactory.

Acknowledgments

This article is dedicated to the memory of my daughter T.M. Ponisovska.

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