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Biophysical and Biochemical Transmutation of Mitochondrial Function in Cancer Genesis

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Abstract

Interactions between nuclear processes and mitochondrial processes determine stabile basophilic chemical potential in cytoplasm, i.e. stability cellular Internal Energy and Internal Medium. Interactions between all cells of an organism occur due to remote reactions across distance as the results of cellular capacitors operations via production of resonance waves. Interactions between cellular capacitors of cells maintain common stability of Internal Energy and Internal Medium both in cells and in an organism. Considering mechanism maintenance stability cytoplasm of cell there were explained differences between mechanisms occurring in mitochondria of normal cellular cycle and in mitochondria of oncologic cellular cycle which displays mitochondrial mechanism of oncogenesis. The role mitochondrial DNA and production complex ROS/H_2O_2/free radicals in mitochondrial function of both normal cellular cycle and oncologic cellular cycle were explained from the point of view of the offered concepts. The outcomes of some investigations of development processes in cancer cells' mitochondria were critical reviewed from the point of view of offered concepts, and results some experiments were explained eliminating doubts which were expressed by the authors of these experiments. Also there was presented benefits of mitochondrial targeting via the new possibility of cancer disease treatment.

Keywords: Nuclear DNA; ROS; Free Radicals; Mtdna; Glutathione Peroxide

Introduction

Oncogenesis advances upward from able-bodied cells to cancer cells. Therefore role mitochondria in mutagenesis should be considered from the point of views of thermodynamics, biophysics, and biochemistry comparing mechanism of normal development various activities mitochondria in cellular cycle, leading to moderate proliferative processes, with the oncological mitochondria transformation in cellular cycle of cancer cells, leading to excessive proliferative processes. Researchers encounter with difficulties to explain differences of interactions between cells survival and ROS/H_2O_2/free radicals in normal cells and in cancer cells. On the one hand, ROS/H_2O_2/free radicals damage cell. On the second hand, cancer cells exhibit irrepressible proliferative processes and increased quantity ROS/H_2O_2/free radicals versus normal cells which exhibit moderate quantity ROS/H_2O_2/free radicals and moderate proliferative processes. The offered concept of the mechanisms participation ROS/H_2O_2/free radicals in proliferative processes and neutralization ROS/H_2O_2/free radicals in proliferative processes eliminates doubts the authors some experiments concerning explanation of difference these mechanisms in normal cells and in cancer cells. Also this concept gave possibility to explain interactions between nucleus and mitochondria for maintenance stability of cellular Internal Energy, according to first law of thermodynamics, as in normal cells and as well as in cancer cells.

The Pathways of Catabolic Processes in Warburg Effect Mechanism of Cancer Metabolism

The mechanism of Warburg effect displays such concept: As the result of oncogenes operation causing enormous anabolic processes in cancer tissue and the enormous consumption of energy and Acetyl–CoA for anabolic (biosynthetic) processes, it takes place the overload of "nodal point of bifurcation anabolic and catabolic processes [NPBac]" because of the remained lack of Acetyl–CoA for catabolic oxidative processes. Such shift into anabolic processes and lack Acetyl-CoA causes suppression of the development catabolic processes in cancer tissue. The increase of lactic acids production is the necessary endoergonic mechanism of energy accumulation for huge anabolic processes in condition glycolysis metabolism and enormous consumption of energy for anabolic processes in cancer tissue" [1] (Figure 1). However the necessary quantity catabolic processes of oxidative phosphorilation are preserved for cancer cells survival.

The mechanism of Warburg effect is also explained considering the result calculation of "Mayerhof index" which shows the similar values 4–6 for both malignant tumour tissue and normal tissue [oxygen consumption is approximately identical in malignant tumour tissue and normal tissue despite of high level glycolysis in malignant tumor tissue] [2-4]. Generating energy due processes transphosphorylation via ATP/ADP/AMP, catabolic anaerobic processes of glycolysis are the primer for development of both catabolic processes and anabolic processes. Stimulating glycolysis, AKT pathway is also the primer for both catabolic processes and anabolic processes. However the increase of oxygen consumption doesn't happen in cancer tissue as compared with the normal tissue despite of high glycolysis in cancer tissue, because plenty of anaerobic catabolic processes of glycolysis are replaced in the "nodal point of bifurcation anabolic and catabolic processes [NPBac]" into anabolic processes in cancer tissue.

Furthermore necessary aerobic catabolic processes remain the same in cancer tissue as in the able-bodied tissue for cancer cells survival to maintain stability cellular Internal Energy. Just the catabolic aerobic exoergonic processes generate vast quantity energy and dissipate energy into environment for maintenance temperature 36.6°C-37.2°C by which all enzymes operate, exhibiting aerobic glycolysis of Warburg

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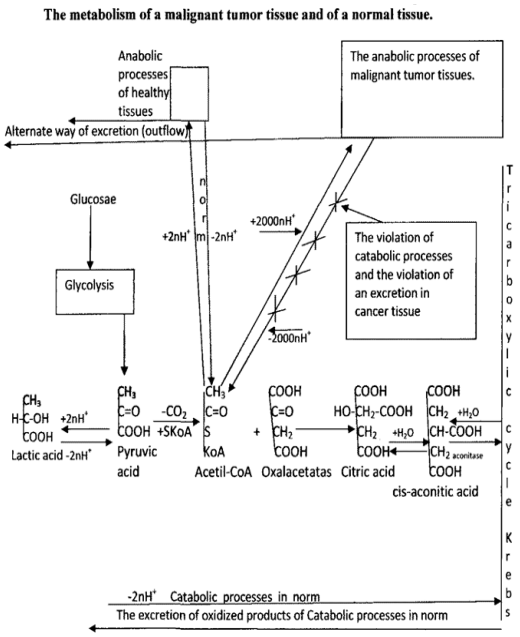

The legends to the article entitled "Biophysical and biochemical transmutation of mitochondrial function in cancer genesis".

Figure 1: The metabolism of a malignant tumor tissue and of a normal tissue
a) Nodal point of bifurcation anabolic and catabolic processes.
b) Huge anabolic processes with huge consumption of energy and Acetyl-CoA for anabolic processes leading to overloading "Nodal point of bifurcation anabolic and catabolic processes" [NPBac] in cancer tissue.
c) Moderate metabolic processes displaying balance anabolic and catabolic processes in able-bodied tissue.
d) Alternative excretion of high-molecular substances within the structure rejected cells and the violation of excretion substances via oxidative processes due to suppression of catabolic oxidative processes in cancer tissue.
e) Accumulation of energy into lactic acid for anabolic processes.
f) Normal excretion substances via catabolic oxidative processes in able-bodied tissue.

effect. Thus generating necessary energy via aerobic oxidation is identical both in malignant tumour tissue and in normal tissue because it promotes stabilization of cellular Internal Energy leading to cells survival. Thus the result calculation of "Mayerhof index" elucidates distinction Warburg effect mechanism from Pasteur Effect mechanism: Warburg effect mechanism in oncogenesis displays compatible combination resisted pathways of glycolysis, which is replaced into anabolic pathway in [NPBac], and catabolic aerobic oxidative pathway. Pasteur Effect mechanism in normal tissue metabolism displays incompatible combination identical pathways of glycolysis, as catabolic anaerobic processes, and catabolic aerobic processes [1].

The role excessive ROS production in oncogenesis exerting cellular cycle and promoting cancer cells survival is described below

Highlight: Catabolic anaerobic processes of glycolysis carry out peculiar functions as the primer for both anabolic endoergonic processes and catabolic exoergonic oxidative processes, maintaining balances catabolic and anabolic processes as in stationary state of able-bodied cells as well as in quasi-stationary state of cancer cells, providing their survival. Catabolic anaerobic processes of glycolysis is divided into anabolic and catabolic processes in "nodal point of bifurcation anabolic and catabolic processes [NPBac]" and generate energy which is accumulated into Lactic acids for excessive anabolic processes of cancer metabolism. The excessive anabolic processes suppress catabolic anaerobic processes remaining the part of the energy oxidative phosphorilation in cycle Krebs for cancer cells survival which generate considerable energy maintaining temperature 36.6ºC-37.5ºC by which all enzymes operate. Thus, the mechanism aerobic glycolysis of Warburg effect is formed in cancer tissue [1].

The Connections between Catabolic Anaerobic/Aerobic Exoergonic Processes and Anabolic Endoergonic Processes in Norm

The mechanism maintenance stability Internal Energy (temperature 36.6ºC-37.2ºC, by which all enzymes operate) and Internal Medium (constant concentrations of substances in blood and in neurolymph) an organism is formed under the influences of mechanisms interactions between intracellular chemical potentials (μ_{intr}) of all cells and extracellular chemical potential (μ_{extr}) which define also stability of Internal Energy and Internal Medium of cells' cytoplasms in norm [5]. Intracellular chemical potential (μ_{intr}) of every cell is formed via interactions between anabolic processes and catabolic processes in a cell. Intracellular anabolic processes are occurred mainly in nucleus. Intracellular catabolic aerobic processes are occurred mainly in mitochondria. Catabolic anaerobic processes of oxidative phosphorilation occur as in intracellular medium as well as in extracellular medium.

Advances of cellular processes occur via cellular cycle, or via intracellular changes due to environment influences, or via cellular aging which create fluctuations chemical potentials (μ_{intr}) via moderate oscillations of intracellular balance anabolic and catabolic processes as result of interactions between nucleus and mitochondria. So the positive fluctuation entropy ($+\Delta_x\beta$), according to Glansdorff and Prigogine theory, advance open non equilibrium non linear thermodynamic system of cell by pathways either cellular cycle, or intracellular changes due to environment influences, or cellular aging [5,6]. The production of ATP for catabolic processes occurs in mitochondria via the process of oxidative phosphorilation. This process is accomplished by transferring electrons through the reducing substances of nicotinamide adenine dinucleotide (NADH) to Complex I (NADH dehydrogenase) and of flavine adenine dinucleotide ($FADH_2$) to Complex II and further through Complex III (cytochrom bc complex) then Complex IV (cytichrom c oxidase) to Complex V (ATP synthase) [7]. Suppression intracellular anaerobic catabolic processes, causing due to expression of anabolic processes, promotes increase of Reactive Oxygen Species (ROS) which is generated by NOX (NADPH oxidase) and Duoxs due to activity mitochondrial aerobic catabolic processes. Increase of Reactive Oxygen Species (ROS) induces forming of excessive quantity of mitochondrial superoxide [O_2*] which don't continue processes of suppressed anaerobic oxidative phosphorilation and don't lead down to final products CO_2 and H_2O. Thus oxygen [O_2] adds electron and is transformed into superoxide [O_2*-] which reduces Ferric iron [Fe^{3+}] into Ferrous iron [Fe^{2+}] with oxygen

1) $O_2 + e- \rightarrow O_2$*-

2) O_2*- + Fe^3+ → Fe^2+ + O_2

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

3) $2O_2$*- + 2H+=H_2O_2 + O_2. In mitochondrial matrix the normal steady concentration of superoxide [O2*] is higher than in cytoplasm

and nucleus. Subsequently it is happened Haber –Weiss reaction of iron catalyzed by superoxide transformations which is passed into Fenton reaction [7,8]

4) $Fe^{3}+ + O^{2}*- \rightarrow Fe^{2}+ + O^{2}$

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

$O_2*- + H_2O_2 \rightarrow -OH + *OH + O_2 + Fe^{3+}$

In mitochondrion the iron of cytochrom c [cytc–Fe] is subjected to the corresponding converting: cytc–Fe^{3+} is changed into cytc–Fe^{2+}. It was tested that generated hydrogen peroxide from ROS can ruin mitochondrial DNA [mtDNA] and thereby it can cause damage of mitochondrion. The abundance hydrogen peroxide [H_2O_2] from ROS is detoxified by mitochondrial glutathione peroxide (GPX) and phospholipid hydroperoxide glutathione peroxide (PHGPX): Glutathione (GSH) is transformed into oxidized glutathione (GSSG) in the reaction of reducing H_2O_2 into H_2O which is stimulated by glutathione peroxide [7,9-13]. Furthermore mitochondrial isoforms of peroxiredoxins such as peroxiredoxin-III and V utilize some molecules of cysteine to reduce H_2O_2 into H_2O and return glutathione peroxide to its reduced state [7,14-16]. Thus there are the summarized reactions of respiratory oxidative processes with generating superoxide [O_2*-], ROS and hydrogen peroxide [H_2O_2] [7].

5) a) $O_2 + e- \rightarrow O_2*$-; b) $_2O_2*- + 2H+ \rightarrow H_2O_2 + O_2$; c) cytc-$Fe^{3+}$ + $O_2*- \rightarrow$ cytc-Fe^{2}+ + O_2;

d) cytc-Fe^{2}+ + $H_2O_2 \rightarrow$ cytc-Fe^{3+} + –OH + *OH. e) H_2O_2 + 2GSH → $2H_2O$ + GSSG

Palacios-Callender et al. have expressed such doubt: "Despite much research on its metabolic fate, the way, in which the concentration of nitric oxide (NO) is regulated in cells and tissues, is at present unresolved" [17]. However the moderate alternating rhythmic interchanges of hypoxic state and oxidized state both in tissues and in cells of tissues are subjected to respiratory rhythm which influence on tissues metabolism through blood circulation of arterial blood and venous blood. These rhythmic alternations of hypoxic state and oxidized state cause alternating rhythmic interchanges of moderate shifts balance catabolic and anabolic processes into catabolic aerobic pathway and also into catabolic anaerobic pathway of glycolysis. Glycolysis generates energy for both catabolic oxidative phosphorilation and anabolic processes promoting expression of proliferative processes (growth of tissue, angiogenesis etc.) [7,17–20] (Figure 1). These rhythmic interchanges, connected with respiratory activity, influence also on rhythmic alternations of cellular cycle through G_0, G_1/S and G_2/M of cellular cycles [5,6]. Being driving mechanism as of cellular respiratory rhythm as well as of cellular cycle the interactions between catabolic aerobic processes and catabolic anaerobic processes are reflected as oxidized state induced by cytochrome c oxidase and as well as hypoxic state induced by concentration of nitric oxide (NO) which are also the driving mechanisms of these processes [17]. Also mitochondrial catabolic exoergonic oxidative processes and nuclear anabolic endoergonic reducing processes are mutual subjected on one another maintaining stabile basophilic chemical potential in cytoplasm (μ_{cytopl}) which oscillates in moderate normal limits.

Role of Mitochondrial Functions and Nuclear Function in Maintenance Stability Internal Energy and Internal Medium both an Organism and Cells of an Organism in Norm

The common mechanism of maintenance stability of Internal Medium (constant concentration substances in blood and in neurolymph) and Internal Energy (stable temperature 36.6°C-37.2°C by which all enzymes operate) in processes development of an organism and each cell of an organism occurs via the moderate fluctuating shifts of balance anabolic endoergonic and catabolic exoergonic processes either in anabolic pathway or in catabolic pathway, both in an organism and in each cell of an organism [5,6,21]. These shifts occur in low level regulation of an organism's regulatory system which consists of "Equilibrium Constant of energy exchange" and "Equilibrium Constant of metabolism" [21] (Figure 2).

"Equilibrium Constant of energy exchange" is substantiated indirectly owing to some indices which reflect mechanism of balance exoergonic and endoergonic processes: stable temperature 36.6°C–37.2°C by which all enzymes operate; stable index pH=7.35 in blood and in neurolymph; the stable index of osmotic pressure-285 ± 5 mil-osm/kg H2O, corresponding to 0,14-0,15 molar sodium chloride or the other univalent ions; the stable index of colloidal-oncotic pressure-18-25 mm Hg, corresponding to human serum albumin solution up to 300 grams per liter etc. "Equilibrium Constant of metabolism" is substantiated indirectly owing to balance of anabolic and catabolic processes resulting in stable indices of concentrations of all substances in blood and in neurolymph. Low level regulation is subjected to the regulative mechanisms of an organism's high level regulation which consists of "Equilibrium Constant of ionic metabolism", "Equilibrium Constant of acid–alkaline metabolism", "Equilibrium Constant of oxidative–reduction Potentials of metabolism" and "Equilibrium Constant of coagulating system of blood" [21] (Figure 2).

"Equilibrium Constant of ionic metabolism" is substantiated indirectly owing to balance cations and anions providing the stable indices of concentration as cations K+, Na+, Ca^{2}+, Mg^{2}+, H+ etc., as well as anions Cl- and General hydrocarbonates {HCO_3- (95.8–132.0 mg%)} in blood. "Equilibrium Constant of acid –- alkaline metabolism" is substantiated indirectly owing to stable index pH=7,35 in blood and in neurolymph. "Equilibrium Constant of oxidative–reduction Potentials of metabolism" is substantiated indirectly owing to stable index of respiratory coefficient 0,7–1,0; stable index of ratio partial pressure Oxygen (O2) to partial pressure carbon dioxide (CO2) that is in 4 times more in arterial blood than in venous blood; stable index of Mayerhof coefficient from 3 up to 6 of oxygen consumption as by normal tissue as well as by cancer tissues [2-4]. "Equilibrium Constant of coagulating system of blood" is substantiated indirectly owing to stable normal indices of blood coagulation. Simultaneously high level regulation and low level regulation of an organism are mutually influenced on one another [21] (Figure 2). Just the mutual influences of high level and low levels of regulation occur via mutual influences between "Equilibrium Constant of oxidative–reduction Potentials of metabolism" and "Equilibrium Constant of metabolism" [21] (Figure 2). Central Nervous System is highest level regulation which affects both on high level of regulation and on low level of regulation [21] (Figure 2). An organism's low, high and highest levels regulations cause stability Internal Medium and Internal Energy as all cells of an organism as well as tissues of an organism [21].

The maintenance stability of cellular Internal Energy (stable temperature 36.6°C-37.2°C by which all enzymes operate) and cellular Internal Medium (stable concentrations of all substances in cytoplasm) depends on both the mutual influences between the mechanism maintenance stability of an organism and the mechanisms maintenance stability cytoplasms of all cells [5,6,21] (Figures 2 and 3). Intracellular

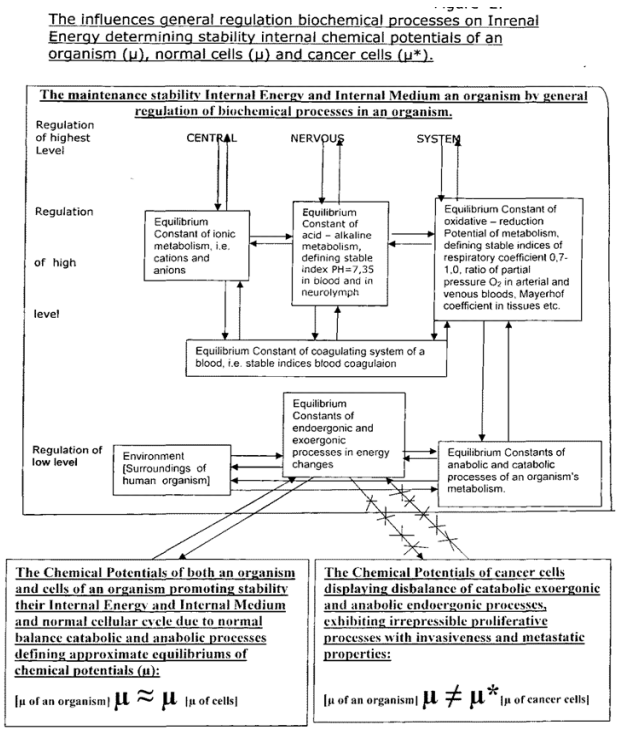

Figure 2: The influences general regulation biochemical processes on Internal Energy determining stability internal chemical potentials of an organism (μ), normal cells (μ) and cancer cells (μ*).
a) General regulation biochemical processes exhibits mutual influences between Low level Regulation, High level Regulation and Highest level Regulation.
b) Low level Regulation consists of "Equilibrium Constants of balance endoergonic and exoergonic processes of energy exchange" and "Equilibrium Constants of balance anabolic and catabolic processes of metabolism" which cause mutual influences one another.
c) Low level Regulation is subjected to Environment influences and effects against Environment influences for maintenance stability Internal Energy and Internal Medium as an organism as well as cells of an organism.
d) High level Regulation consists of mutual interacted "Equilibrium Constants of ionic metabolism", "Equilibrium Constants of acid – alkaline metabolism" and "Equilibrium Constants of oxidative – reductive Potentials of metabolism", which cause mutual influences with "Equilibrium Constants of coagulating system of a blood".
d) The Regulation both Low level Regulation and High level Regulation is occurred via mutual influences between "Equilibrium Constants of oxidative – reductive Potentials of metabolism" of High level Regulation and "Equilibrium Constants of anabolic and catabolic processes of metabolism" of Low level Regulation.
e) Highest level Regulation is presented by CENTRAL NERVOUS SYSTEM.
f) General regulation biochemical processes creates chemical potential an organism (μ) which induces related chemical potentials of cells an organism (μ) which create mutual influences on one another.
g) Chemical potentials of cancer cells (μ*) were created by penetrating oncogens that destroys interactions between chemical potentials of an organism (μ) and chemical potentials of cancer cells (μ*).

chemical potential (μ_{intr}) is induced by intracellular balance of catabolic exoergonic processes and anabolic endoergonic processes [5,6]. Thus intracellular chemical potential (μ_{intr}) is the indicator of cellular Internal Energy which interacts with extracellular chemical potential (μ_{extr}). Besides, intracellular chemical potential (μ_{intr}) of each cell interacts with intracellular chemical potentials (μ_{intr}) of all cells an organism via resonance waves of remote reaction due to operations of cellular capacitors [5]. Also the intracellular chemical potentials (μ_{intr}) of all cells interact with the general intracellular chemical potential of an organism (μ) creating mechanisms maintenance stability of cellular Internal Energy and Internal Medium of all normal cells which chemical potentials are related to chemical potential of an organism (Figures 2 and 3).

Cellular central mechanism of anabolic processes is located in nucleus, and the cellular central mechanism of catabolic processes is located in mitochondrion. Thus interactions between cellular anabolic processes and cellular catabolic processes occur due to interactions between activity of nuclear functions and mitochondrial respiratory activity of system cytochromes. Just the interactions between such resisted systems as nucleus and mitochondria can function due to intermediate mechanism which is the mechanism of mitochondrial DNA [mtDNA]. Taking into account that mtDNA locates into cellular central mechanism of mitochondrial catabolic processes, mtDNA oscillation via fusion/fission, as oscillations anabolic processes/ catabolic processes, carry out function of driving mechanism rhythmic processes of cellular cycle in transiting G_0, G1/S, G2/M phases cellular cycle.

On the one hand, mitochondrial DNA is subjected to permanent fissions with its lesion due to permanent ruining effect of oxidized free radicals created by permanent arising of ROS, H_2O_2 and superoxide [O_2*-] which are mediated by GTPase, dynamin-related protein 1 (Drp 1) [7-11]. Also mitochondria are subjected to fission due to mitochondrial factor (Mff), reflecting expression of catabolic oxidative processes [7–11]. On the other hand, there are the permanent repairing mechanisms via alkylation and mtDNA ligase activity for permanent fusion of destructing mtDNA preventing mtDNA loss via mtDNA repair and maintenance of copy number, reflecting expression of anabolic reductive processes [7]. Thus dynamics of mtDNA fission/fusion is occurred via oscillation balance catabolic/anabolic processes [7,22-24]. Besides, mitochondrial fusion is mediated by OPA1, Mfn1, Mfn2 proteins which are generated by the genes of the same names [7,25]. Just both mitochondria and mtDNA dynamic alternations of fission, as shifts into catabolic processes, and fusion, as shifts into anabolic processes, is connected with nuclear dynamic alternations of the destructive function of nuclear DNA (nDNA) via fragmentation, as shift into catabolic processes, in which the caspase-activated DNase (CAD) is an activator, and the function reparations of nuclear DNA (nDNA), as shift into anabolic processes, which is stimulated by mismatch repair proteins (MMR). Thus these connections between oscillations nucleus and mitochondria induce stable moderate oscillations of cellular chemical potential in cytoplasm (μ_{cytopl}) connecting with rhythms of cellular advances via respiratory rhythm, maintaining cellular stability of Internal Energy and Internal Medium, and also via cellular cycle, promoting cellular development. Also chemical potentials of all cells (μ_{cell}) create mutual influences with chemical potential of an organism (μ_{org}) for maintenance common stability Internal Energy and Internal Medium (Figures 2 and 3).

Mitochondrial Function in Normal Cellular Cycle and in Oncologic Cellular Cycle

There is the following order of interaction between nucleus and mitochondria for maintenance stability Internal Medium and Internal Energy of cytoplasm in normal cellular cycle and in oncologic cellular cycle: 1) Complex ROS/H_2O_2 generates superoxide [O_2*] inducing free radicals (*OH). 2) On the one hand, complex ROS/H_2O_2/O_2* causes permanent fission of both mtDNA and mitochondrion, and, on the other hand, there occurs the permanent fusion of both mtDNA and mitochondrion which are mediated by mitochondrial fusion proteins [OPA1, Mfn1 and Mfn2] and by mtDNA ligase activity. Thus the

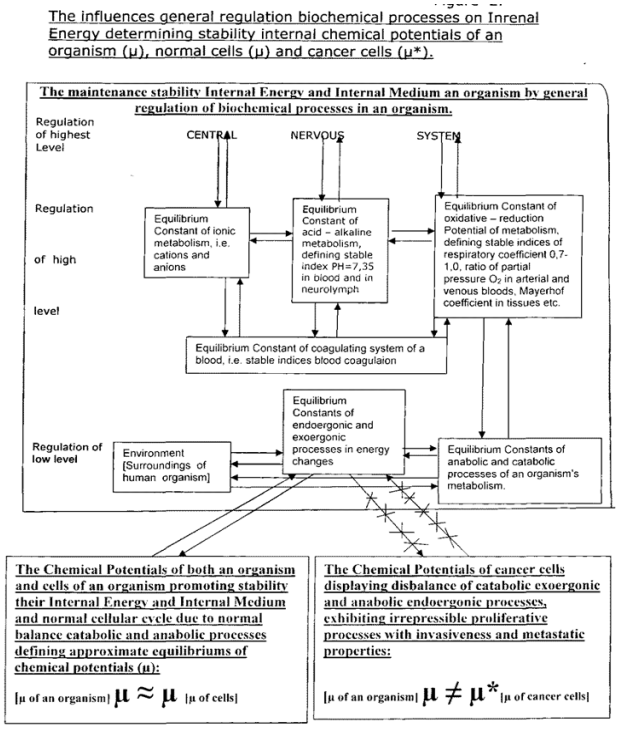

Figure 3: Balance between Internal Energy cells and an organism due to their chemical potentials (μ) and disbalance with chemical potentials (μ*) of cancer cells.
a) Chemical potential of an organism (μ) is the indicator of stability Internal Energy an organism.
b) Chemical potential of an organism (μ) defines related chemical potentials of cells an organism (μ) as the indicators of stability Internal Energy of cells an organism.
c) Chemical potentials of cancer cells (μ*) are the unrelated potential for chemical potential of an organism (μ) and chemical potentials of cells an organism (μ) showing distinct development with excessive expression of proliferation.

mitochondria exhibit permanent oscillating fission (as catabolic processes) and fusion (as anabolic processes). 3) The oscillations fission /fusion of mtDNA function determine the moderate oscillation of mitochondrial chemical potential (μ_{mt}) which also causes the charge on the inner mitochondrial membrane (IMM) of mitochondrial capacitor. 4) Also there occurs the destructive function of nuclear DNA (nDNA) via fragmentation (as catabolic processes) in which the caspase-activated DNase (CAD) is an activator, on the one hand [26–28], and the function reparations of nuclear DNA (nDNA) (as anabolic processes) which is stimulated by mismatch repair proteins (MMR) which are generated by nine genes of MMR function and among them the main five genes of mismatch repair proteins (MMR) function (MLH1, PMS1, PMS2, MSH2, and MSH6) [29–31]. 5) The oscillations fragmentation /reparation of nDNA function determine the moderate fluctuation of nuclear chemical potential (μ_n) which causes the charge on the inner nuclear membrane (INM) of nuclear capacitor. 6) The basophilic chemical potential of cytoplasm (μ_{cytopl}) causes the charge both on the outer nuclear membrane (ONM) and on the outer mitochondrial membrane (OMM) of both nuclear capacitor and mitochondrial capacitor. 7) The interactions between the related resonance waves of the nuclear capacitors and the mitochondrial capacitors create the remote reaction for maintenance of stable balance catabolic and anabolic processes in cytoplasm which induces stable basophilic chemical potential of cytoplasm (μ_{cytopl}) defining stable Internal Energy and Internal Medium of cytoplasm. 8) The mechanism of maintenance stability chemical potential of cytoplasm (μ_{cytopl}) displays the balance of mutual influences between moderately oscillating nDNA fragmentations/reparations in nucleus and conformably moderately oscillating mtDNA fusion/fission in mitochondria in normal quiescent G0 phase of cellular cycle.

The little quantity of ROS is also formed and neutralized in oxidative metabolism of lipids in normal quiescent G0 phase of cellular cycle where phospholipid hydroperoxide glutathione peroxidise (PHGPX) is produced. 9) In normal G1/S phases of cellular cycle the mechanism of maintenance stability chemical potential of cytoplasm (μ_{cytopl}) displays the shift balance moderately oscillating nDNA reparations / fragmentations into moderate anabolic endoergonic processes of reparations that leads to processes RNA transcription and translation for protein biosynthesis due to expression of an inhibitor of caspase-activated DNase (ICAD) in nucleus. Simultaneously the moderate oscillation of balance mtDNA catabolic /anabolic processes shifts into moderate catabolic exoergonic aerobic processes in mitochondria, and surplus of produced ROS is neutralized by glutathione peroxidise (GPX) and phospholipid hydroperoxide glutathione peroxidise (PHGPX) in normal G1/S phases of cellular cycle. 10) In normal G2 phase of cellular cycle it occurs transit moderate anabolic processes into intensive anabolic processes in nucleus, and mechanism maintenance stability chemical potential of cytoplasm (μ_{cytopl}) transits from moderate catabolic processes into intensive catabolic processes in mitochondria that leads to surplus complex ROS/H2O2 production.

However oscillations of mtDNA fusion/fission were accelerated considerably for rescue of mtDNA and mitochondrion. Therefore complex ROS/H_2O_2 pass through mitochondrial membranes and cytoplasm into nucleus and generates superoxide [O_2*] inducing free radicals (*OH). Free radicals (*OH) react on nDNA and induce process replication via realizing of 2nDNA [32]:

6) *OH + H_2-nDNA-DNA −−> H_2O + H•-nDNA-DNA;

O*+ $2H_2O$ −−> 2H• + $2OH^-$;

2H•-nDNA-DNA + 2H• −−> 2nDNA-H• + 2nDNA-H•;

2nDNA-H• + 2*OH −−> 2nDNA + H2O

Thus the free radicals (*OH and H•) are neutralized in final G2 phase of DNA replication.11) Then Mitosis in M phase of cellular cycle of cell division transfers the new cells into G_0 phase of normal cellular cycle. Thus nuclei DNA (nDNA) of formed new cells are not subjected to ruining capability of ROS/H_2O_2/free radicals in normal development cellular cycle [1,5,6]. Moreover, chemical potentials of G_0, G_1/S, G_2/M phases normal cellular cycle are related to chemical potentials an organism maintaining stable Internal Energy and Internal Medium both in an organism and cells of an organism (Figures 2 and 3).

The great acceleration of cellular cycle, induced by oncogene, leads to unnoticeable G0 phase in oncologic cellular cycle. Oncologic cellular cycle is characterized by expression huge anabolic processes in cellular oncogenesis. Hence the excessive shift of the balance anabolic and catabolic processes into abundance anabolic processes in cancer tissue advances cellular cycle in cellular oncogenesis via G_1/S, G_2 and M/G_1/S phases which create chemical potentials unrelated to chemical potentials as an organism as well as between new formed cells that is driver mechanism of proliferative processes leading to formation Warburg effect, excessive proliferative processes, irrepressible cancer growth, unhealed cancer wounds, mechanisms of metastasis and Apoptosis Resistance. Thus cellular oncogenesis exhibits abundance

ROS which is also driving mechanism of excessive processes of DNA replication in G2 phase cellular cycle [1,5,6].

Besides ROS/H_2O_2/Free radicals exert excessive processes of DNA replication which promote the full neutralization of ROS/H_2O_2/Free radicals, eliminating their ruining properties in G_2 phase oncologic cellular cycle. Division cell in M phase oncologic cellular cycle leads to forming new cells in G1/S cellular cycle due to acceleration cellular cycle and unnoticeable G_0 phase cellular cycle. The great acceleration of cellular cycle, induced by oncogene, with combination of abundance ROS and excessive processes of DNA replication causing neutralization ROS/H_2O_2/Free radicals eliminates these incompatible resisted situations in metabolism of cancer cells, induced by mechanism of abundance ROS function: On the one hand, large amount of ROS production with hydrogen peroxide in mitochondria of cancer cells which would lead to apoptotic damage of cancer cells, and, on the other hand, cancer metabolism is characterized by Apoptosis Resistance [7,13,26]. Just it is the mechanism Apoptosis Resistance in oncologic cellular cycle which is formed due to acceleration cellular cycle in comparison to normal cellular cycle: Cancer cells are subjected to penetration of v-oncogenes in their nucleus.

The v-oncogenes cycle changes cancer cells' cellular cycle causing shift balance catabolic and anabolic processes into excessive anabolic processes and expression of excessive proliferative processes, considerably accelerating cellular cycle with unnoticeable G_0 phase cellular cycle. The excessive anabolic processes and expression of excessive proliferative processes make chemical potentials of cancer cells' cytoplasm unrelated to the normal cells of an organism [1,33,34]. Cancer cells' nuclei arise great expression of G_1/S phases cellular cycle which display permanent shift balance oscillating nDNA reparations/fragmentations into excessive anabolic endoergonic processes of reparation leading to processes RNA transcription and translation for protein biosynthesis, and simultaneously the acceleration of oscillating mtDNA fusion/fission induces the shift into excessive catabolic exoergonic processes with production of complex ROS/H_2O_2 in mitochondria which is neutralized by glutathione peroxidise (GPX) and phospholipid hydroperoxide glutathione peroxidise (PHGPX) in G1 phase oncologic cellular cycle.

The produced excessive abundance of complex ROS/H_2O_2 in G2 phases oncologic cellular cycle pass through mitochondrial membranes and cytoplasm into nucleus and generates excessive abundance of superoxide [O2*] inducing excessive abundance of free radicals (*OH). The excessive free radicals influence on nuclear DNA inducing processes of permanent DNA replications which cause neutralization of abundance complex ROS/H_2O_2/Free radicals [32]. Then Mitosis (M phase of cellular cycle) causes cell division and transfers the new cells into G_1/S phase cellular cycle, which are not subjected to ruining capability of complex ROS/H_2O_2 on nDNA and mtDNA in new cancer cells. Thus the mechanism of Apoptosis Resistance is exerted in cancer tissue. Chemical potentials of new cancer cells are unrelated to chemical potential of an organism. All processes of mitochondrial biogenesis are advanced due to nitric oxide both in normal cellular cycle development and in oncologic cellular cycle development exhibiting transfer from catabolic processes into anabolic processes [35].

Discussion of Role ROS in Advance Of Cellular Cycle as in Norm as Well as in Processes of Oncogenesis from the Point of Views of Offered Concepts

There are the incompatible resisted situations of mitochondria functions both in norm and in oncogenesis, induced by similar mechanism of ROS: On the one hand, the large amounts of ROS occur in mitochondria of cancer cells which would lead to apoptosis. On the other hand, cancer metabolism is characterized by Apoptosis Resistance [7,13,36]. Various authors offered different pathways of convergence these resisted properties of ROS: cellular damaging role of ROS due to mtDNA damage and role of ROS as the mediator of some proliferative processes for rescue of cellular life. Researching activity of reactive oxygen species (ROS) in oncogenesis, Shinohara et al. have noted: "Overproduction of intracellular ROS has been considered as a risk factor in cancer development", and simultaneously they described role ROS as a mediator of growth, apoptosis and inflammation [37]. They offered the mechanism that ROS, generated by NADPH oxidase 1 (Nox1), is required for Ras transformation phenotypes as vascular endothelial growth factor (VEGF) production promoting tumor angiogenesis and oncogenesis. Thus it was described two resisted incompatible functions of reactive oxygen species (ROS). Therefore they have expressed such doubts: "However, little is known about whether Nox1 signaling regulates cell invasiveness" and "Currently, little is known of how Nox1 signaling directs protease production and cell motogenesis during malignant cell transformation". They have also studied the H_2O_2 capability migration-inducing by diffusion into the cytoplasm and modulating intracellular redox-sensitive proteins for activity neutrophilic cells making migration. However, they have observed increase migration of cells and, simultaneously, were compelled to note absence of mechanism migration: "However, this study did not explore the involvement of RhoGTPase signalling, and its relevance to our study is unclear at present" [37]. Thus these experiments did not detect the mechanism of connection between migration capability of cancer cells and capability of H_2O_2.

Liu L.Z. et al. studied the regulative role of Ras in expression growth factor through activation of AKT and P70S6K1 and noted that biochemical mechanism of these stimulations remains unclear [38]. Also Chang et al. described the regulative role ROS on angiogenesis and tumor growth through Vascular Endothelial Growth Factor (VEGF) and Hypoxia-inducible factors 1 (HIF1) and expressed also doubt: "However the direct roles of endogenous ROS production still remain to be elucidated" [39]. All these researches don't elucidate the mechanisms as an important role of moderate level ROS in the modulation normal cellular activity, and as well as role of excessive level ROS in exerting advance of irrepressible proliferative processes causing mechanism of oncogenesis.

The explanations of these ROS activities demand the comparison oncogenesis in nucleus and mitochondria considering Apoptosis Resistance, which is characterized to cancer tissue development, and excessive generation of ROS with H_2O_2 in mitochondria of cancer cells versus moderate level ROS in mitochondria of normal cells. Just ROS and H_2O_2 can damage mitochondrial DNA and nuclear DNA of cell, leading to apoptosis, which must be considerably greater in cancer cells than in normal cells, although cancer cells manifest obvious Apoptosis Resistance [1,7,13,36]. These incompatible situations can not been explained considering only neutralized function of glutathione peroxide (GPX) and phospholipid hydroperoxide glutathione peroxidise (PHGPX), which decrease the rate of ROS and H_2O_2 in cancer tissue [7,9-16]. Also these incompatible situations can not been explained by permanent existence of OPA1, Mfn1 and Mfn2 proteins, mediated mitochondrial fusion, and as well as permanent fusion of destructing mtDNA by mtDNA ligase activity, because balance of permanent existence of destructive abundant ROS and H_2O_2 and permanent existence of mediated mitochondrial fusion OPA1, Mfn1,

Mfn2 proteins and as well as permanent fusion of destructing mtDNA by mtDNA ligase activity causing reparation of cells destruction would not be able to create shift balance catabolic and anabolic processes into excessive anabolic processes resulting in expression proliferative processes with irrepressible growth of cancer tissue which characterize the disbalance catabolic and anabolic processes of cancer tissue metabolism [7-11,22–25].

Furthermore the shift balance catabolic and anabolic processes into excessive anabolic processes resulting in expression proliferative processes with irrepressible growth of cancer tissue and also Apoptosis Resistance, which characterize the disbalance catabolic and anabolic processes of cancer tissue metabolism, must eliminate ruining capability of abundant ROS and H_2O_2 in mitochondria of cancer cells [1,6]. Just nuclear excessive anabolic processes promoting expression of huge proliferative processes with partial suppression catabolic anaerobic processes exhibits arising abundance of reactive oxygen species (ROS)-product of catabolic aerobic processes in mitochondria of cancer cells [1,6]. Unlike cancer metabolism, balance catabolic and anabolic processes in normal tissue produce moderate quantity ROS and H2O2 [1,6]. Therefore moderate quantity ROS and H_2O_2 in mitochondria of able-bodied cells and abundance quantity ROS and H_2O_2 in cancer cells promote investigations mechanisms of useful activity ROS and H_2O_2 for cells development in cellular cycle besides existence detoxified property of mitochondrial glutathione peroxide (GPX) and phospholipid hydroperoxide glutathione peroxidise (PHGPX). Gibellini L. et al. described the contradictory situations: On the one hand, ROS lead to DNA damage and cells oxidative stress, and on the other hand, ROS may promote cell survival and proliferation via as the transcription factor FoxM1 which stimulates the detoxifying enzyme catalase and also coordinates transcription factors NFkB, HIF and p53 [13]. Besides Gibellini L. et al. and Sattler M. et al. described transformation of various hematopoetic cells lines due to increase of ROS level that does not occur in quiescent G0 phase of cellular cycle in untransformed cells [13,40]. Just reactive oxygen species generated by NADPH oxidase (Nox1) does not cause stability Internal Energy and Internal Medium of cytoplasm as in able-bodied cell as well as in cancer cell. Production ROS and neutralization ROS/H_2O_2/Free radicals by glutathione peroxide (GPX) in mitochondria are the mechanism of mtDNA fission/fusion oscillations. These processes occur in G_0 and G1/S phases of cellular cycles. Migration ROS into nucleus exerts processes replication of nDNA causing by complex ROS/H_2O_2/Free radicals which was neutralized in processes nDNA replication. These processes occur in G2 phase of cellular cycle. Just the stability Internal Energy and Internal Medium of chemical potential of cytoplasm (μ_{cytopl}) is depended on the interdependent oscillating chemical potentials of nucleus (μ_n) and mitochondria (μ_{mt}), which are generated by interdependent moderate oscillating shifts balances catabolic and anabolic processes into anabolic pathway and into catabolic pathway in normal cellular cycle and into excessive oscillating shifts balances catabolic and anabolic processes into anabolic pathway in oncogenesis [5, 6] (Figures 2 and 3).

The Benefits of Using Prolonged Medical Starvation on Processes Oncogenesis in Mitochondria for the New Approach to Cancer Therapy

Prolonged medical Starvation as the new approach to cancer therapy activates catabolic processes in an organism for maintenance stable temperature 36.6°C-37.2°C by which all enzymes operate. Increase of fat metabolism from fat depot leads to augmentation glutathione peroxide (GPX) and phospholipid hydroperoxide glutathione peroxidise (PHGPX) in all cells of an organism and contributes to neutralization of redundant ROS in mitochondria of cancer cells. Thus Prolonged medical Starvation promote suppression both excessive anabolic proliferative processes, due to expression catabolic processes with relieving of overloaded "nodal point of bifurcation anabolic and catabolic processes" [NPBac] via consumption Acetyl-CoA for catabolic processes, and suppression DNA replication, due to ROS/free radicals neutralization by glutathione peroxide (GPX) and phospholipid hydroperoxide glutathione peroxidise (PHGPX) in G1/S phases cellular cycle before nDNA replication in G2/M phases cellular cycle, as in an organism and as well as in cancer cells which metabolism are characterized by shift into anabolic processes [41,42]. Thereby Warburg effect, characterizing by aerobic glycolysis, is destroyed because of expression aerobic catabolic processes and decrease anaerobic processes of glycolysis. Destruction of Warburg effect violates cancer metabolism and promotes normal metabolism characterized by Pasteur effect. So it occurs depression cancer tumor development that helps for efficient anticancer therapy with considerably decreased dosage of cytotoxic drugs [1,41,42]. Such approach to anticancer chemotherapy prevents damage Internal Energy and Internal Medium both an organism and cells of an organism, preventing damage of immune and hormonal systems as the links of defensive mechanism in regulative system of an organism [41,42]. Prevention damage of immune and hormonal systems as the links of system stability Internal Energy and Internal Medium an organism prevents recurrence of cancer disease after long anticancer chemotherapy and resistance to anticancer drugs in process of intensive anticancer chemotherapy with cytotoxic drugs [1,41,42].

The Practical Observations

The method treatment of cancer disease via Prolonged medical starvation was borrowed from the folk healers Omelchenko A. and Breuss R. [43,44]. The author was convinced of the efficiency of this method treatment by the meetings with cured patients, who were treated by folk healer Omelchenko. The studies of the "Medical cards" some of these cured persons have convinced us that the folk healer Omelchenko A. has treated the incurable ill men and has received positive results: the patients have obtained the initial diagnoses in oncologic hospitals of official medical practice, but further they were treated by the folk healer Omelchenko. Unfortunately the folk healer Omelchenko A. had only the apparatus for ultrasound investigations. Therefore the results of treatment were based only on the data of the ultrasound investigations and the clinical observations.

Thus the patient Gr. was diagnosed with Cancer Kidney Y degree, clinical stage IY, with metastases in the abdomen cavity and liver. This diagnosis was diagnosed in the "Kiev Oncologic dispensary" and was confirmed by the folk healer Omelchenko A. via the clinical investigations and the ultrasound investigations. After treatment the ultrasound investigations and clinical investigations showed disappearance the dense focus of liver. Also the clinical investigations showed disappearance of abdomen metastases. The patient has felt fine and has gone to his work.

The other patient Mo. was diagnosed with Cancer ventricle Y degree, clinical stage IY, with metastases in the abdomen cavity and liver. After treatment the ultrasound investigations and clinical investigations showed disappearance the dense focus of liver. Also the clinical investigations showed disappearance of abdomen metastases. Also we have met with the some other cured patients with various locations of Cancer tumors, who were treated by the folk healer Omelchenko A., although these patients were not incurable Cancer patients from the point of view of the modern medicine. Therefore these patients could not show the initial diagnoses from the oncologic hospitals.

Austrian folk healer Breuss R. used for treatment "Prolonged medical Starvation during 42 days" and described a lot of the patients with various locations of Cancer tumor and with various locations of metastases, who were cured by this method of treatment [43,44]. The data, described by the Austrian folk healer Breuss R., concerning results of this method treatment were also convinced us in efficiency of this method treatment [43,44]. The author was also convinced on own experience the efficiency of treatment the ill man with the incurable cancer stage. Here is own experience in the treatment of the patient with the incurable Cancer disease. At February 1998 the patient Ch. has been operated for Cancer of the left kidney (the diseased kidney was radical detected). 24.02.1999 it was detected by the X-ray inspection in the "Kiev Oncologic dispensary" the diagnosis: Metastatic cancer the intermediate bronchus of the right lung IY degree, clinical stage IY.

After detail examines the patient Ch. has been discharged from Oncologic dispensary how the incurable patient. Then the patient Ch. and relatives of the patient have agreed to receive Prolonged medical starvation treatment with the examinations in the "Kiev Institute of roentgenology, radiology and oncology".

At 24.02.1999 the patient was examined in the "Kiev Institute of roentgenology, radiology and oncology" before Prolonged medical starvation treatment. Histological examination of a sputum from a bronchus: The fragment of necrotic masses of a disintegrating malignant tumour and a clump of polygonal cells of a tumor of not forming complexes and frames is detected in the stuff. The histological pattern mismatches a lung carcinoma but specifies in the metastasis from the tumor of kidney (hypernephroma). The result of X-ray inspection was: Metastatic cancer the intermediate bronchus of the right lung IY degree, clinical stage IY. The diagnosis is remained the same how Oncologic dispensary.

The treatment was occurred from 01.03.1999.

The examination after Prolonged medical treatment: On X-ray patterns there are not found pathological changes in the lungs. The medical examinations of the patient during three years (catamnesis) and the examination in 2002 at the "Kiev Institute of roentgenology, radiology and oncology" show that the patient was cured.

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

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