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Biophysical and Biochemical Mechanisms of Interactions Cytoplasm Processes with Nucleus Processes and Mitochondria Processes in Norm and in Pathology

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Abstract

Interactions nuclear processes and mitochondrial processes determine stabile basophilic chemical potential in cytoplasm, i.e. stability cellular chemical potential. Interactions between all cells occur due to remote reactions across distance as the results of cellular capacitors operations via production of resonance waves. Interactions cellular capacitors of cells maintain common stability of Internal Energy both in cells and in an organism. Study of interactions between nuclear processes and mitochondrial processes reveals processes of mutual influences between catabolic pathways in mitochondria and anabolic pathways in nucleus creating stable chemical potential of cytoplasm. The biochemical processes defining stable cellular chemical potential is stimulated by biophysical processes of cell's capacitors operations. Excessive shifts balance catabolic and anabolic processes into either catabolic processes or into anabolic processes lead to pathologic development of an organism. Results of some experiments were explained eliminating doubts which were expressed by the authors of these experiments. Moreover there were substantiated the benefits using Prolonged medical Starvation with considerably decreased dosage of cytotoxic drug of the new approach to cancer therapy.

Keywords: ROS/[$O_2^{\cdot}$-]/H_2O_2/free radicals; Cytochrome c; RanGTP; Ran GTPase; Cellular capacitors; Chemical potentials (μ); Balance catabolic and anabolic processes; Theorell formula; Warburg effect; Fenton reaction.

Introduction

A human organism is the open non equilibrium nonlinear thermodynamic system which is subjected to thermodynamic laws [1]. Considering first law of thermodynamics, the regulatory system of an organism causing maintenance stability Internal Energy of an open thermodynamic system an organism operates via three levels of regulative mechanism [2,3] (Figure 1). Just the biophysical mechanism of cellular remote reactions due to cellular capacitors operations via resonance waves maintains stability Internal Energy of an open thermodynamic system an organism [4]. Also the regulatory mechanism of an organism is subjected to permanent influences of Environment [2,3]. The organism's mechanisms of resistance to the permanent influences of Environment operate via biophysical mechanisms of cellular reactions on these influences which are supplemental important mechanisms of maintenance stability Internal Energy of an open thermodynamic system an organism, besides biochemical processes of an organism's metabolism. Just cells from all sections of an organism (blood, lymph, neurolymph, tissues) are connected with one another due to remote reactions across distance as the results of their cellular capacitors operation via resonance waves, maintaining common stability of Internal Energy and Internal Medium both in the cells and in an organism creating immune defensive system, autophagy and providing exchanges energy and substances between Environment and both an organism and cells of an organism [1,4,5]. The mechanism maintenance stability cellular Internal Energy includes interactions between cellular capacitors and intracellular capacitors of all cell's organelles including nuclear capacitor and mitochondria capacitors which maintain intracellular balance catabolic and anabolic processes creating stable cellular chemical potential (μcell).

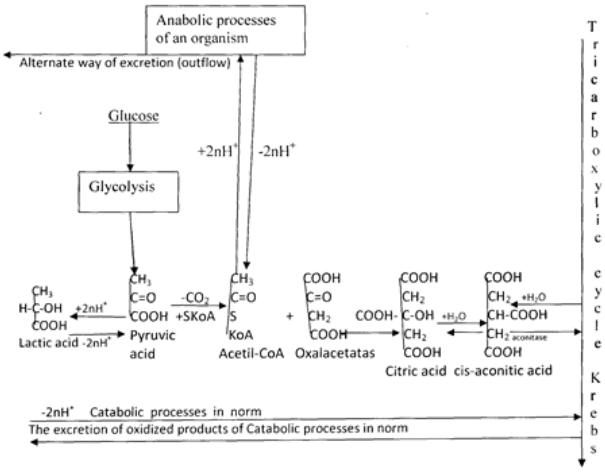

Figure 1: The point of bifurcation anabolic processes and catabolic processes in metabolism of an organism.

a) Nodal point of bifurcation anabolic and catabolic processes in "Nodal point of bifurcation anabolic and catabolic processes" [NPBac], b) Moderate metabolic processes displaying balance anabolic and catabolic processes in able-bodied tissue, c) Accumulation of energy into lactic acid for anabolic processes, d) Normal excretion substances via catabolic oxidative processes in able-bodied tissue.

The mechanisms interactions between nuclear capacitor/mitochondrial capacitors/cellular capacitors for maintenance stability chemical potential of cytoplasm (μ_{cytopl}) cause stability Internal Energy of cellular Stationary State in norm. The violations of the mechanisms interactions between nuclear capacitor/mitochondrial capacitors/cellular capacitors lead to Quasi-stationary pathologic States of an organism [6]. These violations appear because of violations an organism's regulatory mechanism and cellular regulatory mechanisms including cellular capacitors operations, that leads to pathologic maintenance stability cellular Internal Energy.

Cellular mechanisms resistance to Environmental Influences for providing maintenance stability Internal Energy and Internal Medium of both cells and an organism

The biochemical mechanisms maintenance stability Internal Energy (stable temperature 36,0°C -36,9°C etc.) and Internal Medium (stable concentration substances in blood and neurolymph) contain three level regulation: highest level regulation [Central Nervous System], high level regulation ["Basic Equilibrium Constants of all kinds of metabolisms] and low level regulation ["Equilibrium Constant of energy exchanges" and "Equilibrium Constant of metabolism"] (Figure 2).

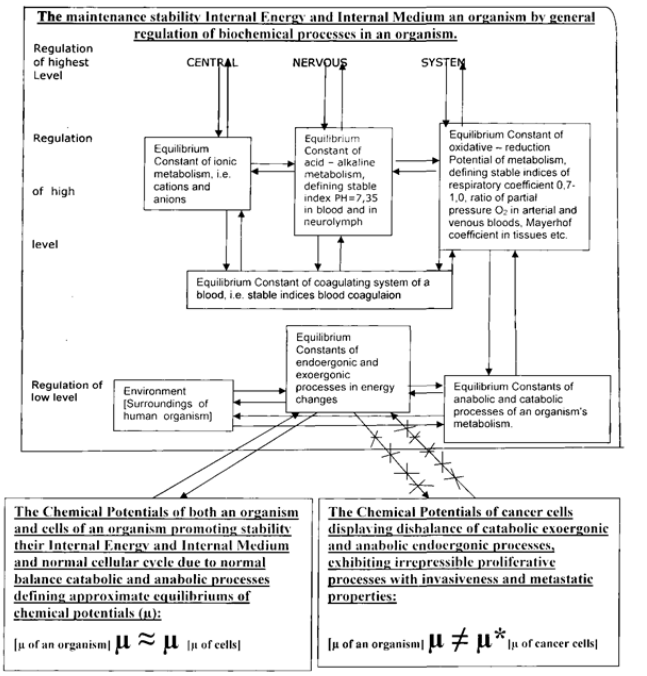

Figure 2: The influences general regulation biochemical processes on Internal Energy determining stability internal chemical potentials of an organism (μ), normal cells (μ) and cancer cells (μ^*).

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", "Equilibrium Constants of oxidative – reductive Potentials of metabolism" and "Equilibrium system of coagulating system", which cause mutual influences with "Equilibrium Constants of coagulating system of a blood", e) 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, f) Highest level Regulation is presented by CENTRAL NERVOUS SYSTEM, g) General regulation biochemical processes creates chemical potential an organism (μ) which mutual influences on one another with related chemical potentials of cells of an organism (μ), h) 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^*) causing chemical potentials of cancer cells inadequate to both chemical potentials of an organism and chemical potentials of an organism's cells.

The mechanism maintenance stability Internal Energy (temperature 36,0°C – 36,9°C, by which all enzymes operate) and Internal Medium (constant concentrations of substances in blood and in neurolymph) an organism are also formed under the influences of interactions between mechanism maintenance stability Internal Energy of all cells and mechanism maintenance stability Internal Energy of an organism [4]. The main parameter of the cellular stable Internal Energy is the cellular chemical potential (μ_{cell}). Corresponding to Theorell formula [$dn/dt = -UcA\, d\mu/dx$], interactions between intracellular chemical potentials ($\mu_{intcell}$) and extracellular chemical potential ($\mu_{extcell}$) are the driving mechanisms of substances transports across cellular membranes providing stability cellular Internal Energy [dn/dt – quantity of diffusing substance molecules in the unit time; U – substance mobility; c – substance concentration; A – membrane area; μ – chemical potential; x – molecule distance from membrane] [7]. Cellular chemical potentials (μ) of all cells of an organism stimulate also cellular metabolism for maintenance stability cellular Internal Energy which influence on mechanism stability of Internal Energy an organism [2-7]. Besides chemical potentials (μ) both in cytoplasm and in extracellular medium induce the electric charges on inner cellular membranes and on outer cellular membranes, forming cellular capacitors in cell's wall [1,4,5]. The capacitors of all cells cause maintenance stability Internal Energy and Internal Medium both cells of an organism and an organism due operations of their resonance waves [1,4,5].

The Mechanisms Interactions between Nucleus, Cytoplasm and Mitochondria for Maintenance Stability Internal Energy in Nucleus, Cytoplasm and Mitochondria, which Induce Mechanism Maintenance

Stability Internal Energy both in Cells and in an Organism in Norm

The mechanism operation of mitochondria capacitors in processes of transport substances across mitochondrial shell and cytoplasm in norm

Driving mechanism of transport substances across mitochondrial shell is the difference chemical potentials of both sides a mitochondrial shell according to Theorell formula:

[dn/dt = -UcA dμ/dx] [dn/dt – quantity of diffusing substance molecules in the unit time; U – substance mobility; c – substance concentration; A – membrane area; μ – chemical potential; x – molecule distance from membrane] [7]. Mitochondrion consists of the five parts: 1. Outer mitochondrial membrane, 2. Intermembrane space (the space between the outer and inner membranes), 3. Inner mitochondrial membrane, 4. Cristae space (formed by inserting of the inner membrane), 5. The matrix (space within the inner membrane). An inner mitochondrial membrane is highly impermeable. The inner mitochondrial membrane forms a tight permeability barrier to all polar molecules, including ATP; ADP; Pi; anions such as pyruvate; and cations such as Ca^{2+}, H^+, and K^+. Ions and other polar molecules are transported across the inner mitochondrial membrane by help of specific protein "translocase". Besides the inner mitochondrial membrane is included into numerous cristae, which expand the surface area of the inner mitochondrial membrane, enhancing its ability to produce ATP. Formed in the mitochondrial matrix ATP is transported to the intermembrane space by ATP–ADP translocase via ADP forming energy-requiring reactions outside of the mitochondria. Because ATP contains four negative charges and ADP contains only three charges, the exchange of negative charges is promoted by the electrochemical potentials (μ) according Theorell formula as antiport from the matrix into the cytosol. Similar antiports exist for most metabolic anions. Other transporters include the dicarboxylate transporter for phosphate–malate exchange, the tricarboxylate transporter for citrate–malate exchange, the aspartate–glutamate transporter, and the malate–α-ketoglutarate transporter. The transporters and the translocases help to realize transport substances according to Theorell formula in order to get over obstacles of an inner mitochondrial membrane of chemical complicated high molecular polar molecules. Versus an inner mitochondrial membrane, an outer mitochondrial membrane is permeable to compound molecules with a molecular weight up to approximately 6,000 Da because it contains large nonspecific pores of voltage-dependent anion channels (VDACs) forming by mitochondrial porins. Thus presence of VDACs in an outer mitochondrial membrane helps to realize facilitated mechanism transport of substances across an outer mitochondrial membrane according to Theorell formula. So realizing mechanism of molecule transport according to Theorell formula, high molecular proteins can enter the mitochondrion if their N-terminus is bound to the large multisubunit protein of translocase of the outer membrane. An outer membrane is freely permeable to small molecules. Thus transport substances between mitochondria and cytoplasm across mitochondrial membranes are exerted by the biophysical mechanisms of substances transport according to Theorell formula which is supported by biochemical reactive substances. Chemical potentials (μ) in mitochondrion and in cytoplasm induce the electric charges on inner membrane of mitochondrial shell and on outer membrane mitochondrial shell respectively, forming mitochondrial capacitor. Mitochondrial capacitors maintain the oxidizing function of mitochondria. Cellular central mechanism of catabolic exoergonic processes [-2nH^+] is located in mitochondria which realizes the oxidizing function. The oxidizing function of mitochondrion occurs due to cytochromes reactions. Cytochrome c is hemeprotein which is associated with inner mitochondrial membrane, cristae space and intermembrane space. Cytochrome c oxidase is a protein as key enzyme in aerobic metabolism which operates as proton pumping heme-copper oxidases representing energy-transfer enzymes of respiratory chains in mitochondria. Cytochromes are also responsible for the generation of ATP via transport of electrons which are found often as monomeric proteins in cytochrome c. 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 occurs because oxygen [O_2] adds electron and is transformed into superoxide [O_2^{*-}] which reduces Ferric iron [Fe^{3+}] of cytc–Fe^{3+} into Ferrous iron [Fe^{2+}] of cytc–Fe^{2+} with oxygen:

1) $O_2 + e^- \rightarrow O_2^{*-}$; 2) $O_2^{*-} + Fe^{3+} \rightarrow Fe^{2+} + O_2$. Also superoxide anion [O_2^{*-}] 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 [O_2^{*}] 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 [8,9]:

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

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

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

There occur suppression intracellular anaerobic catabolic processes, causing 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 excessive quantity of mitochondrial superoxide [O_2^{*}] which don't lead down to final products CO_2 and H_2O but lead to H_2O_2 forming. It was tested that generated hydrogen peroxide from ROS can ruin mitochondrial DNA [mtDNA] with mitochondrion and thereby it can cause damage of mitochondrion. However there occurs the permanent repair via fusion of both mtDNA and mitochondrion which are mediated by mtDNA ligase activity and by mitochondrial fusion proteins [OPA1, Mfn1 and Mfn2]. The abundance hydrogen peroxide [H_2O_2] from ROS is detoxified by mitochondrial glutathione peroxide (GPX) and phospholipid hydroperoxide glutathione peroxide (PHGPX) that occur either in G0 phase cellular cycle or in G1/S phases cellular cycle: 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 [8,10-14]. 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 [8,15-17]. Thus there are the summarized reactions of respiratory oxidative processes with generating superoxide [O_2^{*}-], ROS and hydrogen peroxide [H_2O_2] [8]:

5) a) $O_2 + e^- \rightarrow O_2^{*-}$; b) $2O_2^{*-} + 2H+ \rightarrow H_2O_2 + O_2$; c) cytc-Fe3+ + $O_2^{*-} \rightarrow$ cytc-$Fe^{2+} + O_2$;

d) cytc-$Fe^{2+} + H_2O_2 \rightarrow$ cytc-$Fe^{3+} + {-}OH + {}^{*}OH$. e) $H_2O_2 + 2GSH \rightarrow 2H_2O$ + 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" [18]. 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 mechanisms of these processes [18]. 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 due to blood circulation. 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 catabolic anaerobic pathway of glycolysis and as well as into anabolic processes which is induced by reactions of nitric oxide (NO) (see below). Glycolysis generates energy for both catabolic oxidative phosphorylation and anabolic processes promoting expression of proliferative processes (growth of tissue, angiogenesis etc.) [5-7] (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]. Just the main role for the mitochondria is the production of ATP which is the carrier energy for oxidative phosphorylation of glycolysis. Also mitochondria have their own genetic materials, which operate in mitochondrial DNA (mtDNA) with the machinery to manufacture their own RNAs (22 tRNA, 2 rRNA, and 13 peptide genes) and proteins [5]. Just the 13 mitochondrial peptides are integrated into the inner mitochondrial membrane, along with proteins encoded by genes. All of these processes increase mitochondrial chemical potential ($\mu_{mitochond.}$) considerably due to production plenty of supplemental substances via anabolic processes created by mtDNA. Therefore export substances from mitochondria and the substances, which were produced in cytoplasm, increase cytoplasmic chemical potential ($\mu_{cytoplasm}$) considerably. It is occurred great disbalance between mitochondrial chemical potential ($\mu_{mitochond.}$) and cytoplasmic chemical potential ($\mu_{cytoplasm}$), i.e. $\mu_{mitochond.} < \mu_{cytoplasm}$. These chemical potentials induce corresponding charges in inner membrane (IMM) and outer membrane (OMM) of mitochondrial shell that influence corresponding on electrocapacity (C) of mitochondrial capacitor and cause disbalance between electrocapacity (C) of mitochondrial capacitor and electrocapacity (C) of cellular capacitor that stimulates, according to Theorell formula, fast export substances from cytoplasm across cellular wall. Thus the substances [as ATP; ADP; Pi; anions such as pyruvate, cations such as Ca^{2+}, H^+, K^+, some H_2O_2 and free radicals, proteins both high molecular substances and small molecular substances etc.] get into extracellular medium. Just this export of the substances from cytoplasm increases mitochondrial chemical potential ($\mu_{mitochond.}$) considerably, i.e. $\mu_{cytoplasm}<\mu_{mitochond.}$. These chemical potentials induce corresponding charges in inner and outer membranes of mitochondrial shell that causes reverse disbalance between electrocapacity (C) of mitochondrial capacitor and electrocapacity (C) of cellular capacitor and stimulates, according to Theorell formula, supplemental both oxidative processes and anabolic processes in mitochondria with transport substances from mitochondrion into cytoplasm across mitochondrial shell approaching state to balance of mitochondrial potential ($\mu_{mitochond.}$) and cytoplasmic potential ($\mu_{cytoplasm}$) approximately, i.e. $\mu_{mitochond.} \leq \geq \mu_{cytoplasm}$. Thus the driving mechanisms of all cells' transport substances between mitochondria and cytoplasm across mitochondrial shell are the biophysical mechanisms of substances transport according to Theorell formula which is stimulated also by mitochondrial capacitors operations.

The mechanism operation of nucleus capacitors in processes of transport substances across nucleus and cytoplasm

Cellular central mechanism of anabolic endoergonic processes [$+2nH^+$] is located in nucleus exhibiting great basophilic chemical potential due to staining cells ($\mu_{nucleus}$). The acidophilic properties of phosphate group in each nucleoside of nucleic acids (DNA or RNA) are weaker than alkaline properties of purines and pyrimidines bases that leads to chemical reaction of accepting electrons via accepting a lot of alkaline staining agents. Thus great basophilic chemical potential of nucleus ($\mu_{nucleus}$) is formed due to great biochemical reaction of accepting electrons which correspond to great anabolic endoergonic processes [$+2nH^+$] in nucleus. Cytoplasm is subjected to the dual simultaneous influences as from great anabolic endoergonic processes [$+2nH^+$] of nucleus as well as from catabolic exoergonic processes [$-2nH^+$] of mitochondria. Unlike nucleus, cytoplasm exhibits only moderate basophilic chemical potential ($\mu_{cytoplasm}$). Anabolic endoerginic processes prevail over catabolic exoergonic processes in cytoplasm in a little degree because anabolic processes produce supplementary substances and accumulate energy for cells' development showing positive fluctuation entropy ($+\Delta x\beta$) according to Glansdorff and Prigogine theory [4-6]. The nuclear great basophilic chemical potential ($\mu_{nucleus}$) generates great charge on inner membrane (INM) of nuclear shell, and the influence of cytoplasmic moderate basophilic chemical potential ($\mu_{cytoplasm}$) generates smaller charge on outer membrane (ONM) of nuclear shell, forming nucleus capacitor. Operations of nucleus capacitor cause supplementary mechanism of maintenance stability Internal Energy and Internal Medium both in cells and in an organism. Driving mechanism of transport substances across nuclear shell is also corresponded to Theorell formula:

$dn/dt = -UcA\, d\mu/dx$: [dn/dt – quantity of diffusing substance molecules in the unit time; U – substance mobility; c – substance concentration; A – membrane area; μ – chemical potential; x – molecule distance from membrane] [7].

Also export substances from nucleus into cytoplasm and the substances, which were produced in cytoplasm, increase cytoplasmic chemical potential ($\mu_{cytoplasm}$) considerably. It is occurred great disbalance between nuclear chemical potential ($\mu_{nuclear}$) and cytoplasmic chemical potential (μcytoplasm), i.e. $\mu_{cytoplasm}>\mu_{nuclear}$. These chemical potentials induce corresponding charges on inner nuclear membrane (INM) and on outer nuclear membrane (ONM) of nuclear shell that causes reverse disbalance between electrocapacity (C) of nuclear capacitor and electrocapacity (C) of cellular capacitors and stimulates, according to Theorell formula, processes as import substance from cytoplasm into nucleus as well as export substances from cytoplasm into extracellular medium across cellular wall approaching to approximated balance of nuclear potential ($\mu_{nuclear.}$) and cytoplasmic potential ($\mu_{cytoplasm}$), i.e. $\mu_{nuclear} \leq \geq \mu_{cytoplasm}$. Nuclear capacitor promotes also the anabolic endoergonic function of nucleus exerting both cellular cycle of tissue proliferation and biosynthesis proteins. Hence movements of RanGTP / RanGTPase / RanGDP between the nucleus and cytoplasm reflect transport substances due to nuclear capacitors operation and subjecting to Theorell formula which is exerted by the difference chemical potentials between the nucleus and cytoplasm, i.e. both sides of a nuclear shell [7,19-21]. The events, which happen in interphase of cellular cycle, demand on import of amino acids from cytoplasm into nucleus for anabolic endoergonic processes of proteins biosynthesis causing transcription and translation processes due to transfer RNA to

DNA in which occurs processes biosynthesis polypeptide chains of proteins using amino acids [as codons (triplet) on the mRNA with amino acids]. All these substances were produced in cytoplasm that leads to increase cytoplasmic chemical potential ($\mu_{cytoplasm}$) considerably, i.e. $\mu_{cytoplasm}>\mu_{nuclear}$. Therefore according Theorell formula and due to reverse energy of RanGDP/Ran GTPase/RanGTP there is realized fast import of macromolecules substances such as RNA and proteins with karyopherins called importins into nucleus across nuclear pore complexes (NPCs) supporting by Cargo-NLS [19-21]. These anabolic endoergonic processes increase nuclear chemical potential ($\mu_{nuclear}$) considerably. Thus it is occurred great disbalance between nuclear chemical potential ($\mu_{nuclear}$) and cytoplasmic chemical potential ($\mu_{cytoplasm}$), i.e. $\mu_{nuclear}>\mu_{cytoplasm}$. These chemical potentials in nucleus and cytoplasm induce corresponding charges on inner membrane (INM) and outer membranes (ONM) of nuclear shell that influence on electrocapacity (C) of nuclear capacitor and cause disbalance between electrocapacity (C) of nuclear capacitor and electrocapacity (C) of cellular capacitors that stimulates, according to Theorell formula and due to energy of RanGTP/Ran GTPase/RanGDP, fast export substances such as forming polypeptide chains of proteins, proteins, assembled ribosomal subunits and transfer RNA across nuclear pore complexes (NPCs) supporting by Cargo-NES [7,19-21]. Also these processes advance cellular cycle from G_0 phase into G_1/S phases [7]. Then on the one hand, there occurs G_2 phase cellular cycle with the destructive processes of nuclear DNA (nDNA) via fragmentation (as catabolic processes) in which the caspase-activated DNAase (CAD) is an activator [22-24], and on the other hand, there occur the processes repairs of nuclear DNA (nDNA) (as anabolic processes) 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) [25-27]. The oscillations of fragmentation /reparation nDNA function determine the moderate fluctuation of nuclear chemical potential (μnuclear) which is connected with the oscillations of fusion/fission mitochondrial mtDNA function that determine cell's development [5]. Thus the driving mechanisms of all cells' transport substances between nucleus and cytoplasm across nuclear shell are the biophysical mechanisms of substances transport according to Theorell formula which is stimulated also nuclear capacitor operations.

The mechanisms interactions between nucleus, cytoplasm and mitochondria for maintenance stability cellular Internal Energy in norm

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 due to blood circulation. 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 processes and anabolic processes that promotes cells development leading to growth of tissue, angiogenesis etc. [8,28-30] (Figure 1). These rhythmic interchanges influence also on rhythmic alternations of mitochondrial catabolic exoergonic oxidative processes and nuclear anabolic endoergonic processes [4,6]. The rhythmic alternations of 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 also oscillates in moderate normal limits. The maintenance stability of cellular Internal Energy (stable temperature 36,0°C – 36,9°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 which induce related chemical potentials of an organism and cells of an organism in norm [2-4,6] (Figure 2). Cellular chemical potential (μ_{cell}) is induced by intracellular balance of catabolic exoergonic processes and anabolic endoergonic processes [4,6]. Thus cellular chemical potential (μ_{cell}) is the indicator of cellular Internal Energy which interacts with extracellular chemical potential ($\mu_{extr.cell}$). Besides, cellular chemical potential (μ_{cell}) of each cell interacts with cellular chemical potentials (μ_{cell}) of all cells an organism via related resonance waves of remote reaction due to operations of cellular capacitors [4] (Figure 3). Also the related resonance waves, generated by cellular capacitors operations, create supplementary mechanisms of maintenance stability cellular Internal Energy and Internal Medium of all cells (Figure 3). The interactions between nucleus and mitochondria occur also via interactions of the mechanism nuclear DNA [nDNA] and mechanism mitochondrial DNA [mtDNA]. Locating into cellular central mechanism of mitochondrial catabolic processes, the mtDNA is subjected to oscillation of fusion/fission, reflecting oscillations anabolic processes and catabolic processes. These oscillations carry out function of driving mechanism rhythmic processes of cellular cycle in transiting G_0, G_1/S, G_2/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 with dynamin-related protein 1 (Drp 1) [8-12]. Also mitochondria are subjected to fission due to mitochondrial factor (Mff), reflecting expression of catabolic oxidative processes [8-12]. On the other hand, there occur the permanent mtDNA repairing mechanisms via ligase activity for permanent fusion of destructing mtDNA preventing mtDNA loss and creating also mtDNA copy number, i.e. expression of anabolic reductive processes [8]. Thus dynamics of mtDNA fission/fusion is occurred via oscillation balance catabolic/anabolic processes [8,22,23,31]. The rhythmic oscillating anabolic/catabolic shifts of mtDNA are also exerted by the rhythmic oscillating oxidative mitochondrial processes via rhythmic production of oxidative enzymes as cytochrom c oxidase, NADPH oxidase, GTPase, superoxide dismutase (MnSOD) and copper, zinc superoxide dismutase (Cu, ZnSOD) and the others. Besides 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 DNAase (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) [2-6,25-27]. Also the rhythmic oscillating shifts of anabolic endoergonic processes and catabolic exoergonic processes in nucleus and in mitochondria induce interactions between resonance waves of nuclear capacitors and resonance waves of mitochondrial capacitors which exert cellular development influencing on all cellular reactions including C_0, C_1/S, C_2/M phases of cellular cycle, cell aging, apoptotic processes leading to cell death [4-6]. Furthermore the moderate oscillations of stable chemical potential in cytoplasm (μcytopl) maintains stability of cell's Internal Energy and Internal Medium and promotes cellular capacitors operations [4,5]. The

mutual influences between moderately oscillating nDNA fragmentations / reparations in nucleus and conformably moderately oscillating mtDNA fusion / fission in mitochondria are displayed in normal quiescent G_0 phase of cellular cycle. 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 of cells and an organism [5] (Figures 2 and 3). In normal G_1/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 processes into moderate anabolic endoergonic processes of reparations that leads to processes RNA transcription and translation for proteins biosynthesis due to expression of an inhibitor of caspase-activated DNAase (ICAD) in nucleus. Simultaneously the moderate oscillation of balance mtDNA catabolic /anabolic processes shifts into moderate catabolic exoergonic aerobic processes in mitochondria. The produced ROS is neutralized by glutathione peroxidise (GPX) and phospholipid hydroperoxide glutathione peroxidise (PHGPX) in normal G_1/S phases of cellular cycle. In normal G_2 phase of cellular cycle it occurs transit moderate anabolic processes into intensive anabolic processes in nucleus and simultaneously transit from moderate catabolic processes into intensive catabolic processes in mitochondria that leads to impel production of surplus complex ROS/H_2O_2. On the one hand, these processes in nucleus and in mitochondria promote mechanism maintenance stability chemical potential of cytoplasm (μ_{cytopl}) and normalizing cellular capacitors functions with normalizing transport substances across cellular wall according Theorell formula. On the other hand, the complex ROS/H_2O_2 pass through mitochondrial membranes and cytoplasm into nucleus and generates superoxide [$O_2^{\bullet}$] inducing free radicals ($^{\bullet}OH$). Free radicals ($^{\bullet}OH$) react on nDNA and induce process replication via realizing of 2nDNA:

$^{\bullet}OH + H_2$-nDNA-DNA −−> $H_2O + H^{\bullet}$-nDNA-DNA;

$O^{\bullet} + 2H_2O$ −−> $2H^{\bullet} + 2OH^{-}$;

$2H^{\bullet}$-nDNA-DNA + $2H^{\bullet}$ −−> 2nDNA-$H^{\bullet}$ + 2nDNA-$H^{\bullet}$;

2nDNA-$H^{\bullet}$ + $2^{\bullet}OH$ −−> 2nDNA + H_2O

Thus the free radicals ($^{\bullet}OH$ and $H^{\bullet}$) are neutralized in final G_2 phase of DNA replication [5,6,32]. Mitosis [M phase cellular cycle] realizes cell division and 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 [4,6,7]. Moreover chemical potentials of cell (μ_{cell}) during G_0, G_1/S, G_2/M and G_0 phases normal cellular cycle are related to chemical potential an organism (μorganism) maintaining stable Internal Energy and Internal Medium both in an organism and cells of an organism (Figures 2 and 3). Catabolic oxidative processes and excretion of the excess products of catabolic oxidative reactions as well as inflow substances across cellular wall in G_1/S phases cellular cycle advance cellular cycle, causing proliferation processes. Anabolic processes are impossible without efficient endocytosis and exocytosis. Therefore the exocytosis is the link which ties anabolic processes with catabolic processes maintaining balance catabolic and anabolic processes as for cell survival as well as for advance cellular cycle and proliferation [4-7] (Figure 1). The moderate shifts of balance catabolic and anabolic processes into anabolic processes promote as proliferative processes via advance of cellular cycle as well as development cell from young cell till senescence due to gradual transition anabolic processes into prevailing catabolic processes leading to cells death, i.e. Apoptosis, due to gradual increase of disbalance of chemical potentials (μ) between extracellular and intracellular mediums leading to gradual increase of gain entropy [4,6]. Also the moderate shifts of balance catabolic and anabolic processes into catabolic processes promote cellular survival due to cleaning of cell via exocytosis of oxidized metabolic Products [4,6].

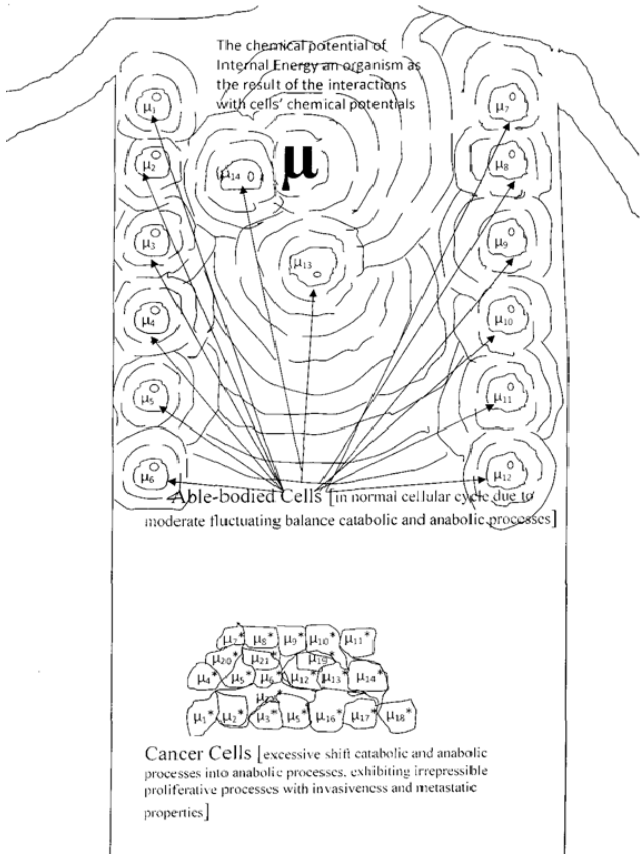

Figure 3: Balance Internal Energy both cells and an organism due to their chemical potentials (μ) promoting operation resonance waves of cellular capacitors and disbalance of chemical potentials (μ^{*}) cancer cells.

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) Resonance waves between an organism and cells of an organism are produced by cellular capacitors which reflect interactions between cells of an organism and between an organism and cells of an organism due to related chemical potentials of cells an organism (μ), d) Chemical potentials of cancer cells (μ^{*}) are unrelated to chemical potentials of an organism (μ) and chemical potentials of an organism's cells (μ) that results in absent cohesive resonance waves joining them and absent regulating influences of an organism showing autonomous development of cancer cells via excessive expression of proliferative processes.

The moderate shifts of balance catabolic and anabolic processes both into catabolic and into anabolic processes contribute to normal development of cellular cycle for maintenance of stability cellular

Internal Energy and Internal Medium, i.e. positive fluctuations of entropy (+Δxβ) according to Glansdorff and Prigogine theory [6]. G_1/S phases of cellular cycle are induced by inflow of energy and substances into cell, i.e. endocytosis [7]. So endocytosis and anabolic endoerginic processes prevail in G_1 and S phases cellular cycle [4,6,7]. The outflow of accumulating energy and synthesized substances due to cells division in G_2 and Mitosis phases releases the new cell from the excess of anabolic products in normal tissue [6]. So G_2 phase and Mitotic phase (M) of cellular cycle in normal tissue follow after G_1 and S phases of cellular cycle causing the cell division in which anabolic high-molecular products are distributed between new cells realizing Alternative excretion of these substances [7] (Figure 1). The cells, which don't move from S phase into G_2 and then into Mitotic phase (M) of cellular cycle, move towards senescence and then were subjected to death due to increase an entropy according to second law of thermodynamics [1]. Therefore processes of senescence were compelled by decrease of anabolic processes during ageing. Hence senescence exhibits processes very gradual cumulation of excess intracellular substances during cell life that cause violation of balance catabolic and anabolic processes in intracellular medium which are settled on the blood vessel as the sediments [atherosclerosis plaques, salts, fatness etc.] [1,4-6]. On the contrary, the changes of normal balance catabolic and anabolic processes in Intracellular Medium causes the moderate changes of normal balance between Intracellular Medium and Extracellular Medium which leads to exerting processes of substances transport across cellular wall according Theorell formula promoting advance cellular cycle for the minimization increment of gain entropy and causing the stability of the open non-equilibrium thermodynamic system of formed cells according to Prigogine theorem [1,4,7]. Indeed the cells of cambial layer of epithelium propagate via Mitosis phase of cellular cycle and remain alive. The next layer of cells does not propagate and then cells get into keratoid epithelium which is rejected as keratoid cells, hairs, nails and so on.

The Pathologic Mechanism Stability Internal Energy both in Cells and in an Organism

The main pathways of violations stability internal energy leading to pathologic mechanism stability internal energy both in cells and in an organism

Normal proliferative processes lead to anti-apoptotic mechanisms and display the oscillations of moderate shift the balance anabolic and catabolic processes into moderate anabolic endoergonic processes and moderate shift the balance catabolic and anabolic processes into moderate catabolic exoergonic processes. The proliferative processes are decreased in an organism with the senescence due to decreasing sexual function of an organism that leads gradually to pathologic states as atherosclerosis, cardiac infarction etc. [4]. The excessive shift balance anabolic and catabolic processes into excessive catabolic exoergonic processes leads to great dissipation energy into Environment with increase of a body temperature stimulating cellular capacitors operations via generation of resonance waves which exert remote reaction across distance [4]. Then phagocytes with their proteolytic and cytolytic reaction are transited in contact reactions causing damage infectious agents. Thus the mechanism of phagocytosis displays immune defensive mechanism of an organism. The excessive shifts of balance catabolic and anabolic processes into excessive catabolic processes promote huge dissipation of energy into environment via huge increase of body temperature and exocytosis substances resulting in processes of acute inflammations and infectious diseases [6] (Figure 4). These processes destroy a lot of cells owing to disbalance both chemical potentials (μ) and osmotic pressures between extracellular and intracellular mediums. Indeed the excessive shift of the balance anabolic and catabolic processes into excessive catabolic processes leads to death a cell or ever an organism due to expression of pro-apoptotic processes in them [4,6] (Figure 4). Also the excessive shifts of balance catabolic and anabolic processes into catabolic processes cause expression of huge exocytosis which transits into huge endocytosis that stimulates cellular cycle filling by substances of G_1/S phases cellular cycle according to Theorell formula [7]. Thus it occurs increase of anabolic processes simultaneously with huge catabolic processes that causes defensive reaction of an organism via biosynthesis of immune antibodies with expression of phagocytosis and the other immune mechanisms owing also to cellular capacitors operations. The excessive shift of the balance anabolic and catabolic processes into excessive anabolic processes cause transmutations of able-bodied cells into cancer cells displaying irrepressible proliferative processes [6,7] (Figure 4). The huge proliferative processes in cancer tissue cause Warburg effect with disbalance of the anabolic and catabolic processes because excessive anabolic endoergonic processes partially suppress catabolic exoergonic processes, which lead to irrepressible tumor growth and metastasis [7]. The huge anabolic (biosynthetic) processes consume enormous quantity of Acetyl-CoA and energy that cause overloading of "Nodal point of bifurcation catabolic and anabolic processes (NPBac)" and block as oxidative processes and as well as excretion of high-molecular substances, i.e. block exocytosis of high-molecular substances [7] (Figure 5). It takes place immeasurable production of the high-molecular substances in cancer tissue: proteins, lipoproteins and so on. The formed high-molecular substances cannot be excreted from cytoplasm of cancer cells via oxidative processes because of large consumption Acetyl-CoA and energy for anabolic processes and lack Acetyl-CoA and energy for oxidizing processes [7] (Figure 5). Therefore the Alternative mechanism excretion of high-molecular substances within cells prevails in metabolism cancer cells due to great acceleration of cellular cycle. Thus unlike able-bodied tissue, the anabolic endoergonic processes in G_1/S phases of cellular cycle prevail over catabolic exoergonic processes excessively in cancer tissue exerting proliferative processes and creating Warburg effect mechanism in cancer tissue metabolism [5-7] (Figure 5). The high-molecular substances are excreted within the new cells in cancer proliferative process as Alternative excretion of high-molecular substances. These new cancer cells find new matrices without overloading of "Nodal point of bifurcation catabolic and anabolic processes (NPBac)", and so they receive sufficient Acetyl-CoA and energy for oxidizing processes of high-molecular substances. Thus Alternative excretion of high-molecular substances forms metastasis of cancer tumor [7] (Figure 5). Also the process of cancer metastasis forms the mechanism of Apoptosis Resistance of cancer cells [7]. The excessive shifts of balance catabolic and anabolic processes into anabolic processes promote such pathologic diseases as cancer, sarcoma, leukemia etc. [6,7]. The shift balance anabolic and catabolic processes into catabolic exoergonic processes leads to oxidation substances and dissipate a lot of energy into environment that leads to cells senescence due to expression of pro-apoptotic mechanisms exhibiting increase of entropy according second law of thermodynamics. But on the contrary, the shift balance anabolic and catabolic processes into catabolic exoergonic processes and dissipation energy into Environment leads to maintenance stability of temperature 36.0-36.9°C, by which all enzymes operate, creating resistance to influences of environmental temperature. Just

the stable temperature 36.0-36.9°C promotes oxidative processes leading to exocytosis of granules, i.e. stability both cellular Internal Energy / Internal Medium and an organism's Internal Energy/Internal Medium promoting survival cells and an organism in norm. The moderate oscillating shifts balance anabolic and catabolic processes both to anabolic processes and to catabolic processes cause the positive fluctuation of entropy (+Δxβ) that results in linear development cellular thermodynamic system according to Glansdorff and Prigogine theory, i.e. the development during life of a cell due to proliferation and anti-apoptotic effect [4,6]. However Apoptosis is the inherent characteristic of any alive process owing to step-by-step entropy increase, according to the second law of thermodynamics and even Prigogine theory too.

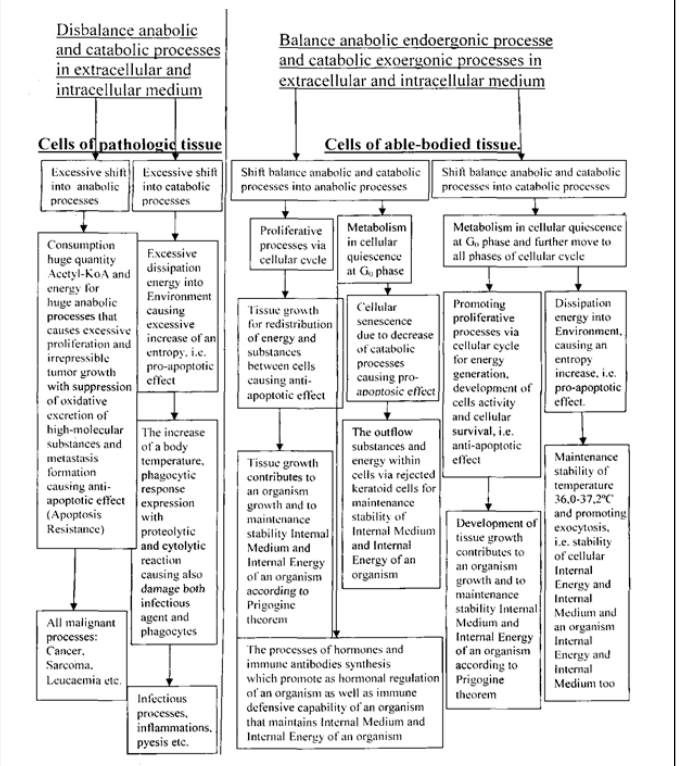

Figure 4: The maintenance stability of Internal Medium and Internal Energy as in cells of able-bodied tissue as well as in cells of pathologic tissue.

a) Balance anabolic and catabolic processes are divided into shifts balance anabolic and catabolic processes into anabolic processes and into catabolic processes in able-bodied tissue, b) Shifts balance anabolic and catabolic processes into anabolic processes advances into Proliferative processes via cellular cycle and into Metabolism in cellular quiescence at G0 phase in able-bodied tissue, c) Proliferative processes via cellular cycle promote tissue growth and maintenance stability Internal Medium and Internal Energy as in cells as well as in an organism in able-bodied tissue, d) Metabolism in cellular quiescence at G0 phase contributes to cellular senescence and outflow substances and energy within cells via rejected keratoid cells for maintenance stability of Internal Medium and Internal Energy of an organism in able-bodied tissue, e) Balance anabolic and catabolic processes contributes to processes of hormones and immune antibodies synthesis which promote as hormonal regulation of an organism as well as immune defensive capability of an organism that maintains Internal Medium and Internal Energy of an organism in able-bodied tissue, f) Shift balance anabolic and catabolic processes into catabolic processes exhibits metabolism in cellular quiescence at G0 phase and further move to all phases of cellular cycle as promoting proliferative processes via cellular cycle for generating energy and developing tissue growth as well as dissipation energy into Environment for maintenance stability of temperature 36,0-37,2°C and promoting exocytosis, i.e. stability of cellular Internal Energy and Internal Medium and an organism's Internal Energy and Internal Medium in able-bodied tissue, g) Disbalance anabolic and catabolic processes is divided into excessive shifts into anabolic and into catabolic processes in pathologic tissue, h) Shifts balance anabolic and catabolic processes into excessive anabolic processes leads to all malignant processes: Cancer, Sarcoma, Leucaemia etc., i) Shifts balance anabolic and catabolic processes into excessive catabolic processes promote Infectious processes, inflammations, pyesis etc.

Highlights: The balance of catabolic and anabolic processes maintains the stability cellular Internal Energy and Internal Medium due to normal balance of chemical potentials (μ) between Extracellular and Intracellular Mediums. The moderate shifts of balance catabolic and anabolic processes into anabolic processes promote normal proliferative processes via cellular cycle which induce anti-apoptotic processes and also exert immune defensive processes via production of immune antibodies which take part in immune defensive mechanism of an organism. The excessive shifts of balance catabolic and anabolic processes into excessive anabolic processes promote excessive proliferative processes and form Warburg effect mechanism leading to irrepressible proliferative processes of growth tumor, metastasis, Apoptosis Resistance and Alternative mechanism excretion of high-molecular substances within cells in cancer tissue. The moderate shifts of balance catabolic and anabolic processes into catabolic processes promote increase exocytosis of oxidized products and induce oxidative phosphorilation generating energy for maintenance of stable cellular Internal Energy (temperature 36,0°C – 36,9°C by which all enzymes operate) via dissipation of energy and substances into environment, that promote cellular survival and also exert immune defensive mechanisms of phagocytes' cellular capacitors operations via resonance waves inducing remote reaction across distance transiting into contact reactions of immune reactions for decomposition of strange molecules displaying immune defensive capability. The excessive shifts of balance catabolic and anabolic processes into excessive catabolic processes lead to the huge dissipation of energy and substances into environment causing the high temperature body of an organism and destroy of cellular Internal Energy / Internal Medium that occurs in processes of inflammation and infectious diseases. The huge catabolic processes also induce pro-apoptotic processes which transit into anabolic processes of nuclear reactions expression due to interdependence between nuclear capacitors and mitochondrial capacitors leading to production of immune antibodies and the other immune mechanisms as defensive reaction of an organism. Cellular factors are the links which either participate in the biochemical processes or stimulate the biochemical processes being exerted by remote reactions of cellular capacitors operations via resonance waves of cellular signals [4].

Mitochondrial function in oncologic cellular cycle

Cellular oncogenesis due to oncogenes operations in nucleus induces abundance production of ROS/H_2O_2/Free radicals in

mitochondria because of interactions resonance waves between nuclear capacitor and mitochondria capacitors. Further the huge ROS/H_2O_2/Free radicals, due to differences of chemical potentials (μ) between nucleus and mitochondria, transit across mitochondrial shells, cytoplasm and nuclear shell [according to Theorell theorem] and are the driving mechanism of accelerated DNA replication in G_2 phase cellular cycle causing excessive proliferative processes and irrepressible cancer tumour growth. There are the induced by huge quantity free radicals (*OH) process accelerated DNA replication via realizing of 2nDNA in cancer cells [5,6,32]:

$^*OH + H_2$-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 + H_2O

Thus 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 G_1/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 causes neutralization ROS/H_2O_2/Free radicals eliminating the 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 [7,8-13,33-38]. Just it is the mechanism of 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 inadequate to the normal cells of an organism [5,7,39,40] (Figure 3). Cancer cells' nuclei arise great expression of G_1/S phases cellular cycle which display permanent oscillating nDNA reparations/fragmentations into excessive anabolic endoergonic processes of reparation leading also 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 [5]. The produced excessive abundance of complex ROS/H_2O_2 pass through mitochondrial membranes and cytoplasm into nucleus in G_2 phases oncologic cellular cycle and generates excessive abundance of superoxide [O_2^{*}] inducing excessive abundance of free radicals (*OH) [7,8-13]. 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 [5,6,32]. 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 [5,33-38]. Thus the mechanism of Apoptosis Resistance occurs in cancer tissue. Chemical potentials of new cancer cells are inadequate to chemical potential of an organism [5] (Figures 2 and 3). All processes of mitochondrial biogenesis are advanced due to nitric oxide both in normal cellular cycle and in oncologic cellular cycle exhibiting transfer from catabolic processes into anabolic processes [41]. The excessive shift of the balance anabolic and catabolic processes into abundance anabolic processes create cancer cells' chemical potentials ($\mu_{cancell}$) inadequate to chemical potentials as an organism (μ_{org}) as well as able-bodied cells (μ_{cell}) [4,5] (Figure 3). These cancer cells' chemical potentials ($\mu_{cancell}$) are the driver mechanisms of proliferative processes leading to Warburg effect, excessive proliferation, irrepressible cancer growth, unhealed cancer wounds, metastasis and Apoptosis Resistance (Figure 5).

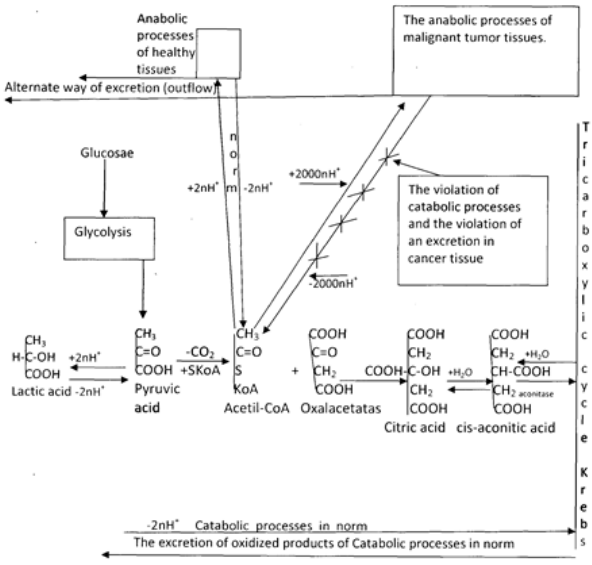

Figure 5: The metabolism of a malignant tumor tissue and of a normal tissue.

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.

The benefits using Prolonged medical Starvation with considerably decreased dosage of cytotoxic drug of the new approach to cancer therapy

As the new approach to cancer therapy, "Prolonged medical Starvation 42 – 45 days with considerably decreased dosage of

cytotoxic drug" activates catabolic processes in an organism for maintenance stable temperature 36.0°C – 36.9°C by which all enzymes operate [42-44]. Increase of fat metabolism from fat depot due to prolonged starvation 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 G_1/S phases of cancer cellular cycle. 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 use of Acetyl-CoA for catabolic processes, and suppression DNA replication, due to ROS/free radicals neutralization in G1/S phases cellular cycle before nDNA replication in G_2/M phases cellular cycle, as in an organism and as well as in cancer cells which metabolism are characterized by shift into anabolic processes [5,42-44]. Thereby Warburg effect, characterizing by aerobic glycolysis, is destroyed because of expression aerobic catabolic processes and decrease anaerobic processes of glycolysis. Warburg effect destruction violates cancer pathway of metabolism and promote normal pathway of metabolism, characterized by Pasteur effect as incomparability of glycolysis with aerobic oxidation in norm. So it occurs depression of cancer metabolism that helps for efficient anticancer therapy with decreased dosage of cytotoxic drugs [42-44]. Such approach to anticancer chemotherapy prevents damage Internal Energy and Internal Medium both an organism and able-bodied cells of an organism, preventing damage of immune and hormonal systems as the links of defensive mechanism in regulative system of an organism, unlike up-to-date methods of chemotherapy with great dosage of cytotoxic drugs [43,44]. 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 anticancer chemotherapy and resistance to anticancer drugs versus up-to-data intensive anticancer chemotherapy with great dosage of cytotoxic drugs [44].

Reviews of the role mutual influences cell's capacitors in mechanisms of interactions nucleus processes / cytoplasm processes / mitochondria processes in norm and pathology

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 [35]. 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 also 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" [35]. Thus these experiments did not detect the mechanism of connection between migration capability of cancer cells and properties of H_2O_2. Just the biochemical mechanisms stability cellular Internal Energy are maintained by biophysical mechanisms of mutual influences between cellular capacitors, nuclear capacitor, mitochondrial capacitors and the other organelles' capacitors which regulate transports substances across cellular wall, nuclear shell, mitochondrial shells and shells of other organelles being subjected to Theorell formula [2-7]. These mechanisms exert intracellular ROS/H_2O_2 transport across mitochondrial shells and nuclear shell and generate free radicals (*OH) which induce process replication via realizing reaction forming 2nDNA [nDNA + nDNA ---> 2nDNA] in cancer metabolism. These cellular transformations occur due to oncogenes operations which result in acceleration of cellular cycle and Warburg effect mechanism: As outcome of oncogenes operation the huge anabolic processes cause huge consumption of energy and Acetyl-CoA and partial suppress the catabolic processes for cells survival in cancer tissue. Lactic acids accumulate energy for anabolic processes in condition increased glycolysis metabolism in cancer tissue. This concept gives possibility to explain Warburg effect mechanism and distinction between mechanisms Pasteur effect and Warburg effect [7] (Figure 5). The mechanisms of cancer cell invasiveness and metastasis are also explained by explanation of Warburg effect mechanism in which vascular endothelial growth factor (VEGF) is produced as the link of tumor angiogenesis and oncogenesis. Besides the mechanism Alternative excretion of high-molecular substances within cancer cells was explained as the result of lack Acetyl-CoA for excretion via oxidative processes [7] (Figure 5).

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 [36]. Just AKT is the primer of advancing Glycolysis which is divided into anabolic and catabolic pathways in nodal point of bifurcation anabolic and catabolic processes [NPBac] through Acetyl-CoA [7] (Figure 5). The huge anabolic processes cause huge consumption of energy and Acetyl-CoA and partial suppress the catabolic processes for cells survival in oncogenesis of cancer tissue metabolism according to Warburg effect mechanism [7] (Figure 5). Thus advancing Glycolysis through activation of AKT promotes exertion of huge anabolic processes for excessive proliferative processes and expression cancer tissue growth. Also oncogenesis causes chemical potentials in cancer cells ($\mu_{can.cell}$) inadequate to chemical potentials of able-bodied cells (μ_{cell}) and an organism (μ_{org}) [5] (Figure 3). Therefore cancer cells are not subjected to regulative mechanisms as of an organism and as well as of normal cellular capacitors' resonance waves [5] (Figure 3).

Xia 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 doubt: "However the direct roles of endogenous ROS production still remain to be elucidated" [37]. 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. Just excessive generation of ROS/H_2O_2 is produced in mitochondria of cancer cells versus moderate level ROS in mitochondria of normal cells. The excessive ROS/H_2O_2 would be able to 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 [5,7,8,14,34). These incompatible

situations cannot been explained considering only neutralized function of glutathione peroxide (GPX) and phospholipid hydroperoxide glutathione peroxidise (PHGPX), which decrease the rate of ROS/H_2O_2 in G_0 and G_1/S phases cellular cycles of cancer tissue [5,8,10-17]. Also these incompatible situations cannot 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 / 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 occurs due to disbalance catabolic and anabolic processes in cancer tissue metabolism (5,7–12,22-24,31). The intracellular ROS/H_2O_2 transport across mitochondrial shells and nuclear shell and chemical transformation ROS ? superoxide [O_2^{*}] ? H_2O_2 ? free radicals (*OH) generate free radicals (*OH) which huge quantities induce accelerated nDNA replication via realizing reaction nDNA + nDNA ---> 2nDNA in G_2 phase of cellular cycle showing irrepressible proliferative processes of cancer tumor. These reactions are induced by interactions between cellular capacitors, nuclear capacitor, mitochondrial capacitors and the other organelles' capacitors which regulate transports substances across cellular wall, nuclear shell, mitochondrial shells and shells of other organelles according to Theorell formula [2,5-7].

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 the transcription factor FoxM1 which stimulates the detoxifying enzyme catalase and also coordinates transcription factors NFkB, HIF and p53 [14]. Besides Gibellini et al. [14] and Sattler M et al. [38] described transformation of various hematopoetic cells lines due to increase of ROS level that does not occur in quiescent G_0 phase of cellular cycle in untransformed cells. Just reactive oxygen species (ROS) 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 oscillations of mtDNA fission/fusion. These processes occur in G0 and G1/S phases of cellular cycles too. 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 G_2 phase of cellular cycle. Just the stability Internal Energy and Internal Medium of cytoplasm chemical potential (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. Unlike normal cellular cycle, it occurs permanent excessive shift balances catabolic and anabolic processes into excessive anabolic pathway in oncogenesis [4-6] (Figures 2 and 3). Thus oncogenesis causes chemical potentials in cancer cells ($\mu_{can.cell}$) inadequate to chemical potentials of able-bodied cells (μ_{cell}) and an organism (μ_{org}) that results in absent cohesive resonance waves joining the cancer cells with an organism's cells and absent regulating influences of an organism showing autonomous development of cancer cells via excessive expression of proliferative processes [5] (Figure 3). Therefore cancer cells are not subjected to regulative mechanisms as of an organism and as well as of cellular capacitors' resonance waves of able-bodied cells [5] (Figure 3).

Studying mechanism cellular respiratory rhythm in cellular oxidized processes induced by cytochrome c oxidase and hypoxic state in cells induced by Hypoxia-inducible factors 1 (HIF1) with concentration of nitric oxide (NO), 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" [18]. They noted that 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 mechanisms of these processes [18]. Really maximal common energy of molecular triple bonds nitrogen N_2 (N≡N) is 945kj/mol and common energy of molecular double bonds nitrogen N_2 (N═N) is 456kj/mol [45,46]. The molecular energy nitric oxide NO (N═O) is 678kj/mol [45,46]. On the one hand, the surplus of molecular energy nitric oxide NO 267 kj/mol [945-678=267] is used for catabolic exoergonic processes of further nitric oxide NO (N═O) oxidation. Furthermore the remained one free bond of nitric oxide NO (N═O) 222kj/mol [678-456=222] is used into anabolic endoergonic processes of cellular cycle, i.e. processes repairing mtDNA via mtDNA fusion etc. Thus nitric oxide (NO) takes part in oscillation of alterations catabolic exoergonic processes and anabolic endoergonic processes in mutual interactions nuclear processes/cytoplasm processes/mitochondria processes which are also induced by mutual influences nuclear capacitors/mitochondrial capacitors/cellular capacitors being driving mechanisms of all these processes in cellular cycle [4,5].

Elisabeth et al. (47) discussed the importance of cells autophagy for understanding of mechanisms various diseases, including cancer. However the mechanism of Warburg effect in cancer metabolism promotes the state of Apoptosis Resistance due to consumption huge quantity energy with accumulation into lactic acids of energy for huge anabolic processes [7]. But huge anabolic pathway decreases lysosome-dependent catabolic pathway, which promotes autophagy, according to data of Elisabeth et al. [47]. Remained catabolic processes produce calories only for maintenance the temperature 36,0°C – 36,9°C by which all enzymes operate in cancer tissue that contributes to survival cancer cells and Apoptosis Resistance [7,42]. The tendency of uncontrollable growth of a tumor as a result of a total prevalence of anabolic processes over catabolic processes decreases role of oxidative exocytosis in tumor tissue. Thus cancer cells have inadequate resonance waves to an organism and an organism's cells that leads to absent functions of remote responses of an organism's cellular capacitors via resonance waves on cancer cells and cancer celluler capacitors [5] (Figure 3). Therefore regulatory mechanisms of an organism cannot influence on cancer cells' cellular cycle. These properties of cancer cells cause impossibility for organism's defensive mechanisms of autophagy and phagocytosis to influence on cancer cells' cellular cycle (Figure 3). However the organism's defensive mechanisms of autophagy and phagocytosis can react via remote reaction on strange substances which present in mechanism of cancer metabolism promoting operation of ever decreased dosage of cytotoxic drugs in cancer therapy. Thereby also Riffell Brian et al. doubt "However, mechanisms by which the CSF-1/CSF-1 receptor pathway and macrophages sustain tumor growth and/or repress response to cytotoxic therapy are unclear" is eliminated [48].

Conclusions

1. Cellular mechanisms of resistance to Environment are exerted via the mutual influences between biophysical mechanisms via cellular capacitors operations and biochemical mechanism maintenance stability Internal Energy and Internal Medium of an organism.

2. The cellular biophysical mechanisms operate via interactions between nuclear chemical potentials, cytoplasm chemical potentials, mitochondrial chemical potentials and chemical potential of an organism due to biochemical processes in them which exert interactions between nuclear capacitor operations, mitochondrial capacitors operations, cellular capacitors operations.

3. ROS/H_2O_2/free radicals induce interactions between resisted systems of mitochondrial catabolic oxidative processes and nuclear anabolic processes which stimulate as catabolic destructive processes as well as anabolic reparative processes both in nucleus and in mitochondria exerting cellular cycle advance and supporting to all cells' capacitors operations.

4. The violated mechanisms stability Internal Energy in nucleus, cytoplasm and mitochondria cause pathologic mechanisms stability Internal Energy both in cells and in an organism which result either in excessive sift balance catabolic and anabolic processes into excessive catabolic processes forming inflammatory and infectious processes or in excessive sift balance catabolic and anabolic processes into excessive anabolic processes forming oncologic processes.

5. Cancer cells are not subjected to regulative mechanisms as of an organism and as well as of normal cellular capacitors' resonance waves because huge anabolic (biosynthetic) processes consume huge quantity of Acetyl-CoA and energy in cancer tissue that cause overloading of "Nodal point of bifurcation catabolic and anabolic processes (NPBac)" and create chemical potentials of cancer cells inadequate to chemical potentials of normal cells and an organism.

6. The influences nuclear capacitor's resonance waves on mitochondrial capacitors' resonance waves in cancer cells induce abundance ROS/H_2O_2/free radicals production in mitochondria which exert accelerated nuclear DNA replication, causing excessive proliferative processes, irrepressible cancer growth.

7. H_2O_2 and excessive free radicals are neutralized in processes of accelerated DNA replication in cancer cells that also promotes Apoptosis Resistance of cancer cells.

8. Inducing via Prolonged medical starvation, the expression catabolic processes suppress excessive anabolic processes that lead to cancer metabolism depression which is susceptible to chemotherapy with considerably decreased dosage cytotoxic drugs that leads to prevention recurrence cancer disease and resistance to anticancer drugs in comparison with intensive anticancer chemotherapy with great dosages of cytotoxic drugs in cancer therapy. The efficiency of such approach to cancer therapy should be examined via Clinical Trials.

Acknowledgments

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

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