Review Article

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Journal of Genetic Disorders

2018
Vol.2 No. 2:8

The Mechanism of Cancer Cellular Genome Disorder and Comparison Therapeutic Effects of Modern Methods and New Method Cancer Treatment

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Citation: Michail P, Ponizovskiy MR (2018) The Mechanism of Cancer Cellular Genome Disorder and Comparison Therapeutic Effects of Modern Methods and New Method Cancer Treatment. J Genet Disord. Vol.2 No. 2:8

Abstract

There were described influences of viral oncogene affecting cellular genome which causes rearrangement nuclear chromosomes division with changing mitochondrial oxidative mechanism. The changed mitochondrial oxidative mechanism causes reverse influences on nuclear genome. Besides changed nuclear genome exerts change in cellular metabolic processes. These influences both in nuclear genome, in mitochondrial oxidative mechanism and in cellular metabolic processes change Internal Energy of cancer cells via changing chemical potential of cancer cells' cytoplasms. The changes chemical potentials of cytoplasms in cancer cells change electrocapacity of cancer cellular capacitors promoting mechanism of autonomic cancer development. The mechanisms of all these transformations were explained in the article from the point of view of thermodynamics. Also there was described the comparisons between new method cancer treatment causing the damage of disorder cancer cellular genome via targeting Warburg effect mechanisms by using very small dosage cytotoxic substance against depressed cancer cells and modern methods cancer chemotherapy with using great dosage cytotoxic drugs.

Keywords: Cellular genome; Haploid cellular cycle; Diploid cellular cycle; v-oncogenes; Cellular capacitors; Warburg effect; Pasteur effect

Received: October 16, 2018; **Accepted:** November 19, 2018; **Published:** November 26, 2018

Introduction

The affecting nucleus by v-oncogene is the main driving mechanism of transition normal cellular cycle into oncologic cellular cycle exerting processes of oncogenesis. Processes of oncogenesis in nucleus induce processes transmutation in mitochondria which exert shift Stationary State of cells into Quanty-stationary State of cancer cells. Just cancer cells need huge quantity energy for excessive anabolic processes which form cancer cellular cycle with irrepressible cancer tumors growth, metastases and cancer invasions. The mechanism of cancer cells' cycle is induced by Warburg effect mechanism of cancer tissue metabolism. The mechanism of healthy cells' cycle is exerted by healthy tissue metabolism of Pasteur Effect mechanism. Also there were made comparisons between the therapeutic targets of cancer cells' nuclei, in which cancer treatments are realized with great dosage cytotoxic drugs in modern methods chemotherapy, and target of Warburg effect mechanism in the new method cancer treatment in which depressed cancer cells are treated with very small dosage of cytotoxic drugs providing efficient therapy.

Interactions between Genetic and Oxidative Mechanisms in Prokaryotic Organisms and Eukaryotic Organisms from the Point of View of Thermodynamics

Genetic mechanism of diploid cellular cycle from the point of view of thermodynamics

The maintenance stability Internal Energy (U) of an organism occurs by biochemical mechanism via three levels regulations: highest level regulation (CENTRAL NERVOUS SYSTEM), high level regulation ("Equilibrium Constant of ionic metabolism", "Equilibrium Constant of acid - alkaline metabolism", "Equilibrium

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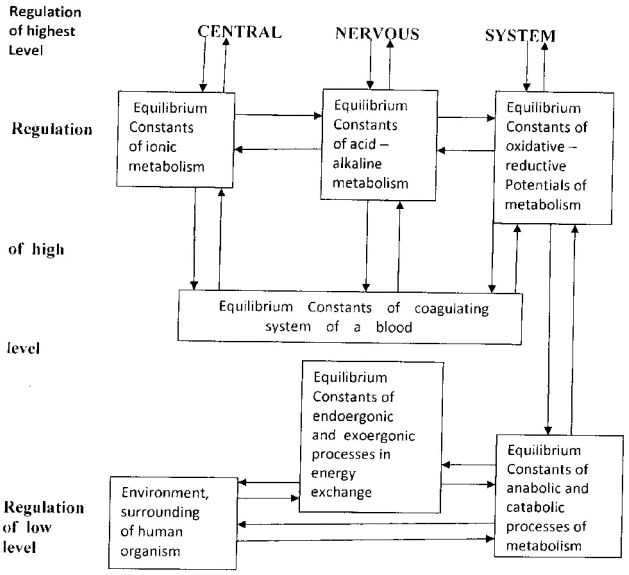
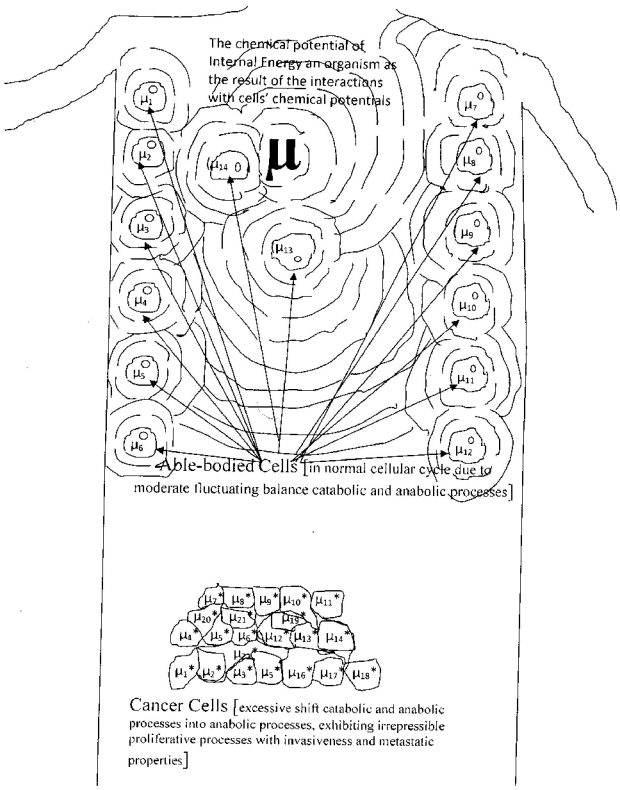
Constant of oxidative - reduction Potentials of metabolism" and "Equilibrium Constant of coagulating system of blood"), low level regulation ("Equilibrium Constant of energy exchanges" and "Equilibrium Constant of metabolism") **Figure 1** [1-3]. Genetic mechanism of diploid cellular cycle operates in strict interaction with mitochondrial electron transport chain through fifth oxidative complexes. Just the interaction of genetic mechanism of diploid cellular cycle with mitochondrial electron transport chain promotes stability Internal Energy (U) as in cells of an organism as well as of an organism [stable temperature 36,3°C-36,8°C by which all enzymes operate; stable index pH=7.35 in blood and in neurolymph and so on] according first law of thermodynamics: Ecommon=ΔU+W_{int}+W_{ext} [Ecommon-common energy, U-Internal Energy, W_{int}-internal work, W_{ext}-external work] (**Figure 1**) [1-3]. Besides the interaction genetic mechanism of diploid cellular cycle with mitochondrial electron transport chain forms stability cells' Internal Energy (Ucell) due to relative resonance waves of cellular capacitors operations which creates cellular stable Internal Energy due to cytoplasms' basophilic chemical potentials (μcytopl) via staining cells (**Figure 2**) [4,5]. Just stability Internal Energy of an organism is put together cells' mechanism stability Internal Energy and biochemical mechanism stability Internal Energy of an organism (U) displaying common balance anabolic endergonic biosynthetic processes & catabolic anaerobic exergonic processes of oxidative phosphorilation & catabolic aerobic exergonic processes of oxidative respiration [6,7]. External Work (W_{ext}) of an organism receives energy and substances from Environment and transmits this energy and substances to Internal Work (W_{int}) of an organism. Also the energy of External Work (W_{ext}) is resisted to negative environmental influences [weather, infections etc.]. Basic Internal Energy (Ebasic) is located in Basic Stem Cells which are neurons of Central Nervous System [8]. Just Basic Internal Energy (Ebasic) operates between both two Works [External Works (W_{ext}) and Internal Works (W_{int})] of an organism and Internal Energy (U) of an organism. Thus Basic Internal Energy (Ebasic) is the store of inherited from both parents energy which is expended for activity sequence [Basic stem cells → Totipotent stem cells → Pluripotent stem cells → Multipotent stem cells → Oligopotent stem cells → Unipotent stem cells and then various type cells] being molecular bonds' energy all of these cells. Therefore Basic Internal Energy (Ebasic) participates in saving stability Internal Energy (U) of an organism too. All cells of an organism proliferate through eukaryotic cellular cycle of G0, G1/S, G2, M (Mitosis) phases showing diploid proliferative processes. M phase cellular cycle consists of two processes: karyokinesis and cytokinesis. Karyokinesis processes cause division cell's chromosomes. Cytokinesis processes exert division cell's cytoplasm with all its organelles forming two daughter cells. The G0 phase cellular cycle is characterized the quiescence in which it occurs DNA translation and transcription for biosynthesis of proteins. The G1 phase cellular cycle is characteraized as preparing to DNA synthesis. During this phase, it is continued the biosynthetic activities of the cell increasing its supplies of proteins, enzymes, lipids etc. The S phase cellular cycle starts with DNAs replications and, when it is completed, all of the chromosomes have been replicated, i.e. each chromosome has



Footnotes: Metabolic and Energy "Equilibrium Constants" regulate interactions of intracellular and extracellular chemical potentials ($\mu_{int} \leftrightarrow \mu_{ext}$) for maintenance stability of Internal Energy and Internal Medium an organism. The intracellular and extracellular chemical potentials (μ_{int} and μ_{ext}) cause the formations of the positive/negative charges on internal and external membranes of cellular wall, promoting operation of remote cellular reactions via cellular capacitors operation.

- The regulative mechanism maintenance stability Internal Energy and Internal Medium of an organism exhibits Low level Regulation, High level Regulation and Highest level Regulation.
- 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.
- 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.
- High level Regulation consists of interacting "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 between them.
- 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.
- Highest level Regulation is presented by CENTRAL NERVOUS SYSTEM causing regulation both High level regulation and Low level regulation.

Figure 1 The mechanism of maintenance stability of Internal Energy and Internal Medium an organism.



- Chemical potential of an organism (μ) is the indicator of stability Internal Energy an organism.
- Chemical potential of an organism (μ) defines relative chemical potentials of cells an organism (μ) as the indicator of stability Internal Energy of cells an organism.
- Resonance waves between an organism and cells of an organism are produced by cellular capacitors which reflect interactions between all cells of an organism and between an organism and cells of an organism due to related chemical potentials of cella an organism (μ).

Figure 2 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.

two sister chromatid. Thus, during this phase, the amount of DNA in the cell has effectively doubled, i.e. taken place diploidy of the cell. Besides there are histone productions during the S phase. Then G2 phase cellular cycle occurs after DNA replication in which occurs protein synthesis and preparation the cell for mitosis creating reorganization of microtubules to form a spindle. The M phase cellular cycle (Mitosis) is the process by which a eukaryotic cell separates the chromosomes in its cell nucleus into two identical sets in two nuclei via prophase, prometaphase, metaphase, anaphase and telophase. After mitotic karyokinesis there is followed cytokinesis which increases the number of organelles (such as mitochondria, ribosome, lysosome and the others) and divides the nuclei, mitochondria, cytoplasm, organelles and cell membrane into two cells containing equal shares of these cellular components. Thus Mitosis and Cytokinesis cause the division of the mother cell into two daughter cells, genetically identical to each other and to their parent cell [9]. Just all these nuclear processes of cells divisions are subjected interations between nuclei and mitochondria. Considering dynamic development cellular cycle mechanisms in developing human organism, it should been considered development interactions between aerobic processes and anaerobic processes in cellular cycle. Catabolic aerobic exergonic processes use outer energy from Environment operating in aerobic condition supplying energy via External Works (W_{ext}) of an organism and an organism's cells. Just mechanism of cellular cycle exhibits anabolic endergonic processes to a large degree which operate in anaerobic hypoxic condition, i.e. supporting by Hypoxia-induced Factors (HIF), which energy is obtained from Environment via catabolic aerobic processes operation. Also catabolic anaerobic exergonic processes are hypoxic processes causing oxidative phosphorilations, i.e. supporting by Hypoxia-induced Factors (HIF), which energy is also obtained from Environment via catabolic aerobic processes operation. Just both anaerobic processes use energy from Environment via both External Works (W_{ext}) and Internal Works (W_{int}) of an organism. Thus common balance catabolic aerobic exergonic processes & catabolic anaerobic exergonic processes & anabolic endergonic processes consist of anaerobic hypoxic pathway and aerobic environmental respiratory pathway which anaerobic hypoxic processes are also mechanisms cellular cycles of different tissues' cells types. Besides these anaerobic hypoxic processes are based on the obtained energy from the stored energy in Basic Internal Energy of the inherited energy genes' molecular bonds of Basic stem cells (neurons). This energy was obtained by type cells via sequence from unipotent stem cells ←oligopotent stem cells ← multipotent stem cells ← pluripotent stem cells ←totipotent stem cells ←basic potent stem cells (neurons) [8]. As concerning to processes in mitochondria, the catabolic anaerobic Krebs tricarboxylic acids cycle expends energy of Internal Work (W_{int}) via „electron transport chain" through sequence [NADH-Q oxidoreductase of Complex I → Succinate-Q oxidoreductase via flavin adenine dinucleotide (FAD) coenzyme of Complex II → Q-cytochrome c oxidoreductase of Complex III → Cytochrome c oxydase of Complex IV]. Then the catabolic anaerobic Krebs tricarboxylic acids cycle transmits into anabolic processes of mDNA operation biosynthesis ATP syntetase of Complex V. All these connections between catabolic processes and anabolic processes occur in G0 quiescence phase cellular cycle. Further the expended Basic Internal Energy exerts following cellular movements: The genes encode protein synthesis, named cyclins, and cyclin-dependent kinases (CDKs) which advance cellular cycles of different tissues' cells types determining different cells' division cycles of proliferative processes, e.g. cdc 20 or cdc 25 [9]. These cellular division cycles via G1, S, G2 phases cellular cycle are finished with Mitosis (M phase cellular cycle) continuing by kariokinesis and then cytokinesis. Obtaining from Basic Internal Energy, the energy of the gene's molecular bonds determine different cells' lifetimes via creating different their cycle lifetimes. Thus taking into account the quantity 50 times of each cell divisions, the quantity obtained energy in the cellular gene's molecular bonds are determined due to the different cellular cycles' times of different type cells. These quantity obtained

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energy from Basic Internal Energy determines different lifetimes of different type cells. Furthermore results from the study of E2F transcriptional dynamics at the single-cell prove that the role of cyclin-CDK (Cyclin-dependent kinases complex) activities in G1 phase cellular cycle, in particular cyclin D-CDK4/6, creates the timing rather in G1 phase than the inducing cell cycle entry in S phase cellular cycle [10,11] although cyclin-CDK complex promotes expression of transcription factors E2F which stimulated by Hypoxia-induced aFactor (HIFa) and cFactor (HIFc) [10]. Just active cyclin S -CDK complex phosphorilates proteins that prepares pre-replication complexes in G1 phase cellular cycle for DNA replication in S phase cellular cycle. Just each chromatid is condensed in chromosome. Therefore after DNA is copied, chromosome consists of two sister chromatids connected by proteins [cohesins]. Two sister chromatids are tightly connected at the centromere in chromosome. The driving mechanisms of these transformations in nucleus are operated due to obtained some cellular energy which is expeneded in G1 phase cellular cycle for anabolic endergonic biosynthetic processes in hypoxic condition supporting by HIFa and HIFc. The moderate increased anabolic endergonic processes leads to moderate shift balance anabolic endergonic processes & catabolic anaerobic exergonic processes into moderate anabolic endergonic processes with moderate partial suppression Krebs tricarcoxilic acids cycle (TCA). The moderate increased anabolic proceses cause partial suppression Krebs tricarcoxilic acids cycle (TCA). Moderate suppression Krebs tricarcoxylic acids cycle (TCA) in mitochondria leads to some lack Hydrogen ions which are produced in Krebs tricarboxylic acid cycle. The lack Hydrogen ions don't neutralize whole arrived oxygen (O_2) due to stable respiratore index (RI) [RI = CO_2: O_2 = 0,8-1,0]. Just oxygen (O_2) come from lungs and is carried by systems of Hemoglobins and Cytochroms. Therefore there are formed surplus Superoxide (O_2*) due to adding electron to surplus oxygen (O_2) which is produced by transformings NAD↔NADH and FAD↔FADH2 in Electron Transport Chains of both Complex I and Complex II : n[O_2] + n[e-] → n[O_2*]. Superoxide (O_2*) induces complex ROS/ H_2O_2/Free radicals [12,13]. Free radicals (*OH) pass fron mitochondria through cytoplasm into nucleus and react on nuclear DNA inducing process replication in S phase cellular cycle via realizing of 2nDNA reaction [12,13]:

*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 the oxidative processes exert process replication which advances in such mode. The each portion of the cell's genome replicates once and only once via expending of obtained stored portion energy. Thus daughter cells touch on all parts of crucial genes of cell's genome only once promoting replication in S phase cellular cycle only once. Also S anaerobic phase cellular cycle induces exertion in Mitochondria catabolic aerobic exergonic respiratory processes of link [from lungs O_2 → oxyhemoglobin → mitochondrial system cytochromes] which interrupts anabolic processes via suppression increased anabolic endergonic biosynthetic processes in G1 phase cellular cycle. Catabolic aerobic exergonic respiratory proceses consume much energy as through an organism's cellular system of stem cells and tissues' type cells exerting catabolic anaerobic exergonic processes as well as through Environment accepting oxygen (O_2) which exerts metabolic oxidative processes causing oxidative excretion waste substances via CO_2 and H_2O. Such oxidative excretion waste substances via aerobic processes eliminate metabolic blocking anaerobic hypoxic processes exerting anabolic endergonic processes transition in S phase cellular cycle. The replication in S phase cellular cycle is finished when replicative energy is exhausted in the gene's molecular bonds, and increased catabolic aerobic exergonic processes are suppressed by exerted anabolic endergonic processes causing transition into G2 phase cellular cycle which receive supplementary energy via link [Basic stem cells (neurons) → sequence of stem cells → tissue's cells types]. The increased anabolic endergonic processes in G2 phase cellular cycle induce biosynthesis of proteins and other substances preparing to Mitosis (M phase cellular cycle) of karyokinesis and then cytokinesis. Transition G2 phase cellular cycle into M phase cellular cycle occurs due to exhaustion supplementary energy received via link [Basic stem cells (neurons) → sequence of stem cells → tissue's cells types]. M phase cellular cycle (Mitosis) receive supplementary energy also via link [Basic stem cells (neurons) → sequence of stem cells → tissue's cells types] and use this energy in anaerobic hypoxic processes of both catabolic anaerobic exergonic processes and anabolic endergonic processes. Mitosis (M phase cellular cycle) is asexual reproduction in which the chromosomes are separated in two new nuclei. During Mitosis the chromosomes, which have already duplicated chromatid, condense and attach to spindle fibers that pull one copy of each chromosome to opposite sides of the cell [14]. As the result of chromosomes separation, there are formed two genetically identical daughter nuclei. Cytokinesis is followed after Mitosis, which divides the cytoplasm, organelles and cell membrane into two new cells containing equal shares of these cellular components [14]. Thus the divided nucleus, cytoplasm, organelles and cell membrane by cytokinesis produce two daughter cells [14]. Mitosis and cytokinesis together define the division of the mother cell into two daughter cells genetically identical to each other as well as to parents. The process of Mitosis division is occurred into sequence stages which are following prophase, prometaphase, metaphase, anaphase, and telophase [15-26]. Each daughter cell has a complete copy of the genome of its parents'cells. Thus interactions anabolic processes and catabolic processes are driver mechanism of cellular cycle. Only such compound thermodynamic systems of eukaryotic multicellular organisms can maintain stability Internal Energy of eukaryotic organisms providing them long lives.

Genetic mechanism of haploid cellular cycle from the point of view of thermodynamics

Genetic mechanism of haploid cellular cycle operates in strong

interaction with one of oxidative complex as well as with fifth complex of ATP synthetase *versus* genetic mechanism of diploid cellular cycle which operstes in interaction with five oxidative complexes. Just it can be observed difference mechanisms of eukaryotic organisms, e.g. animals, men etc., from prokaryotic organisms and some intermediate organisms, e.g. some plants, bacteria, flies etc. For example, these plants have alternative NADH oxidases, which oxidize NADH in the cytosol and pass these electrons to the ubiquinone pool as compared to mitochondria in more compound eukaryotic organisms [27]. The other examle, electron transport chain in some plants, fungi is alternative oxidase which transfers electrons directly from ubiquinol to oxygen [28-30]. Some of these organisms are dated to ancient organisms which are considered between eukryotic and prokaryotic organisms. As concerning to prokaryotic electron transport chain, bacteria use many other substances to donate or accept electrons, e.g. either Pyruvate / Lactate with Lactate dehydrogenase or Succinate / Fumarate with Succinate dehydrogenase or NAD+ / NADH with NADH dehydrogenase and so on [31-34]. Therefore prokaryotes show perpetual growth in order to save their nature. Thus considering that all organisms, both prokaryotic and eukaryotic organisms, are subjected to thermodynamic laws, the difference between mechanism of haploid cellular cycle and diploid cellular cycle should be considered from the point of view of second law of thermodynamics using Boltzmann equation:

$S = k_0 \ln \omega$ [S-Entropy, k_0 - Boltzmann constant, ω-thermodynamic probability]. Boltzmann constant is k_0=1, 38 Joule K^{-1}. Thermodynamic probability defines the quantity possibilities to produce microstates from macrostate of thermodynamic system. Hence Entropy (S) is the measure of molecular chaos, and increased Entropy reflects increasing disorganization of thermodynamic system according Boltzmann formulation. It is meant that, firstly, dissipating disintegrated microstates from macrostate thermodynamic system reflect chaos due to break up of thermodynamic system via complete increased Entropy. Secondly, compact integrated microstates into macrostate thermodynamic system reflect full synthesized of thermodynamic system via complete decreased Entropy, and thirdly, balance of middle disintegrated microstates & middle integrated microstates of thermodynamic system reflects stable balance catabolic exergonic processes & anabolic endergonic processes in normal Stationary State of thermodynamic system of an organism due to minimization gain of fluctuating middle characteristic Entropy according Prigogine theorem [4]. Thus haploid primitive advance division cell occurs via shift Meiosis I into Meiosis II because prokaryotic unicellular organism stores insufficient Basic Internal Energy in one cell in order to provide large-scale cell division. Therefore as compared to Mitosis phase of eukaryotic cellular cycle sharing into Prophase → Prometaphase → Metaphase → Anaphase → Telophase, the Meiosis phase of haploid energy has two parts: Meiosis I is shared into Prophase I, Metaphase I, Anaphase I, Telophase I then Meiosis II is shared into Prophase II, Metaphase II, Anaphase II, Telophase II. During Prophase I of Meiosis I homologous chromosomes are paired and exchange with genes of DNA (homologous recombination), i.e. without processes DNA replication. It results in chromosomal crossover. This process is critical for pairing between homologous chromosomes and hence for accurate segregation of the chromosomes at the first Meiosis division. The new combinations of DNA created during crossover are a significant source of genetic variation and result in new combinations. Then Meiosis I segregates homologous chromosomes which are joined as tetrads (2n, 4c), producing two haploid cells from one haploid cell in which each cell contains chromatid, i.e. results in two haploid cells having half the number of chromosomes *versus* human cell's 46 chromosomes via division through Mitosis phase cellular cycle. Thus prokaryotic cell shares haploid division's cellular cycle in Meiosis I and Meiosis II through 8 phases and receives haploid cells with half the number chromosomes, i.e. approximately 23 chromosomes. Just eukaryotic human cell shares diploid division cellular cycle in Mitosis through 5 phases and receives two daughter diploid cells with 46 chromosomes each cell. Hence mitotic diploid division corresponds to balance of middle disintegrated microstates & middle integrated microstates of thermodynamic system according to Boltzmann theory. This balance reflects minimization gain Entropy according Prigogine theorem and leads to normal cells'balance catabolic exergonic processes & anabolic endergonic processes in normal Stationary State of thermodynamic system of a eukaryotic organism's cell. But meiotic haploid cells with half the number chromosomes corresponds to balance of disintegrated microstates & integrated microstates of thermodynamic system according to Boltzmann theory. This balance shows insufficient mechanism for minimization gain Entropy according Prigogine theorem due to less Basic Internal Energy for interactions sufficient flows energy and substances [4] that leads to unstable cellular balance catabolic exergonic processes & anabolic endergonic processes due to fluctuating prevalence either catabolic exergonic processes or anabolic endergonic processes causing accelerating cellular cycles with short life of each cell in Stationary State of prokaryotic thermodynamic system. Hence also accelerating proliferation processes and short lifetime by unicellular prokaryotic cell promote economic expenditure energy from insufficient Basic Internal Energy, *versus* moderate proliferation processes and considerably longer lifetime of multicellular eukaryotic cells expend energy from sufficient Basic Internal Energy for supply with energy via sequence Basic stem cells → Totipotent stem cells → Pluripotent stem cells → Multipotent stem cells → Oligopotent stem cells → Unipotent stem cells and then various type cells causing development Stationary State of normal able-bodied organism.

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Viral Mechanism Creates Disorder in Genetic Mechanism of Normal Cellular Cycle Leading to Violation Mechanism Maintenance Stability Internal Energy of Healthy Cells that Cause Cancer Cellular Genome from the Point of View of Thermodynamics

Virus's germinations by various quanta solar rays cause influenza, HIV etc. and oncologic diseases of an organism

There are arised different viruses causing different diseases as influenza viruses, HIV virus, viral oncogens [v-oncogen] etc. As outcome of viral oncogenes affected human cell's nuclear DNA, oncogenesis is exerted causing cellular genome transmutation that form cancer cells [35]. Taking into account that viruses can not live in Environment *versus* other prokaryotic organisms, e.g. bacteria, viruses are initial generated into living organisms by especial quanta of Solar rays forming by Solar thermonuclear synthesis, and viruses use some an organism's cellular processes for viral prokaryotic cells survival. Just viral initial prokaryotic cells have haploid genome which exerts anabolic endergonic biosynthetic processes but need catabolic exergonic processes both anaerobic processes of oxidative phosphorilation and aerobic processes of respiratory oxidation, i.e. human cell's electron transport chain. Just each cell can function due to balance anabolic endergonic processes & catabolic anaerobic exergonic processes & catabolic aerobic exergonic processes which present also driving mechanism of cellular cycle [6,7]. Therefore it should be considered the coupled viral prokaryotic and human eukaryotic genomic mechanism in cancer cells' cellular cycle [6,7].

Mechanism maintenance stability internal energy in genetic mechanism of normal cellular cycle

Studying regulative mechanisms of cancer cell's cellular cycle, Xiao Y et al. note [36]: "In 1981, Hereford and coworkers discovered that yeast histone mRNAs oscillate in abundance during the cell cycle [37]. Such genes that behaved in a periodic manner consistent with the cell cycles are called cell cycle-dependent genes. Many cell cycle-dependent genes are involved in processes that occur only once per cell cycle [38-40] ". Also studying regulative mechanisms in cancer cellular cycle, Carrassa L. notes that it is unclear whether a CDK1 inhibitor could be dosed sufficiently to achieve tumour control and studies are undergoing [41]. Studying checkpoint of normal cellular cycle Carrassa L, notes [42]: However, none of these studies have yet selected for potentially sensitive tumours, so further insights in determining the most responsive tumors are required in future trials. Also Carrassa L. reports that cdk-cyclin complexes create progression through the G1 phase for preparing the cell to the replicative phase by phosphorylating the oncosuppressor protein pRb which causes the activation of the E2F family transcription factors and activation as CDK4 and CDK6 as well as CDK2 by cyclin E and cyclin A, which in turn initiates DNA replication. As the DNA replication process finishes, the Cdk1/cyclin B complex is activated leading to mitosis [41-44]. Until the end of G2 phase, CDK1 is phos-phorylated at Thr14 and Tyr15 by the kinases WEE1 and MYT1, resulting in inhibition of cyclin BCDK1 activity [41,42]. Further there are following Carrassa L. notes corresponding kinases inhibitors: „Three distinct families of these so called cyclin dependent kinase inhibitors (CKI) can be distinguished. The first one is called INK family and is composed by four members: p15, p16, p18 and p19. The second family of inhibitors is the Cip/Kip family and consists of three members: p21cip1, p27kip1 and p57kip2 regulate the cdk2/cyclinA and cdk2/cyclinE complexes as well as the cdk4/6 cyclinD complexes by stabilizing of cyclin and CDKs. The final class of inhibitors is the pRb protein family which consists of two members: p107 and p130 [41-46]. Also the CDK inactivats kinases Wee1 and Myt1 located respectively in the nucleus and Golgi complex and regulate the intracellular different proteins such as the phosphatase Cdc25C [47].

Really, the role of cycle-dependent genes [either oncogenes or suppressor oncogenes in norm], proteins [protein-protein interactions particularly the two-hybrid data] should been considered taking into account the role of various histones mRNAs in mechanisms cells' lives and cellular cycles in norm and pathology, including cancer cellular cycles [36,37].

In norm the hystones mRNAs can be the carriers of Cyclin dependet kinases as CDK4 and CDK6 as well as CDK1 and CDK2 which enzymatic activity exerts expression anabolic processes causing shift balance catabolic exergonic processes & anabolic endergonic processes into moderate increase anabolic endergonic processes. The moderate increase anabolic endergonic processes cause moderate partial suppression catabolic anaerobic exergonic processes of Krebs tricarboxylic acid cycle. Besides the increased anabolic processes change inner nuclear chemical potential (μinn.nucl) induces charge on innere membrane of nuclear shell. The stable basophilic chemical potential of cytoplasm (μcytopl) induces stable charge on outer membrane of nuclear shell. Thus it is formed nuclear capacitor. The nuclear chemical potential (μnucl) is subjected to some changes due to expenditure Basic Internal Energy through sequence stem cells for advance cell into cellular cycle causing by cdk-cyclin complexes for the progression through G0 phase into G1 phase [41,42]. Also expression anabolic processes of biosynthesis produce D type cyclin which exert activation hystones CDK4 and CDK6 [41,42]. The activation hystones CDK4 and CDK6 change nuclear chemical potentials (μnucl) causing energy flows which exert phosphorylating the oncosuppressor protein pRb and activation the E2F family transcription factors causing changed nuclear chemical potential (μnucl). Also moderate increased anabolic biosynthetic processes produce cyclin E and cyclin A which activate CDK2 causing transition G1 phase into S phase and inducing supplementary changes nuclear chemical potebtial. These processes change charge on inner membrane of nuclear shell. The changed chemical potebtial on inner membrane of nucleus

changes resonance waves of nuclear capacitor. The changed resonance waves of nuclear capacitors exert reversed changed resonance waves of mitochondrial capacitors for maintenance stability cells'Internal Energy as basophilic chemical potential of cytoplasm (μcytopl). Thus reversed changed resonance waves of mitochondrial capacitors are occurred by influences of changed inner mitochondrial chemical potential (μinn.mitoch). The changed inner mitochondrial chemical potential (μinn.mitoch) is caused due to moderate partial suppression catabolic anaerobic exergonic processes of Krebs tricarboxylic acid cycle [TCA]. It creates insufficient produced ions Hydrogen (H+) by suppressed Krebs tricarboxylic acids cycle [TCA]. Besides considering stable Respiratory Index [CO_2/O_2 = 0.8-1.0] in an organism, insufficiency of ions Hydrogen (H^+) does not bind whole ion Oxygen (O_2^-) that violates some links of „electron transport chain" in sequence [NADH-Q oxidoreductase of Complex I → Succinate-Q oxidoreductase via flavin adenine dinucleotide (FAD) coenzyme of Complex II → Q-cytochrome c oxidoreductase of Complex III → Cytochrome c oxydase of Complex IV] leading to forming Superoxide (O_2^{*}) and then ROS/H_2O_2/Free radicals [12,13]. Free radicals (*OH) transit through mitochondrial membranes, cytoplasm, nuclear membranes due to interactions nuclear resonance waves with mitochondrial resonance waves and then react on nuclear DNA inducing process replication via realizing of 2nDNA reaction [12,13] (see above). Thus it occurs stimulation replication of cellular cycle. The increased anabolic endergonic processes of G2 phase cellular cycle induce biosynthesis of proteins as kinases WEE1 and MYT1 [41,42] which exert phosphorilation CDK1 at Thr14 and Tir15 [41,42]. Thus increased anabolic endergonic processes of G2 phase cellular cycle change nuclear chemical potential that results in changed resonance waves of nuclear capacitors causing inhibition BCDK1 activity with suppression increased anabolic endergonic processes. The inhibition activity of BCDK1 changes resonance waves of nuclear capacitors that prepares transition G2 phase cellular cycle into Mitosis (M phase cellular cycle) with karyokinesis and then cytokinesis. Just transition G2 phase cellular cycle into M phase cellular cycle occurs due to further decreasing received energy via link [Basic stem cells (neurons) → sequence of stem cells → tissue's cells types] that causes activation of the Cdk1/cyclin B [41,42] and exerting further changed resonance waves of nuclear capacitors. Then inducing via changed resonance waves of nuclear capacitors, M phase cellular cycle (Mitosis) receive supplementary energy via link [Basic stem cells (neurons)→ sequence of stem cells →tissue's cells types] and use this energy in anaerobic hypoxic processes of both catabolic anaerobic exergonic processes and anabolic endergonic processes. In Mitosis (M phase cellular cycle) the chromosomes are separated in two new nuclei. Then Mitosis is followed with cytokinesis, which divides the cytoplasm, organelles and cell membrane into two new daughter cells containing equal shares of these cellular components [8,14,48]. As concern to three distinct families of cyclin dependent kinase inhibitors (CKI), these kinase inhibitors are driving mechanisms for reversed negative activity *versus* driving mechanisms for advanced positive activity of kinase activators of CDKs exertion progress cellular cycle, i.e. [a) firstly, INK family (p15, p16, p18, p19) binding CDK4/CDK6; b) secondly, Cip/Kip family (p21cip1, p27kip1, p57kip2) negative influence on CDK2/cyclins A and E; c) thirdly, pRb protein family (p107 and p130) transcriptional inhibitors binding CDK2-A/E cyclinc and so on]. All of these inhibitors and activators of cellular cycle are links of balance anabolic endergonic processes & catabolic exergonic processes [endergonic processes & exergonic processes] as well as balance anti-apoptosis & proapoptosis, balance antiautophagy & proautophagy, balance anti-Entropy & pro-Entropy reflecting maintenance stability Internal Energy both as cells' basophilic chemical potential of cytoplasms (μcytopl) as well as an organism's common stable chemical potential (μorg) via stable indices of Internal Energy. Just such maintenance stability Internal Energy both cells and an organism via balance anabolic endergonic processes & catabolic exergonic processes is checkpoint of cellular cycle from point of view of thermodynamics which studied Carrassa L. [41,42], Poehlmann A [49], Hartwell LH [50], Takahashi K [51], Maton A [52]. Apropos checkpoint of cellular cycle via changes of flows energy and substances in development cellular cycle was explained by Glansdorff and Prigogine theory. Taking into account minimization of gain entropy according Prigogine theorem as mechanism maintenance stability open thermodynamic system of an organism, Glansdorff and Prigogine expand minimum production entropy into non linear field considering minimization of gain entropy for stability Stationary State of an organism [4,52]. They divided local production Enropy into two data corresponding such formula:

$$d\beta / dt = d/dt \left(\sum_k J_k X_k\right) = \sum_k J_k dX_k/dt + \sum_k X_k dJ_k/dt$$

[β - Entropy, t - time, X - Force, J -Stream]

Here there is following datum in stability Stationary State: $dJ_k/dt=0$.

Hence $d\beta/dt = \sum_k J_k dX_k/dt$. It is meant that stability thermodynamic system is defined by Force (X). Thus state stability Stationary State is described so: 1) $d_x\beta/dt = \sum_k dJ_k dX_k/dt>0$. It corresponds to positive fluctuations entropy. However the positive fluctuations entropy ($d_x\beta>0$) are fast disappeared in some situations of Stationary States thermodynamic system, e.g. due to principle the minimization gain entropy in Stationary State as well as because of expenditure some quantity energy from Basic Internal Energy in Basic stem cells [neurons]. Therefore in this situation thermodynamic system must return to initial state. But there arise negative fluctuations entropy ($d_x\beta<0$) which transits thermodynamic system into new Stationary State with decreased common entropy ($\Delta S_x<0$). Thus Glansdorff and Prigogine theory explains mechanism development of a human organism as open non equilibrium non linear thermodynamic system from its birth to death (**Figure 3**). Just Force of energy (X) defines as stability Stationary State of open thermodynamic system via positive fluctuation entropy ($+\Delta_x\beta$) of anabolic processes in G1/S phases cellular cycle as well as negatve fluctuation entropy ($-\Delta_x\beta$) causing obstacle further development thermodynamic system that result in transition thermodynamic system into new Stationary State with decreased entropy ($\Delta S_x < 0$), i.e. minimization gain

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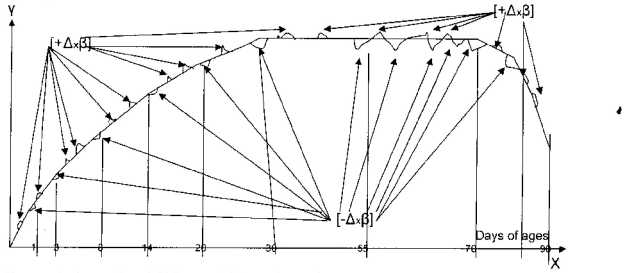


The organism's ages: from 0 till 3years – babyhood; from 3 till 14 years - young age; from 14 till 20 - juvenile age; from 20 till 30 years - middle age; from 30 till 55 years - full age; from 55 till 70 years – elderly age; after 70 years - old age.

- The considerable advantage positive fluctuation gain entropy ($+\Delta_x\beta$) over rare negative fluctuation gain entropy ($-\Delta_x\beta$) from babyhood and childhood till young years and juvenile years of an organism's ages reflects ascending line of an organism's metabolic graph.
- The small advantage positive fluctuation gain entropy ($+\Delta_x\beta$) over negative fluctuation gain entropy ($-\Delta_x\beta$) from juvenile years till middle years of an organism's ages reflects small ascending line of an organism's metabolic graph which define decreased metabolic processes.
- The considerable decreased positive fluctuation gain entropy ($+\Delta_x\beta$) in middle years of an organism's age shows weak horizontal line of an organism's metabolic graph.
- The equilibrium between positive fluctuation gain entropy ($+\Delta_x\beta$) and negative fluctuation gain entropy ($-\Delta_x\beta$) from middle years till full years of an organism's ages reflects strained horizontal line of an organism's metabolic graph which defines lack forces of energy for metabolic processes.
- The considerable advantage negative fluctuation gain entropy ($-\Delta_x\beta$) over positive fluctuation gain entropy ($+\Delta_x\beta$) from full years till elderly years of an organism's ages reflects descending line of an organism's metabolic graph.
- The very small positive fluctuation gain entropy ($+\Delta_x\beta$) on the descending line of an organism's metabolic graph from elderly years and during old years of an organism's ages define fading metabolic activity of an organism.

Figure 3 The changes of metabolism during a life of an organism.

entropy according Prigogine theorem [4]. Just $\sum J_k dX_k/dt$ is the manifestation Force which is meant manifestation anabolic endergonic processes *versus* manifestation Force, $\sum X_k dJ_k/dt$ is the manifestation Stream (J) which is meant manifestation catabolic exergonic processes. Thus mechanism of development cellular cycle via proliferative processes is occurred through progress endocytosis via shift cellular balance catabolic processes & anabolic processes of quiescent G0 phase cellular cycle into moderate expression anabolic processes in G1/S/G2 phases cellular cycle with cumulation substances and energy in G1/S/G2 phases. Then the piled up products of anabolic processes are subjected to exocytosis in G2 and M phases exhibiting alternative outflow energy and substances which are efficient distributed within new forming propagating cells via G2/M (Mitosis) phases cellular cycle [5]. Just proliferative processes in G1/S/G2/M phases also display phenomenon "absent contact inhibition propagating cells". However the phenomenon "contact inhibition propagating cells" results in quiescent G0 phase of cellular cycle where is not distribution energy within new cells due to proliferative processes [53-56]. Just inflow supplementary substances into cells exerts changes of cellular chemical potentials (μcell) leading to advance cellular cycle through G1/S/G2/M phases in proliferative processes due to "absent phenomenon contact inhibition propagating cells" according Theorell formula [55,56].

Here is 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].

The reverse mutual interactions between resonances waive of nuclus capacitor, mitochondria capacitors and cellular capacitors maintain stability Internal Energy of an organ's tissues and their cells (stable temperature 36,6°C and the other indices).

For exemple, reverse pathway of mutual interactions between lost cells of lost organ and active stem cells of an organism are not occurred because of absent reverse mutual interactions between resonance waives of cellular capacitors lost type cells' walls and resonance waives of cellular capacitors active stem cells' walls of an organism [48,55,54-57].

Mechanism maintenance stability internal energy in transmutation normal genetic mechanism into cancer genetic mechanism of cancer cellular cycle

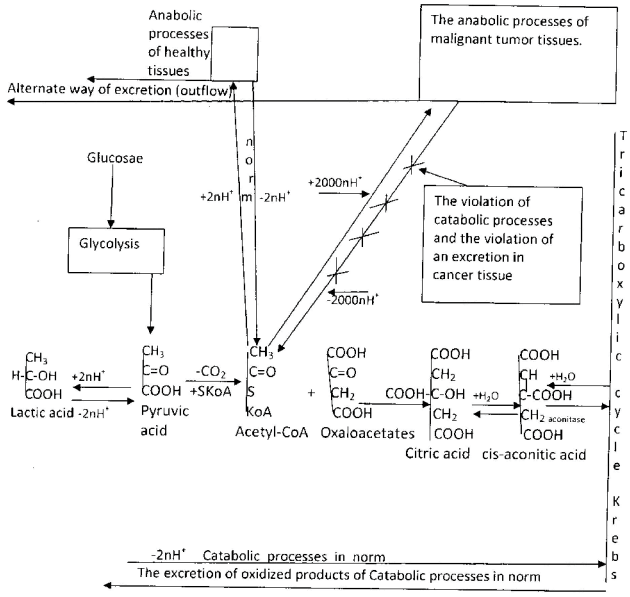
Studying cancer cellular cycle, Collins Kathleen notes that unregulative intricate cancer cellular cycle causes uncontrol proliferation [58]. Then Xiao Y et al. note [36]: "Many cell cycle-dependent genes are either oncogenes or suppressor genes, or are closely associated with the transition of a cell cycle. However, it is unclear how the complicated relationships between these cell cycle-dependent genes are, especially in cancers". Also studying genetic mechanism of cancer cells, Carrassa L. note [41]: ''Cyclins and their associated cyclin-dependent kinases (CDKs) are the key drivers of the cell cycle and specific transitions in the cell cycle are controlled solely by specific CDKs". Further Carrassa L. notes [42]: ''Chk1 protein kinase is one of the main components of DNA damage checkpoints'pathways and represent a vital link between the upstream sensors of the checkpoints (i.e. ATM and ATR) and the cell cycle engine (i.e. cdk/cyclins). A brief description of its network is herein summarized to show just an example of how in general checkpoints proteins are strictly interconnected and inter-related each others. Chk1 regulates the checkpoints by targeting the Cdc25 family of dual specificity phosphatases, Cdc25A at the G1/S and S phase checkpoints and Cdc25A and Cdc25C at the G2/M checkpoint".

All viruses use the human cells' electron transport chain for its cellular oxidative processes to build cancer cells exerting acceleration of viral proliferative processes. However consumption energy for building new cells via cellular cycle is

different by different viruses because different viruses obtain Basic Internal Energy [molecular bonds energy] on different levels of an organism. For example, influenza viruses obtain Basic Internal Energy [molecular bonds energy] from type cells being light separated by an organism, but v-oncogenes intrude in deep level Basic Internal Energy [molecular bonds energy] of cellular genome, maybe on levels either Oligopotent stem cells or even Multipotent stem cells using also mitochondrial oxidative processes of an organism's cells that give cancer cell possibility firm binding in genome and to develop itself in autonomic mode from some regulatory functions of an organism causing even obstacles for cytotoxic drugs. It is meant that several v-oncogenes genome bind affected human cells' genome with covalent bonds causing couple cancer cells'genomes which contain mixed genome containing from 49 till 56 chromosomes exhibiting aneuploidy *versus* 46 chromosomes in normal eukaryotic cells. As concerning to HeLa cells, which are independent from an organism cancer cells, HeLa cells absorb whole mitochondrial oxidative system in their bodies creating metabolisms similar as bacteria.

Thus cancer genetic machinery is the coupled mechanism which contains both several viral genomes and one human genome consisting of 49 till 56 chromosomes because several viruses affect one human cell. The some of these chromosomes are inherited viral haploid division via Meiosis; the other chromosomes are inherited human diploid division via Mitosis. Therefore viral double helix DNA produces hystons with CDKs mRNAs of viral properties, but human double helix DNA produces hystons with CDKs mRNAs of human properties. Furthermore it should be described distribution energy in an organism from the point of view of thermodynamic laws. The formula of first law of thermodynamics (see above) shows an Internal Work (W_{int}) of an organism which includes partially Basic Internal Energy of stored energy in order to build molecular bonds of cells'subtances. The some energy of an Internal Work of an organism (W_{int}) is received from Environment via an External Work (W_{ext}) of an organism. Just affecting by viral oncogenes the nuclear DNAs of some an organism's cells are subjected to viral accelerating cellular cycles which consume abundance energy from an organism for

Great anabolic processes in G1/S phase's cancer cellular cycle exerting excessive proliferative processes of tumor growth [59]. Just this huge quantity energy is consumed energy as from Basic Internal Energy (energy to build molecular bonds in cells'subtances) as well as from Internal Work [W_{int}] (cellular working energy) [48]. Thus viruses genomes use great quantity energy of a human orgaism both some energy to build molecular bonds in cells' subtances from Basic Internal Energy and some energy from Environment of Internal Works energy (W_{ext}) for metabolic processes *versus* the other prokaryotic organisms which use very restricted quantity energy. Therefore it occ urs shift balance anabolic endergonic processes & catabolic exergonic processes into excessive anabolic endergonic processes in cancer tissue [59]. The excessive anabolic endergonic processes in cancer tissue is formed by great oxidative phosphorilation processes of increased Glycolysis causing absorption huge quantity energy and AcetylCoA for excessive anabolic endergonic processes leading to overload "nodal point of bifurcation anabolic and catabolic processes [NPBac]" with partial suppression catabolic exergonic anaerobic processes of oxidative phosphorilation [TCA Krebs cycle] due to lack energy and AcetylCoA for catabolic processes and remaining some catabilic energy for cancer cells' survival reflecting Warburg effect mechanism [6,7,59]. Just excessive quantity Lactic acids accumulate abundance energy for huge anabolic endergonic processes of cancer metabolism in Warburg effect mechanism in **Figure 4** [59]. The partial suppression catabolic exergonic anaerobic processes of TCA Krebs cycle due to exccesive anabolic endergonic processes leads to prevailing aerobic processes displaying Warburg effect mechanism of „aerobic glycolysis in cancer tissue" *versus* Pasteur effect of ''incompatibility glycolysis and aerobic oxidation in healthy tissue" **Figure 5** [6,7]. Besides partial suppression catabolic exergonic anaerobic processes of TCA Krebs cycle leads to forming great



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

Figure 4 The metabolism of a malignant tumor tissue and of a normal tissue.

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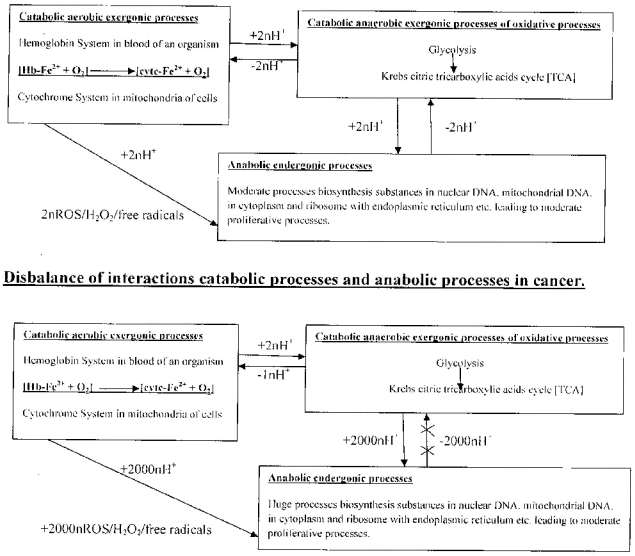
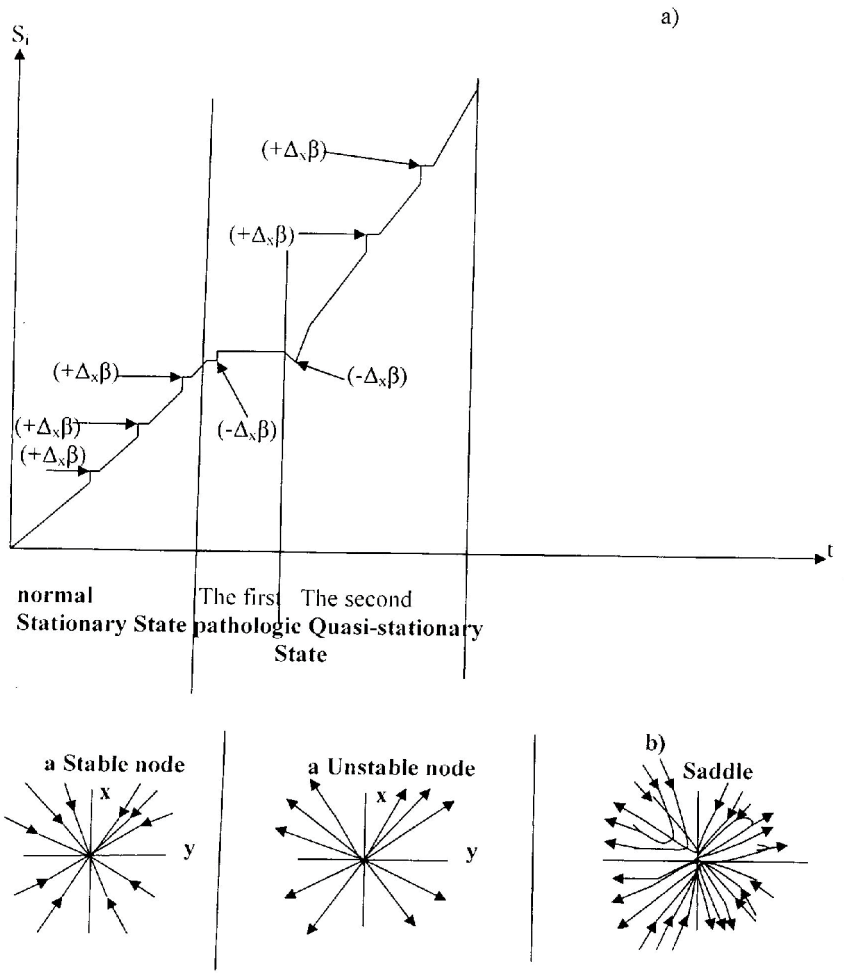


- Balance catabolic aerobic exoergonic processes and catabolic anaerobic processes of oxidative phosphorilation due to mutual exchanges with moderate quantity energy ($2nH^+$) in norm.
- Balance catabolic anaerobic processes of oxidative phosphorilation and anabolic endoergonic processes due to mutual exchanges with moderate quantity energy ($2nH^+$) in norm.
- Inducing via moderate energy ($+2nH^+$) of proliferative processes in nuclear anabolic endoergonic processes by ROS/H_2O_2/free radicals, produced by mitochondrial Cytochrom System in catabolic aerobic exoergonic processes in norm.
- Disbalance between catabolic anaerobic processes of oxidative phosphorilation and anabolic endoergonic processes due to consumption huge quantity energy ($+2000nH^+$) from catabolic anaerobic processes by anabolic endoergonic processes (the stricken off arrow [$-2000nH^+$]) leading to partial suppression catabolic anaerobic processes in cancer metabolism.
- The partial suppression of catabolic anaerobic processes causes disbalance between catabolic aerobic exoergonic processes and catabolic anaerobic processes of oxidative phosphorilation ($+2nH^+$ and $+1nH^+$ by the arrows between them) in cancer metabolism.
- The great quantity ROS/H_2O_2/free radicals, produced by mitochondrial Cytochrom System in catabolic aerobic exoergonic processes, induce excessive irrepressible proliferative processes in nuclear anabolic endoergonic processes by excessive energy ($+2000nH^+$) of free radicals in cancer metabolism.

Figure 5 Influences energy flow on interactions catabolic processes and anabolic processes in norm and in cancer pathology.

quantity superoxide [O*] forming great quantity ROS/H_2O_2/free radicals. Free radicals intrude into nuclei of cancer cells exerting excessive proliferative processes due to realizing of 2nDNA [12,13]. The forming great quantity high-molecular substances due to excessive anabolic biosynthetic processes can not been excreted via oxidative decompositions because of suppressed "nodal point bifurcation anabolic and cataboilic processes [NPBac]" **Figure 4**. Therefore cancer cellular capacitors' resonance waves react on chemical potentials of healthy cells causing transition cancer cells to healthy tissues without suppression "nodal point bifurcation anabolic and catabolic processes [NPBac]" that form metastases [59,60]. Thus cancer disease disseminates via metastases into an organism of absorbed great quantity energy, especially Basic Internal Energy. Besides cancer disease absorbs great quantity substances especially fat substances leading to cachexia of an organism via exhausted also cellular energy via metastasis which are received as from Internal Work [W_{int}] as well as of Basic Internal Energy **Figure 4**. Also metastases damage some organs of an organism, even essential organs. All of these cancer changes lead to transition normal balance anabolic processes & catabolic anaerobic processes & catabolic aerobic processes of normal Stationary State an organism into pathologic cancer disbalance anabolic processes & catabolic anaerobic processes & catabolic aerobic processes of Quasi-stationary State an organism. This cancer disbalance anabolic processes & catabolic anaerobic processes & catabolic aerobic processes causes transition steady Stationary State Graphics due to fluctuating of positive fluctuation Entrapy ($+\Delta x\beta$) into unsteady fluctuating Quasi-stationary State Graphics due to fluctuating of negative fluctuation Entrapy ($-\Delta x\beta$) according Glansdorff and Prigogina theory **Figure 6** [6,7]. Furthermore viral accelerating cellular cycles of cancer cells occur because of prevailing absorption energy by viral genetic mechanism [Meiosis] over cellular genetic mechanism [Mitosis]. Supplied with great quantity energy Meiosis is more facilitated process than Mitosis according Boltzmann theory (see above) because Meiosis phase of haploid energy shares the microstates energy through 8 stages but Mitosis phase of diploid energy shares macrostates energy through 5 phases: [Meiosis I is shared into Prophase I, Metaphase I, Anaphase I, Telophase I then Meiosis II is shared into Prophase II, Metaphase II, Anaphase II, Telophase II], but [Mitosis phase of diploid energy shares into Prophase → Prometaphase → Metaphase → Anaphase → Telophase]. Moreover healthy cells' chromosomes are more related to sequence stem cells [Basic stem cells → Totipotent stem cells → Pluripotent stem cells → Multipotent stem cells → Oligopotent stem cells → Unipotent stem cells and then cancerous type cells] than viral chromosomes. Therefore the initial absorbed energy gets to healthy cells' chromosomes and this energy is absorbed by mitotic chromosomes, but then great part of the energy from mitotic chromosomes are consumed by viral chromosomes causing accelerated cancer cellular cycle. Hence it occurs integrated Mitosis/Meiosis phase of cancer cellular cycle which shows balance increased Entropy & decreased Entropy. However partial suppressed mitochondrial catabolic anaerobic energy of Krebs tricarboxylic acids cycle by excessive increased anabolic processes in cancer cells' metabolism leads to forming very great quantity production of Superoxide / Hydrogen peroxide /Free Radicals [O*/H_2O_2/*OH and *H] vrsus moderate quantity production of Superoxide / Hydrogen peroxide / Free Radicals [O*/H_2O_2/*OH in healthy cells (see above). Great



- The linear up-going graphic of positive gain fluctuation entropy ($+\Delta_x\beta$) showing Stationary State of an organism in norm.
- The negative gain fluctuation entropy ($-\Delta_x\beta$) pulls down linear graphic into the other position.
- The positive gain fluctuation entropy ($+\Delta_x\beta$) pulls up linear graphic in the other position showing Quasi-stationary pathologic State of an organism.

Figure 6 Change fluctuations of an entropy at transition from normal Stationary State into pathologic Quasi-stationary State.

quantity Free radicals (*OH) transit through mitochondrial membranes, cytoplasm, nuclear membranes due to interactions nuclear resonance waves with mitochondrial resonance waves and then react to nuclear DNA of cancer cells inducing processes irrepressible replication via realizing of 2nDNA reaction [12,13]:

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

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

$2H^\bullet$-nDNA-DNA + $2H^\bullet$ —> 2nDNA-$H^\bullet$ + 2nDNA-$H^\bullet$;

2nDNA-$H^\bullet$ + 2^*OH —> 2nDNA + H_2O

Just process irrepressible replication occurs in S phase cancer cellular cycle causing accelerated cancer cellular cycle.

Thus cancer cells'nuclear genomes have increased quantity summarized haploid/diploid chromosomes and mitochondrial abundance quantty Free Radical causing accelerated proliferative processes of cancer cellular cycle. Just accelerated cancer cells'cellular cycle with summarized Mitosis/Meiosis phase leads to state of Resistance Apoptosis. Thus shift balance increased Entropy & decreased Entropy into decreased Entropy via shift balance pro-Apoptosis & anti-Apoptosis into anti-Apoptosis (Resistance Apoptosis) reflects checkpoint of Quasi-stationare pathologic State of cancer disease sick organism. Being under subjection to huge quantity Free radicals, cancer transmutation mitochondrial mechanism exerts acceleration of cancer cellular cycle proliferation which is carried out by joint haploid and diploid genomes of joint Mitosis-Meiosis phase cancer cellular cycle, i.e. combined healthy cell's chromosomes and viral chromosomes. Therefore Collins Kathleen noted that unregulative intricate cancer cellular cycle causes uncontrol proliferation [58]. Just studying role microRNAs in oncogenesis, some authors note that microRNAs have been shown to play crucial roles in the

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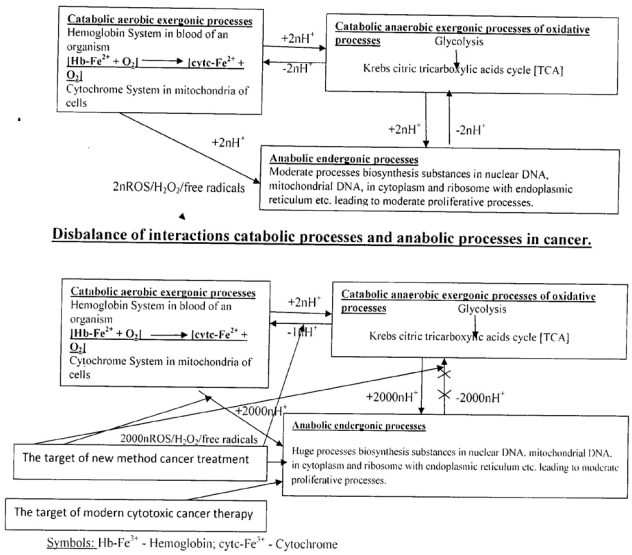
tumorigenicity via inducing different processes even opposite processes. On the one hand, microRNAs induce suppression cancer proliferative processes and metastasis, inhibition cancer cells invasions, cancer tumor growth, cancer cells apoptotic processes [61-69]. On the second hand, microRNAs control CDKN1C/p57, and CDKN1B/p27 increased in human hepatocellular carcinoma [70] and associate with intristic subtype [74]. On the other hand, microRNAs promote cell survival and proliferation by targeting p53 and caspase-9 in lung cancer [72] as well as metastasis [73,74]. However the studing different mechanisms activity of microRNAs, it should determine their places in biochemical reactions of an organism's processes. So increased microRNAs can operate either as Product of ruined nuclear DNAs of dead cells due to apoptosis and autophagy, e.g. as result of chemotherapy, or as Reagent of reactions repairing DNAs by DNA mismatch repair proteins (MMR) either in S phase able-bodied cellular cycle or in joint Mitosis-Meiosis phase of cancer cellular cycles causing cancer cells survival via Resistance Apoptosis due to acceleration cancer cellular cycle increasing cancer proliferations and metastasis. Just excessive quantity Reagents [some microRNAs] promote exerting cellular cycle, but excessive Products [some microRNAs] promote suppression cellular cycle which can be explained using Henderson-Hasselbalch Equilibrium Constant of reverse reactions.

Comparison between Mechanisms the Offered New Method Cancer Treatment and Modern Methods Chemotherapy of Cancer Treatment from the Point of View of Thermodynamics

The targets of modern methods chemotherapy are nuclear mechanisms of cellular cycle which are directed to destroy nuclear mechanisms of cancer cellular cycle with great dosage cytotoxic drugs resulting in either inhibition cellular cycle or to break cellular cycle as well as causing death of cancer cells, i.e. cancer cells Apoptosis **Figure 7** [36,37,41,42]. The target of the offered new method cancer treatment is Warburg effect mechanism which is directed to destroy cancer metabolism via breaking excessive anabolic endergonic processes [62,75-79]. The breaking excessive anabolic endergonic processes cause rearrangement cancer metabolism into normal metabolism due to restoring balance anabolic endergonic processes & catabolic exergonic processes leading to cancer depression which promotes efficient treatment with very small dosage cytotoxic drugs [6,7,77-79].

Carrassa L. examines target CDK4/6 by cytotoxic drugs of cancer cells chemotherapy and notes A number of potential issues make CDK1 a less attractive target than CDK4/6 [41]. Then Carrassa L. examined suppressions of different kinases including Polo-like kinase 1 (PLK1) and Aurora kinase A (AURKA) [42,80] and found that PLK1is essential for inactivating or removing key components of the DNA damage response, such as CHK1 (via Claspin), WEE1 and 53BP1, to inactivate checkpoint signalling and promote cell cycle resumption [42,80]. Inhibition of PLK1 causes cells to arrest



- Balance catabolic aerobic exoergonic processes and catabolic anaerobic processes of oxidative phosphorilation due to mutual exchanges with moderate quantity energy ($2nH^+$) in norm.
- Balance catabolic anaerobic processes of oxidative phosphorilation and anabolic endoergonic processes due to mutual exchanges with moderate quantity energy ($2nH^+$) in norm.
- Inducing via moderate energy ($+2nH^+$) of proliferative processes in nuclear anabolic endoergonic processes by ROS/H_2O_2/free radicals, produced by mitochondrial Cytochrom System in catabolic aerobic exoergonic processes in norm.
- The main targets of modern method cytotoxic cancer therapy are directed to anabolic endoergonic processes in cancer metabolism (The arrow is directed to Anabolic endoergonic processes).
- The main target of the new method cancer therapy is directed to disbalance between catabolic anaerobic processes of oxidative phosphorilation and anabolic endoergonic processes in cancer metabolism (the arrow is directed to the stricken off arrow [$-2000nH^+$]).
- Also the target of the new method cancer therapy is directed to disbalance between catabolic aerobic exoergonic processes and catabolic anaerobic processes of oxidative phosphorilation because of elimination disbalance between them making by elimination disbalance between catabolic anaerobic processes of oxidative phosphorilation and anabolic endoergonic processes in cancer metabolism (the arrow is directed to the arrow near [$-1nH^+$]).
- Also the target of the new method cancer therapy is directed to great quantity ROS/H_2O_2/free radicals which induce excessive irrepressible proliferative processes in nuclear anabolic endoergonic processes in cancer metabolism (the arrow is directed to the arrow near ROS/H_2O_2/free radicals).
- Also the target of the new method cancer therapy is directed to Anabolic endoergonic processes due to elimination of great quantity ROS/H_2O_2/free radicals which induce excessive irrepressible proliferative processes in nuclear anabolic endoergonic processes in cancer metabolism (the arrow is directed to Anabolic endoergonic processes).

Figure 7 The targets of both the new methods cancer treatment and modern method of cancer treatment.

in mitosis with a monopolar or disorganised spindle followed by mitotic cell death [81]. Selective inhibition of AURKA leads to abnormal mitotic spindles and a temporary mitotic arrest followed by chromosome segregation errors as cells exit mitosis" [44,45]. Referring to these data, Carrassa L. notes". The DNA damage response requires the integration of cell cycle control via checkpoint signalling to allow time for repair to prevent DNA damage before DNA replication and mitosis take place. The importance of checkpoints pathways in the cellular response to DNA damage (both endogenous and exogenous) is at the basis of the use of checkpoint inhibitors to increase the efficacy of cancer radio- and chemo-therapy".

These data with Carrassa L. doubt can been explained studying mechanism maintenance stability Quasi-stationary pathologic State in condition acceleration cancer cellular cycle. Just abundance quantity Free radicals (*OH) in cancer cells transit through mitochondrial membranes, cytoplasm, nuclear membranes due to interactions nuclear resonance waves with mitochondrial resonance waves and then react on nuclear DNA of cancer cells inducing processes irrepressible replication via realizing of 2nDNA reaction (see above) [12,13].

The process irrepressible replication occurs in S proliferative phase of cancer cellular cycle causing accelerated cancer cellular cycle. However this process in S phase cellular cycle moves from G1 phase and then S/G2 phases cellular cycles inducing supplementary anabolic biosynthetic endergonic processes for supporting acceleration of cellular cycle. Acceleration of cellular cycle advances biochemical processes due to transition relative chemical potentials (μ) through relative G1 → S → G2 phases cellular cycle. Just Chk1 induce these relative chemical potentials (μ) causing activating the Cdc25 family of dual specificity phosphatases, as Cdc25A at the transitional G1 → S phases cellular cycles as well as Cdc25A and Cdc25C at the G2 and transitional G2 → M phase cancer cellular cycle. Thus the induced relative chemical potentials (μ) via transition chemical potentials (μ) through relative G1 → S → G2 phases cellular cycle are the mechanism maintenance stability Quasi-stationary pathologic State in condition acceleration cancer cellular cycle being subjected to acceleration cancer cellular cycle by influences abundance Free Radicals on cells' DNAs which arise negative fluctuations entropy ($dx\beta<0$) and transits cellular thermodynamic system into new Quasi-stationary State with decreased common entropy ($\Delta Sx<0$) according to Glansdorff & Prigogine theory **Figure 6.**

As concerning to Carrassa L. suggestions, the use chemotherapeutic inhibition prevents DNA damage before DNA replication and mitosis. However these inhibitions will also occur in different degree in all cells of an organism, especially on immune and hormonal cells. Similar effects will occur in all other offered mechanisms of chemotherapy, because these offered chemotherapeutic methodes are based on study normal healthy cellular cycle. Just Mitosis-Meiosis phase of cancer cellular cycle is differed from Mitosis phase normal cellular cycle cardinally. Mitosis-Meiosis phase of cancer cellular cycle produce daughter's cancer cells with long DNAs due to combination haploid cytochromes with diploid cytochromes which cause movement the telomers to end of integrated long DNA. The integrated long DNAs of cancer cells' nuclei pull abundance energy from an organism's Basic Internal Energy for excessive anabolic biosynthetic processes, which provides processes DNA replication leading to prepare transition into Mitosis-Meiosis phase of cancer cellular cycle with Cytokinesis of cells'divisions. Just short interphase for preparation to transit to Mitosis/Meiosis is exerted by accelerated cancer cellular cycle. Therefore this accelerated cancer cellular cycle generates cancer cells'properties which have very restricted function *versus* healthy cells. Just the integrated long DNAs with telomers on end of them store great quantity molecular bonds' energy which cause state of Resistance Apoptosis of cancer cells because this energy is received from two sources as from External Works (W_{ext}) through Internal Works (W_{int}) as well as from Basic Internal Energy (Ebasic) of Basic stem cells (neurons). Also excessive consumption energy for huge anabolic endergonic processes in accelerating cancer cellular cycle causes overloaded nodal point bifurcation anabolic and catabolic processes [NPBac] in AcetylCoA of Glycolysis with partial suppression catabolic anaerobic exergonic processes of oxidative phosphorilation [Krebs tricarboxylic acids cycle] which leads to forming "aerobic glycolysis" of cancer tissue metabolism according Warburg effect mechanism *versus* "incompatibility aerobic oxidation with glycolysis" in healthy tissue metabolism according Pasteur effect mechanism **Figures 4 and 5** [6,7,59]. The offered new method cancer treatment via "Prolonged medical Starvation during 42 – 45 days uses extracts of herbs and cytotoxic activity very small dosage of red cranesbill (*Geranium robertianum*) with plentiful water regime" **Figure 7** [76-79,82]. The prolonged Starvation bereaves of cancer cells' energy, which is received from Environment, for the function of cancer cells' Internal Works (W_{int}). Thus the use of Basic Internal Energy (Ebasic) of organism's neurons is subjected to the confrontation for using this energy between healthy cells through sequence [Basic stem cells → Totipotent stem cells → Pluripotent stem cells → Multipotent stem cells → Oligopotent stem cells → Unipotent stem cells and then healthy type cells] and cancer cells through sequence [Basic stem cells → Totipotent stem cells → some other affected stem cells → then cancer type cells]. The healthy type cells are won being supported by herbal extracts which deliver microelements and vitamins from Environment for the function of healthy cells' cellular cycle. Therefore cancer cells lose much energy from Basic Internal Energy (Ebasic) that damages accelerated cancer cellular cycle causing suppression excessive anabolic enderginic cancer cells' cycle that leads to recover balance anabolic endergonic processes & catabolic exergonic processes breaking Warburg effect mechanism of cancer cells metabolism. Thus prolonged Starvation plunge cancer cells into depression, and very small dosage cytotoxic drugs ruin depressed cancer cells efficiently. Just the offered new method cancer treatment with very small dosage cytotoxic substances does not violate immune and hormonal systems of an organism as compared to mogern methods cancer treatment with great dosage cytotoxic drugs (**Figure 7**).

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Conclusion

- Both chemical mechanisms and cellular mechanisms maintain stability Internal Energy as in cells as well as in an organism in norm.
- Exerting cellular cycle occurs by fluctuating flows energy from Basic Internal Energy via sequence Basic stem cells → Totipotent stem cells → Pluripotent stem cells → Multipotent stem cells → Oligopotent stem cells → Unipotent stem cells and then various type cells in norm.
- Interactions between anabolic endergonic processes and catabolic exergonic processes in cellular cycle are the driving mechanism of advance cellular cycle in norm.
- Interactions between replications of proliferative genomic mechanism and mitochondria oxidative function exert advance cellular cycle via G1, S, G2, and M phase's cellular cycle in norm.
- The obtained energy from Basic Internal Energy of Basic stem cells [neurons] determines different timelives of different cells in norm.
- Enzymatic activity of Cyclin dependet kinases CDK4/6 and CDK1/2 exert shift balance catabolic exergonic processes & anabolic endergonic processes into moderate increase anabolic endergonic processes leading to the changes nuclear chemical potential (μnucl) and resonance waves of nuclear capacitors that causes progression cellular cycle through G1, S, G2, M phases in norm.
- Inherited Lifetime from birth till death as each cell as well as an organism is depended on quantity Basic Internal Energy and exhibit changes positive fluctuations Entropy and negative fluctuations Entropy in norm.
- Complex of all mechanisms exerting cellular cycle is the cellular mechanism maintenance stability Internal Energy as in cells during their cellular cycles as well as in an organism in norm.
- Considering that viruses can not live in Environment, viruses are initial generated into cells of living organisms by especial quanta of Solar Rays causing by Solar Thermonuclear Synthesis.
- Virises use some cells' processes of an organism for their survival, e.g. use the human electron transport chain of an organism's cells.
- Prokaryotic mechanisms of viral cells have only haploid genome which uses only anabolic endergonic processes without catabolic endergonic processes.
- Different virises obtain Basic Internal Energy on different levels: Influenza viruses obtain Basic Internal Energy [molecular bonds energy] from type cells exhibiting weak ties; Cancer viral oncogenes intrude in deep level of Basic Internal Energy [molecular bonds energy] either in Oligopotent stem cells or ever in multipotent stem cells exhibiting firm ties.
- Viruses use mitochondrial electron transport chain of oxidative processes able-bodied cells.
- HeLa cells absorb whole mitochondrial oxidative system in their bodies creating metabolism similar to bacteria.
- Cancer genetic coupled mechanism contains both several viral genomes and one human genome consisting of 49-56 chromosomes because several viruses affect one human cell.
- Cancer cellular cycle has integrated Mitosis-Meiosis phase of cellular cycle via combination healthy cell chromosomes and viral chromosomes.
- Great quantity Free Radicals in cancer cells exert irrepressible, accelerative cellular cycles via realizing irrepressible 2nDNA replicative reactions.
- Targets of modern chemotherapeutic methods cancer treatments are the nuclear mechanisms of cancer cellular cycle which are made with great dosage cytotoxic drugs.
- Target of new method cancer treatment is Warburg effect which uses very small quantity cytotxic substance causing cancer cells depression in condition „Prolonged medical Starvation" and supporting by extracts of herbs.
- Small dosage of cytotoxic substances in new method cancer treatment does not damage immune and hormonal systems of an organism causing efficient therapeutic treatment *versus* great dosage cytotoxic drugs in modern chemotherapeutic methods cancer treatments.

Acknowledgment

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

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