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Driving Mechanisms of Different Tissues Cellular Cycles in Norm and in Cancer Pathology from the Point of View of Thermodynamics, Biophysics and Biochemistry

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ABSTRACT

The thermodynamic system of a human organism is subjected to the laws of thermodynamics which stable Internal Energy (U) and Internal Medium are suppoted by Internal Works (W_{int}) and External Works (W_{ext}) of an organism according to first law of thermodynamics. Just both Internal Works (W_{int}) and External Works (W_{ext}) of an organism are carried out by driving mechanisms cellular cycles of cells in all organs of an organism. Thus driving mechanisms cellular cycles of an open non equilibrium non linear thermodynamic system of a human organism and of the organism's organs in norm and in different pathologies are exerted by driving mechanisms of cells' cellular cycles of an organism's tissues in different organs which are studied both in norm and in cancer pathology. Besides there are studied genetic development of an organism's cells from embryonic single cell state to old aged organism from the point of view of thermodynamics. Also it is studied the influences of driving mechanisms cells' cellular cycles on mechanisms both cells development and an organism development. Moreover there are studied differences driving mechanisms of cellular cycles in different tissues of different organs. Furthermore there are compared driving mechanisms cellular cycles both Viral haploid cellular cycle and Human diploid cellular cycle. Besides there are described transmutation driving mechanisms of healthy genomic cellular cycle into cancer genomic cellular cycle from the point of view of thermodynamics. Also there are discussed driving mechanisms of cellular cycle from point of views of thermodynamics, biophysics and biochemistry.

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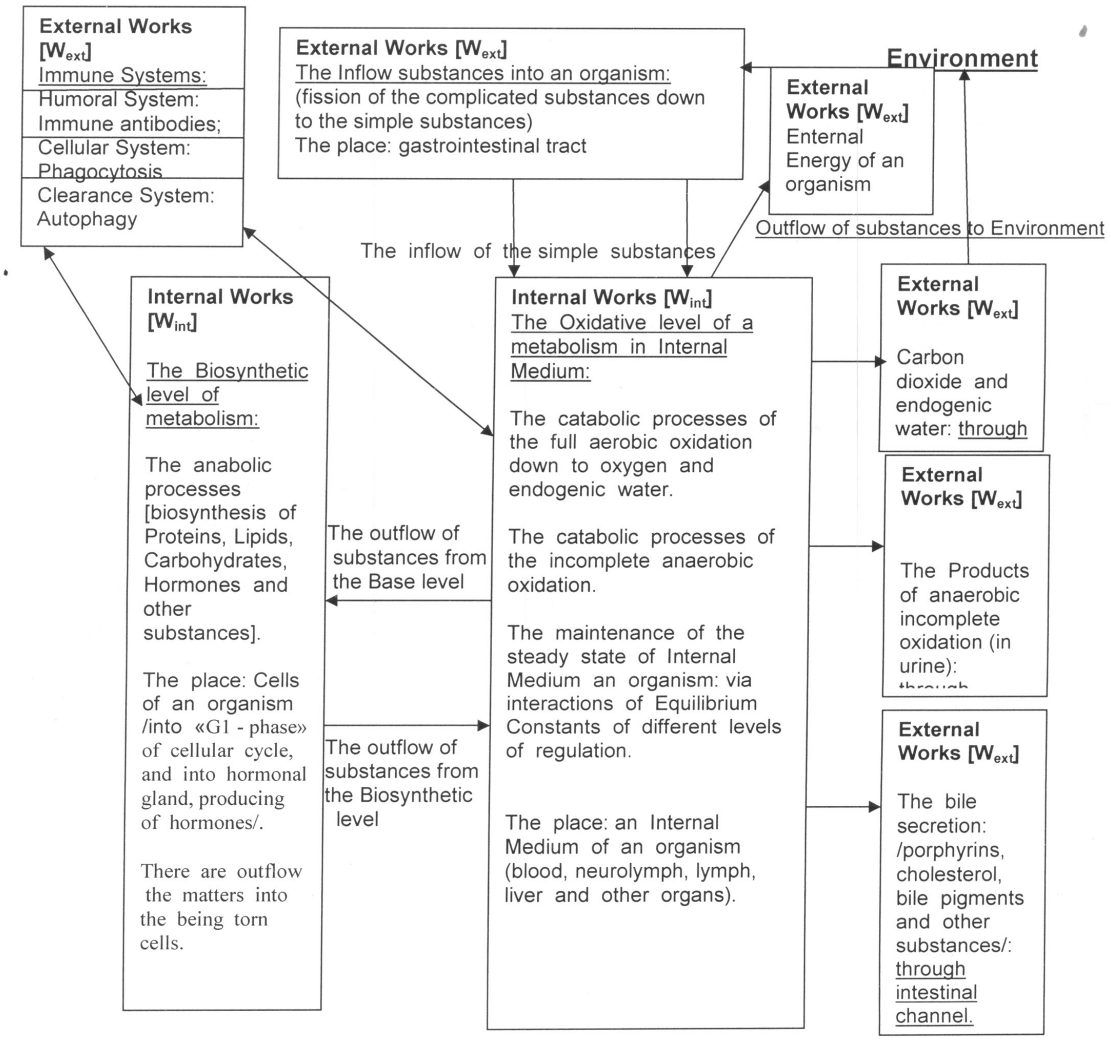
Introduction

Driving mechanism of cancer cellular cycle is considered from the point of view of thermodynamics, biophysics and biochemistry. The development an open non equilibrium non linear thermodynamic system of a human organism is exerted by the development cells of an organism which are subjected to advance cellular cycles. Besides an open thermodynamic system of a human organism is subjected to thermodynamic laws. It is the formula according to first law of thermodynamics: $Q = \Delta U + W_{int} + W_{ext}$ [Q – General Energy, ΔU – Internal Energy, Wint – Internal Work, W_{ext} – External Work] (Figure 1). Stability Stationary State of the open non-equilibrium non-linear thermodynamic systems of a healthy organism is characterized by stability of Internal Energy (ΔU) which is supported by Internal Works (W_{int}) and External Works (W_{ext}) [1,2]. Internal Energy (ΔU) of an organism is characterized by following stable biochemical indices: [stable temperature 36,0°C – 36,9°C by which all enzymes operate.; stable index pH=7,35 in blood and in neurolymph; stable index of blood osmotic pressure - 285 ± 5 mil-osm/kg H_2O, corresponding to 0,14 - 0,15 molar sodium chloride and the other univalent ions; stable index of blood colloidal-oncotic pressure - 18 -25 mm Hg, corresponding to human serum albumin solution up to 300 grams per liter etc.]. The biochemical mechanisms maintenance stability Internal Energy (stable temperature 36,0ºC -36,9ºC etc.) and Internal Medium (stable concentration substances in blood and neurolymph) contain three level regulation: highest level regulation [Central Nervous System], high level regulation ["Equilibrium Constant of ionic metabolism", "Equilibrium Constant of acid –- alkaline metabolism", "Equilibrium Constant of oxidative – reduction Potentials of metabolism" and "Equilibrium Constant of coagulating system of blood"] and low level regulation ["Equilibrium Constant of energy exchanges" and "Equilibrium Constant of metabolism"] [3,4] (Figure 2). The stable biochemical indices of Internal Energy of an organism form chemical potential of an organism (μ_{org}) which mutial links with chemical potentials of all cells of an organism (μ_{cell}) via interactions resonance waves of cellular capacitors of the cells forming stable Stationary State of a healthy organism. The Internal Works (W_{int}) of an organism contribute to following metabolic processes: a) catabolic aerobic processes [Lungs respiratory processes, Oxyhemoglobin in erythrocytes, Cytichrome in mitochondria]; b) catabolic anaerobic processes [Glycolysis, Krebs tricarboxylic acid cycle (TCA) and electron transport chain of Complex I, Complex II, Complex III, Complex IV, Complex V]; c) anabolic biosynthetic processes; and Clearance system of an organism: System Excretions waste substances from an organism and Autophagy [3-7] (Figure 1). Just the Internal Works (W_{int}) of an organism forms common balance catabolic aerobic processes & catabolic anaerobic processes & anabolic biosynthetic processes of an organism which form extracellular chemical potential ($\mu_{extracell}$) in extracellular Medium of an organism's tissues. The External Works (W_{ext}) of an organism contain following processes: a) The metabolic processes of an

organism produce calories as External Energy (E_{ext}) of an organism which resists influences of Environment [Atmosphere, Solar System]; b) Humoral and cellular Immune Systems of an organism's defence against penetration strange substance into an organism (immune antibodies and phagocytosis); c) Systems inflow substances in an organism and excretion substances from an organism into Environment [3-5] (Figure 1). The mechanisms of Immune System of an organism is carried out defensive function via operation cellular capacitors' resonance waves of phagocytes (cellular immunity) as well as immune anti-bodies (humoral immunity).

Figure 1.

Mechanisms Internal Works and External Works for supporting Internal Energy of an organism.



Footnote: Basal metabolic rates (BMR) or Basal Work (W_{basal}) promotes stable state of Internal Energy (ΔU) of an organism stimulating metabolism and causing excretion waste substances into environmet.

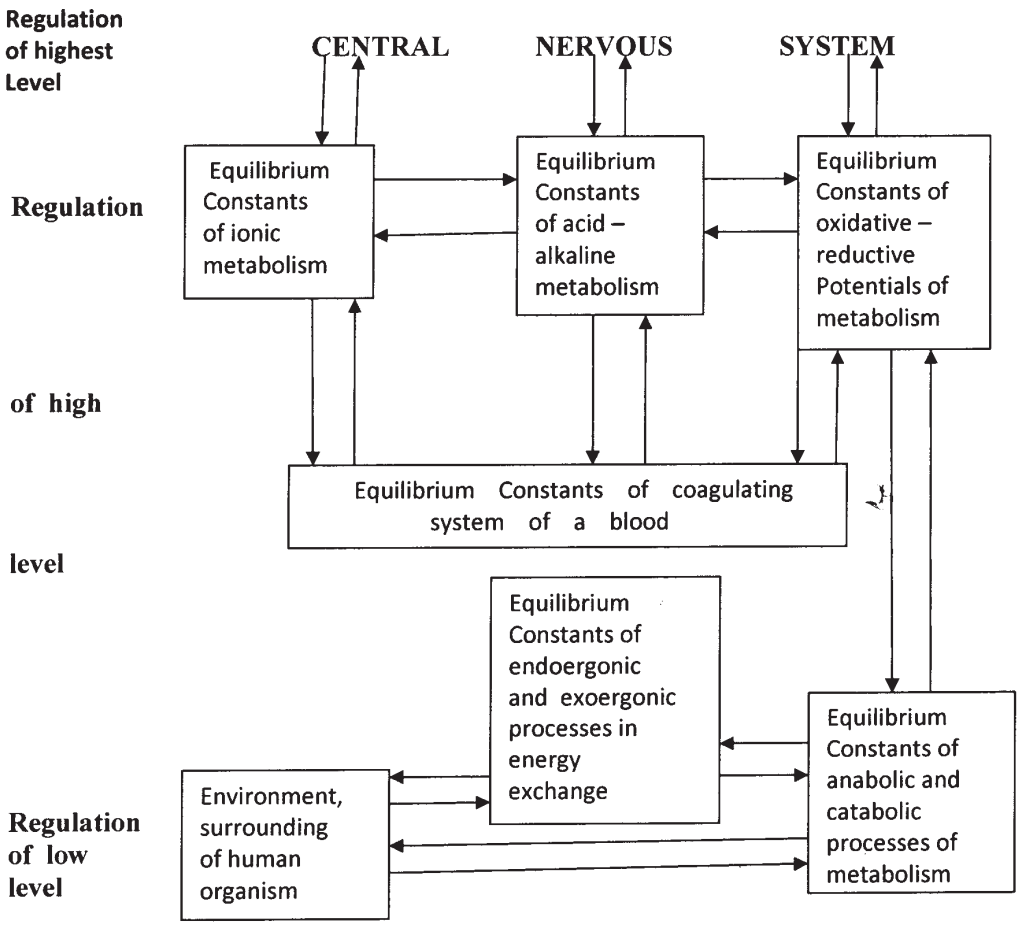
The Mechanisms Maintenance Stability Internal Energy and Internal Medium of The Open Thermodynamic Systems of Cells in Norm and Pathology

According first law of thermodynamics corresponding formule: $Q = \Delta U + W_{int} + W_{ext}$ [Q – General Energy, ΔU – Internal Energy, W_{int} – Internal Work, W_{ext} – External Work], the stability Internal Energy of each cell (ΔU_{cell}) is characterized by stable basophylic chemical potential of cellular cytoplasm (μ_{cytopl}), due to staining cells, which is supported by cell's Internal Work ($W_{cell\ int.}$) consisting of nuclear External Work ($W_{nucl.ext}$), mitochondria External Works ($W_{mitoch.ext}$) and the other organelles External Works ($W_{orgs.ext}$) in norm and in cancer pathology [1-6]. The Intracellular Works ($W_{int.cell}$) is carried out by nuclear External Work ($W_{nucl.ext}$), mitochondria External Works ($W_{mitoch.ext}$) and the other organelles External Works ($W_{orgs.ext}$) in norm and in pathology. Thus Intracellular Works ($W_{int.cell}$) maintain stability Internal Energy of each cell (ΔU_{cell}) causing cellular balance catabolic aerobic processes & catabolic anaerobic processes & anabolic biosynthetic processes in norm and pathology. The shift balance anabolic processes & catabolic processes into excessive anabolic processes leads to cancer tissue metabolism causing cancer cells mechanism [6,7,8] (Figure 3). The shift cellular balance anabolic processes & catabolic processes into excessive catabolic processes leads to inflammation processes in tissue and exerts immune cells activity (Figure 3). The extracellular medium's chemical potential of each cell is the internal medium of an organism's chemical potential ($\mu_{organism}$) in norm and in pathology. Therefore chemical potential of an organism is equal to chemical potential of cell in norm ($\mu_{org} \approx \mu_{cell}$), but chemical potential of an organism is not equal to chemical potential of cancer cell because of shift balance anabolic processes & catabolic

processes into excesive anabolic processe in cancer metabolism ($\mu_{org} \neq \mu_{can.cell}$) (Figure 4). Hence fluctuating processes binding β1-Integirin ↔ free β1-Integirin (as well as α-Integrins) is induced by fluctuating balance inner chemical potential cells ($\mu_{inner\ cell}$) & outer chemical potential cells ($\mu_{outer\ cell}$) due to exchanging inflow substances and energy in cell and outflow substances and energy from cell [7-10]. It is very important interactions between extracellular medium and intracellular medium in activity of cellular cycle in norm and in pathology which fluctuating balance inner chemical potential cells ($\mu_{inner\ cell}$) & outer chemical potential cells ($\mu_{outer\ cell}$) is induced by interactions between intracellular balance anabolic processes & catabolic prosesses and extracellular balance anabolic processes & catabolic prosesses [6, 11]. Just the extracellular medium of cells how the internal medium of tissue contains respiratory electron transport chain with its 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 → ATP synthase for oxidative phosphorylation of Complex V as well as Reactive Oxygen Species (ROS), superoxide (O_2*), Free Radicals operations and so on, i.e. oxidative processes which are extended from lung respiratory processes through oxyhemoglobin in erythrocytes and further respiratory electron transport chain into tissue Internal Medium (extracellular medium) forming balance anabolic processes & catabolic prosesses which cause expression outer chemical potential of cells ($\mu_{outer\ cell}$) [12-17]. Also fluctuating cellular balance inner chemical potential cells ($\mu_{inner\ cell}$) & outer chemical potential cells ($\mu_{outer\ cell}$) stimulates driving mechanisms of cellular capacitors of all cells causing stability Internal Energy and Internal Mediums both an organism and cells of an organism via exchanging inflow substances and energy into cell and outflows substances and enegy from cell according famous Prigogine theorem [5,6,18,19] (Figure 5). Besides fluctuating cellular balance inner chemical potential cells ($\mu_{inner\ cell}$) & outer chemical potential cells ($\mu_{outer\ cell}$) determines intensity cellular cycle [6,11].

Figure 2.

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



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 ($\mu_{int.}$ and $\mu_{ext.}$) 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.

Figure 3.

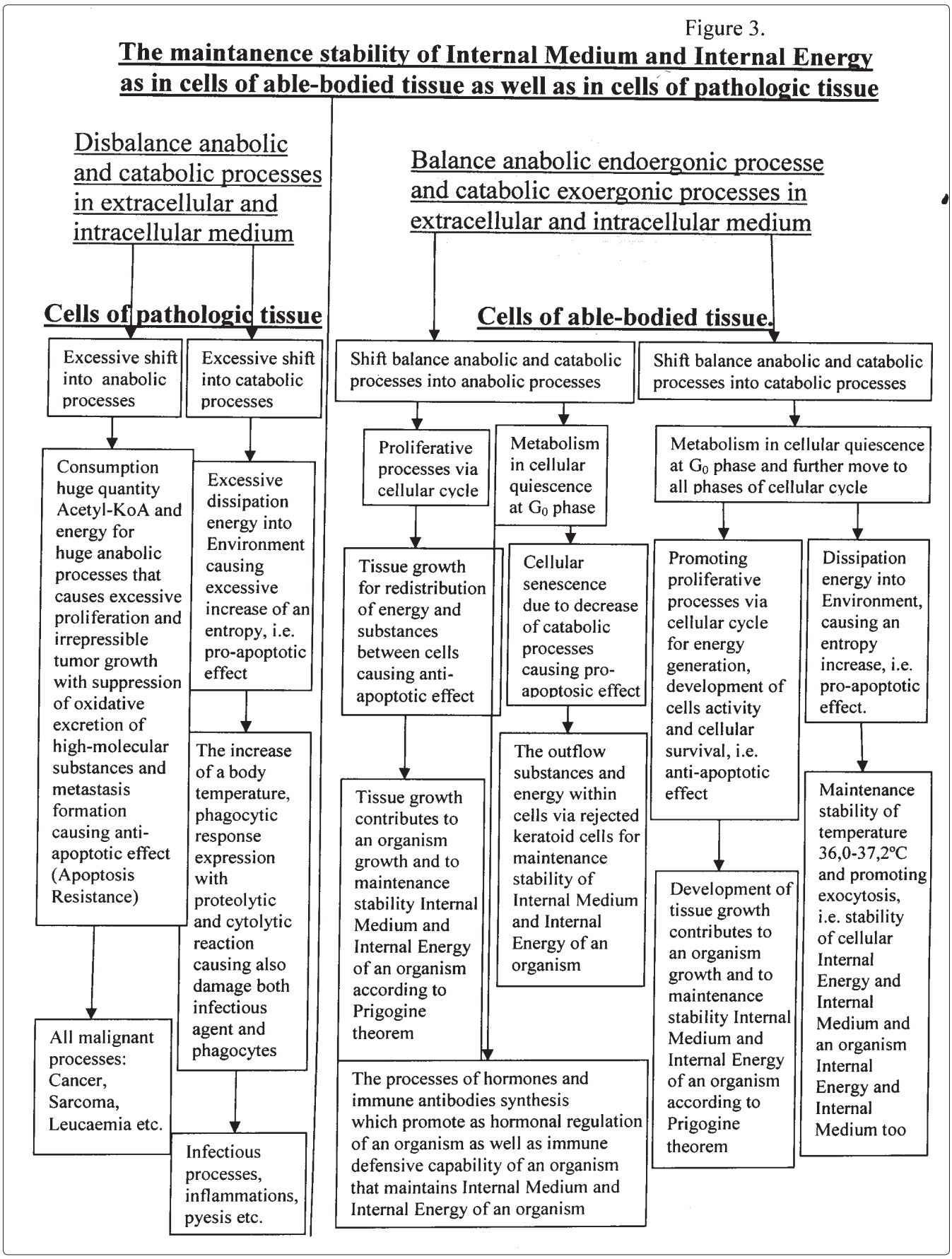

The maintanence stability of Internal Medium and Internal Energy as in cells of able-bodied tissue as well as in cells of pathologic tissue
Disbalance anabolic and catabolic processes in extracellular and intracellular medium
Balance anabolic endoergonic processe and catabolic exoergonic processes in extracellular and intracellular medium
Cells of pathologic tissue
Cells of able-bodied tissue.
Excessive shift into anabolic processes
Excessive shift into catabolic processes
Shift balance anabolic and catabolic processes into anabolic processes
Shift balance anabolic and catabolic processes into catabolic processes
Consumption huge quantity Acetyl-KoA and energy for huge anabolic processes that causes excessive proliferation and irrepressible tumor growth with suppression of oxidative excretion of high-molecular substances and metastasis formation causing anti-apoptotic effect (Apoptosis Resistance)
Excessive dissipation energy into Environment causing excessive increase of an entropy, i.e. pro-apoptotic effect
Proliferative processes via cellular cycle
Metabolism in cellular quiescence at G0 phase
Metabolism in cellular quiescence at G0 phase and further move to all phases of cellular cycle
Tissue growth for redistribution of energy and substances between cells causing anti-apoptotic effect
Cellular senescence due to decrease of catabolic processes causing pro-apoptosic effect
Promoting proliferative processes via cellular cycle for energy generation, development of cells activity and cellular survival, i.e. anti-apoptotic effect
Dissipation energy into Environment, causing an entropy increase, i.e. pro-apoptotic effect.
The increase of a body temperature, phagocytic response expression with proteolytic and cytolytic reaction causing also damage both infectious agent and phagocytes
Tissue growth contributes to an organism growth and to maintenance stability Internal Medium and Internal Energy of an organism according to Prigogine theorem
The outflow substances and energy within cells via rejected keratoid cells for maintenance stability of Internal Medium and Internal Energy of an organism
Development of tissue growth contributes to an organism growth and to maintenance stability Internal Medium and Internal Energy of an organism according to Prigogine theorem
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 Internal Energy and Internal Medium too
All malignant processes: Cancer, Sarcoma, Leucaemia etc.
Infectious processes, inflammations, pyesis etc.
The 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

Figure 4.

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*).

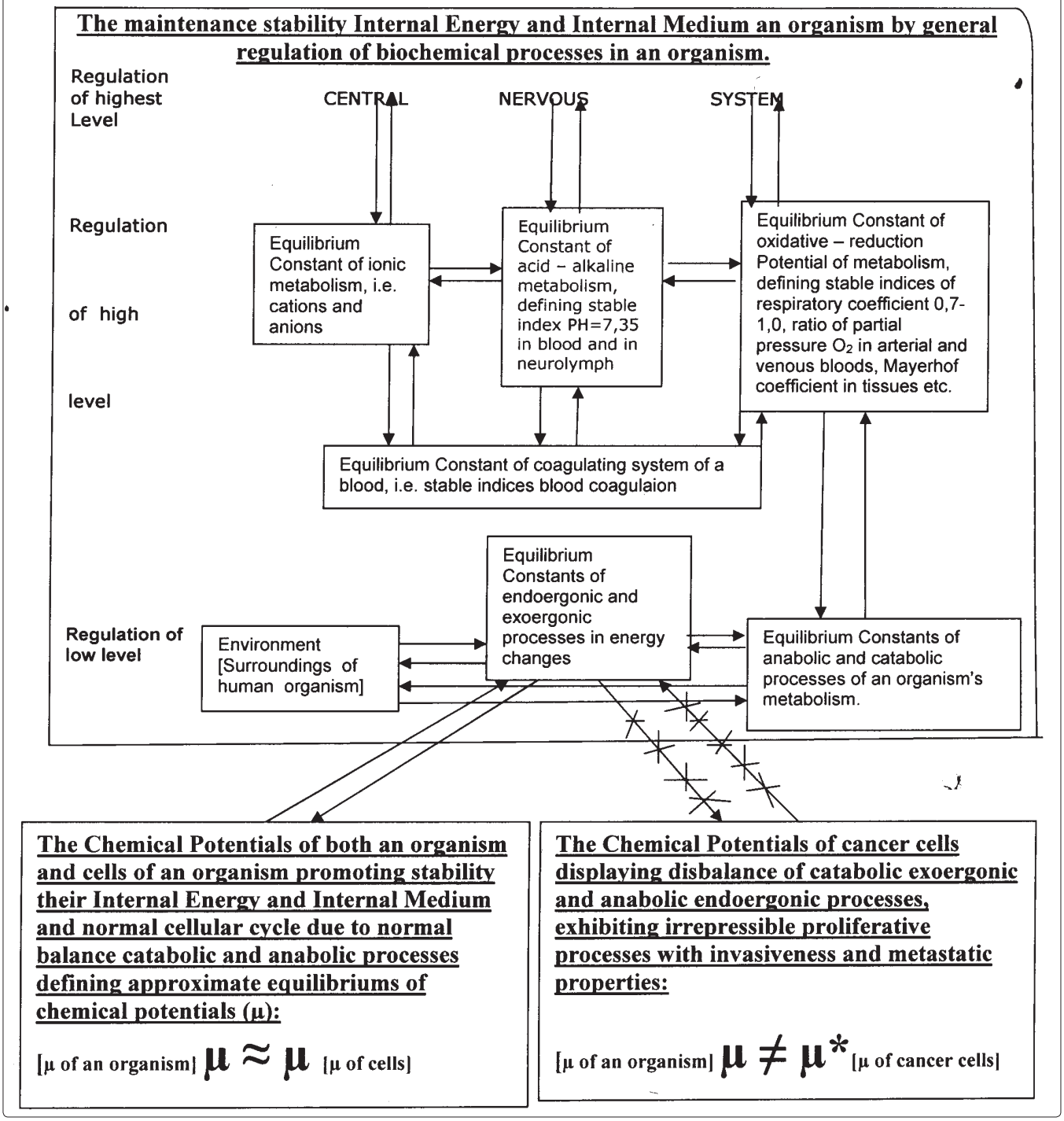
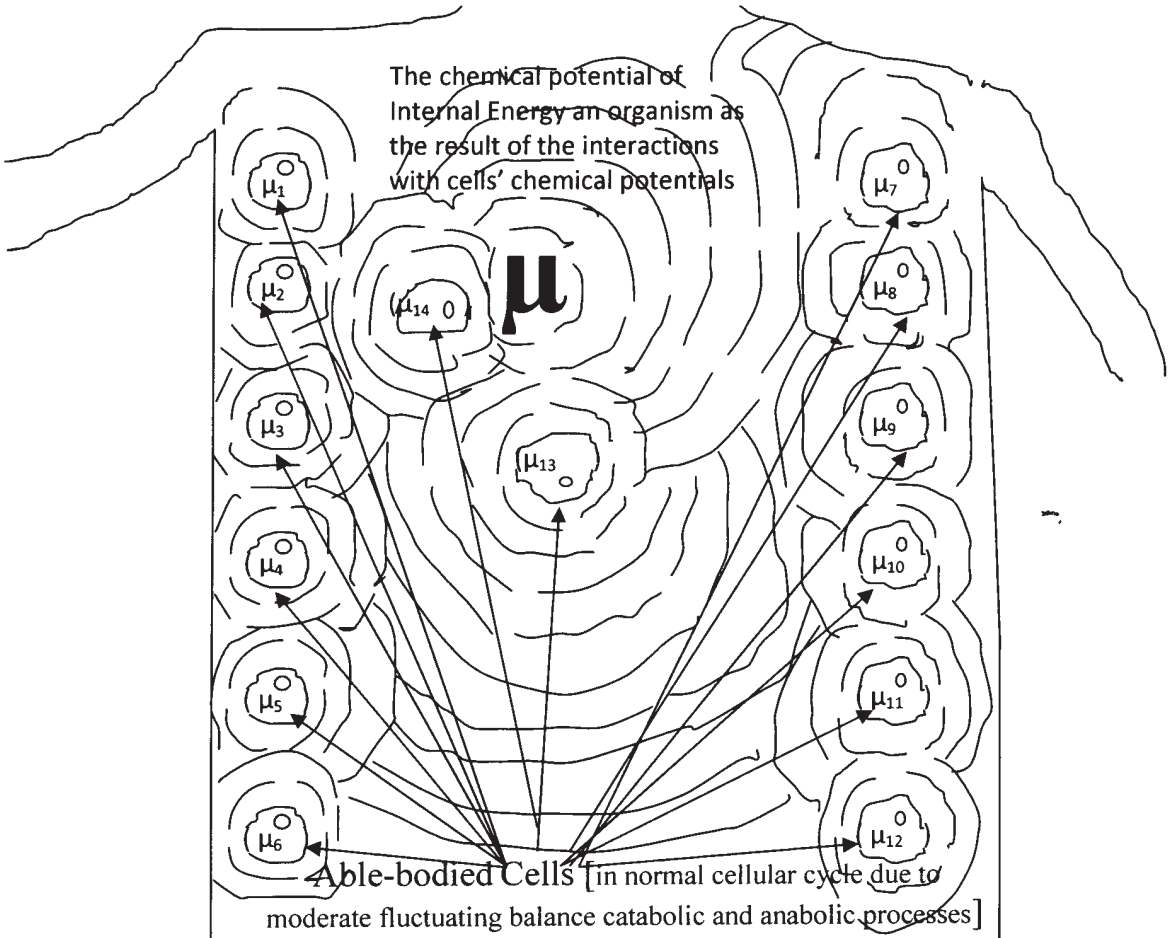
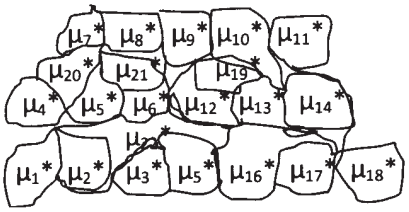


Figure 5.

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.



Able-bodied Cells [in normal cellular cycle due to moderate fluctuating balance catabolic and anabolic processes]



Cancer Cells [excessive shift catabolic and anabolic processes into anabolic processes, exhibiting irrepressible proliferative processes with invasiveness and metastatic properties]

Driving Mechanisms of Normal Cellular Cycle of An Organism from the Point of View of Thermodynamics, Biophysics and Biochemistry

The open non equilibrium non linear thermodynamic system of cell is subjected to first law of thermodynamics according to formula: $Q = \Delta U + W_{int} + W_{ext}$ [Q – General Energy, ΔU – Internal Energy, W_{int} – Internal Work, Wext – External Work] [1,2]. The stability Internal Energy of each cell (ΔU_{cell}) is characterized by stable basophylic chemical potential of cellular cytoplasm (μ_{cytopl}) due to staining cells, in norm. Glycolysis processes occur in hypoxic condition in an organism being supported by HIF hydroxylase operation creating fluctuation stable balance catabolic anaerobic exergonic processes & anabolic anaerobic endergonic processes. The catabolic aerobic exergonic processes operate in oxidative condition and are supported by von Hippel-Lindau (VHL) proteins forming "incompatibility aerobic oxidation with glycolysis" in healthy tissue metabolism according Pasteur effect mechanism [20-24] (Figure 6). The cell's anabolic endergonic processes of biosynthesis proteins occur in G_0, G_1 phases cellular cycle as anaerobic processes. These processes occur via transcription phase (phenomena of RNA synthesis from DNA template) by tRNA transmiting to mRNA of translation phase (phenomena of amino acid assembly from mRNA) then through ribosome forming polypeptide chain and further secondary structure and tertiary structure of the proteins. These processes exert expression hypoxic HIF factor via prolyl hydroxylases domains activity [PHD] that leads to HIF hydroxylation of anabolic endergonic processes causing shift fluctuating balance anabolic anaerobic processes & catabolic anaerobic processes & catabolic aerobic processes into moderate expression both anabolic anaerobic processes & catabolic anaerobic processes in intracellular medium due to inflow energy and substances into inner cells from outer cells. Then expressed inflow energy into moderate expression both anabolic anaerobic processes & catabolic anaerobic processes in intracellular medium is expended that leads to shift fluctuating balance anabolic anaerobic processes & catabolic anaerobic processes & catabolic aerobic processes into moderate expression catabolic aerobic processes in intracellular medium due to outflow energy and substance from inner cells into outer cells. These exchanged intracellular shift fluctuating balance anabolic anaerobic processes & catabolic anaerobic processes & catabolic aerobic processes either into moderate expression both anabolic anaerobic processes & catabolic anaergonic processes or into moderate expression catabolic aerobic exergonic processes are induced either by expression HIF and VHL inhibition or exertion VHL and HIF inhibition [21-26]. These processes in extracellular medium are occurred in reverse order. Then moderate expression both anabolic anaerobic processes & catabolic anaerobic processes in extracellular medium cause shift balance inner chemical potential cells ($\mu_{inner\ cell}$) & outer chemical potential cells ($\mu_{outer\ cell}$) into prevalence outer chemical potential cells ($\mu_{outer\ cell}$) due to consumption energy and substances for biosynthetic processes. Just the prevalence outer chemical potential cells (μouter cell) causes inflow substances into cell from outer cells' medium according to Theorell equation: 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) that promote expression both anabolic anaergonic biosynthetic processes & catabolic anaerobic processes (TCA) causing biosynthesis proteins in intracellular medium in G_0 and G1 phases cellular cycle (see above) [2,21-26]. However sufficient quantity of production proteins induces binding DNA by both HIF-1 alpha subunit [HIF-1α] and HIF-2 alpha subunit [HIF-2α] via C- terminal transactivation domain (CTAD) and N-terminal transactivation domain (NTAD) that causes expression ubiquitination of HIF activity causing by the von Hippel-Lindau (VHL) protein [21 -26]. The suppression HIF activity cause expression oxidative processes via shift fluctuating balance inner chemical potential cells ($\mu_{inner\ cell}$) & outer chemical potential cells ($\mu_{outer\ cell}$) into prevalence inner chemical potential cells ($\mu_{inner\ cell}$) causing outflow energy and substances from cell into extracellular medium according to Theorell equation: 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) in which prevailing VHL over HIF-1a interrupts anabolic endergonic processes via suppression both anabolic anaerobic biosynthetic processes & catabolic anaerobic processes (TCA) in G_0 and G1 phases cellular cycle which cause transition into expression catabolic aerobic exergonic processes. Just DNA proliferative processes are occurred in S, G2, M phases through expression catabolic aerobic exergonic respiratory processes of link [from lungs O_2 → oxyhemoglobin → Mitochondrial system cytochromes] [2,21-26]. The processes of transition between expression both anabolic anaerobic processes & catabolic anaerobic processes and expression catabolic aerobic processes are occurred via binding between VHL and HIF-1a factors being jointed by the FIH-1 link in norm. Thus Hypoxia-inducible factor 1 (HIF-1) is activated by transcription and translation mechanisms in nucleus whose proteins' production increased glycolytic metabolism causing glucose transporters and expression glycolytic enzymes [2,20-26]. Although HIF-1α factors prevail over the von Hippel-Lindau (VHL) protein, DNA proliferative processes in S, G2, M phases cellular cycle need also catabolic aerobic exergonic oxidative functions of oxygen (O_2) availability transiting into superoxide (O_2^*), Reactive Oxygen Species (ROS), Free Radicals operations. Just lack Hydrogen ions don't neutralize whole arrived from lungs oxygen (O_2) because of stable respiratore index in an organism (RI) [$RI = CO_2 : O_2 = 0{,}8 – 1{,}0$]. The 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↔$FADH_2$ in Electron Transport Chains of both Complex I and Complex II : $n[O_2] + n[e\text{-}] \rightarrow n[O_2^*]$. Superoxide ($O_2^*$) induces complex ROS/$H_2O_2$/Free radicals [12-17]. Free radicals (*OH) pass from mitochondria through cytoplasm into nucleus and react on nuclear DNA inducing process replication in S phase cellular cycle via realizing of 2nDNA reaction [15-18]:

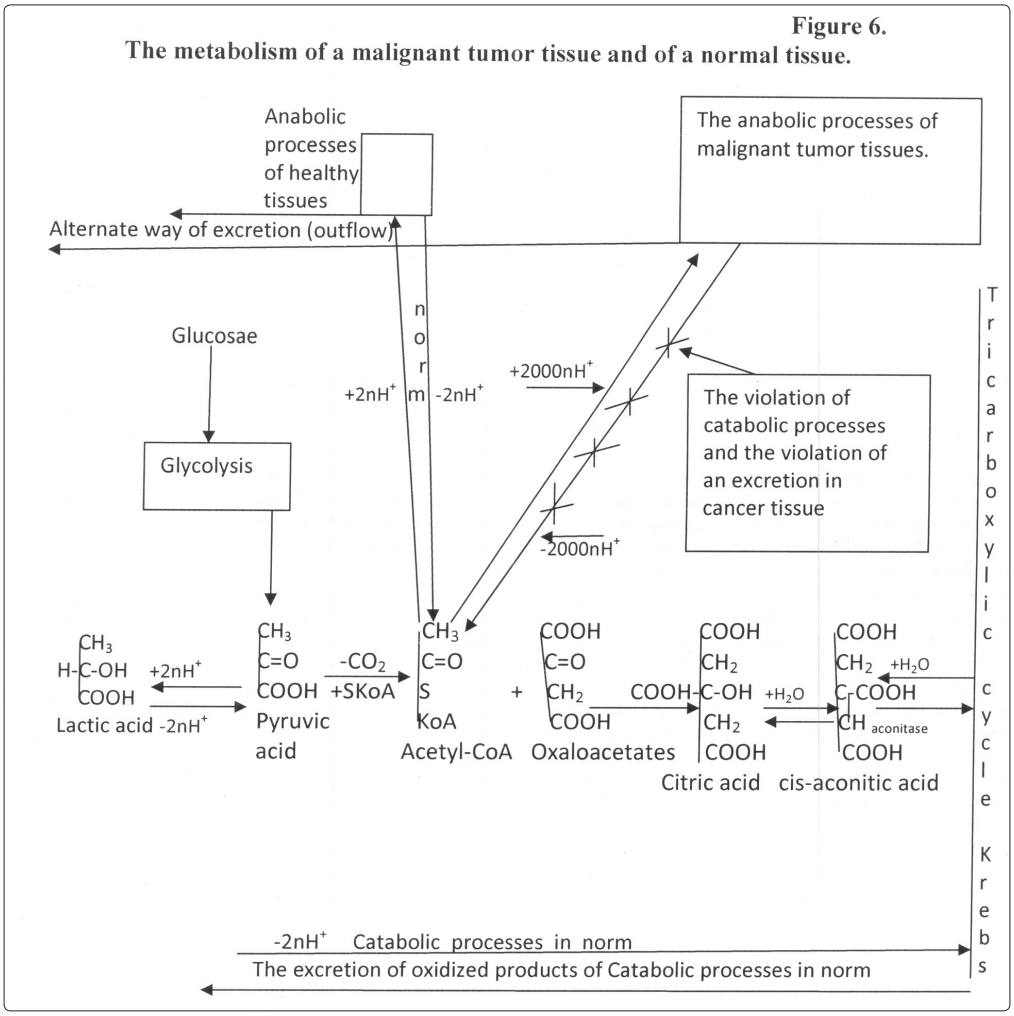
$^*OH + H_2$-nDNA-DNA —> H_2O + H•-nDNA-DNA;

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

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

2nDNA-H• + 2*OH —> 2nDNA + H_2O

Thus mechanisms inducing mutual suppressions between HIF and VHL promote exertion cellular cycle causing proliferative processes which also promote as erythropoiesis due to activation erythropoietin as well as angiogenesis via mechanisms expression vascular endothelial growth factor (VEGF).



Driving Mechanisms of Generation Cellular Cycle from Single Cell into Multicellular Human Organism From the Point of View of Thermodynamics, Biophysics and Biochemistry

The genetic mechanisms of generating an organism from single Sex cell (sSC) (2) must 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 ($k_0 = 1{,}38$ Joule K^{-1}), ω – thermodynamic probability] [6,27,28]. 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 thermodynamic system from macrostate into microstate displays direction to chaos due to breakup of thermodynamic system via complete increased Entropy. Secondly, compact integrated macrostate from microstate of thermodynamic system displays full synthesized of thermodynamic system via complete decreased Entropy, and thirdly, balance of middle disintegrated microstates & middle integrated microstates of thermodynamic system reflects balance catabolic exergonic processes & anabolic endergonic processes in normal Stationary State of thermodynamic system of an organism due to minimization gain of fluctuating middle index Entropy, i.e. leading to minimization gain Entropy leading to maintenance stability open thermodynamic system of an organism and its cells according Prigogine theorem and Boltzmann theory [5, 7, 27, 28]. The forming single Sex cell (sSC), due to fusing sperm and ovum, has as intracellular Internal Medium as well as extracellular External Medium of mother's uterus Internal Medium. Thus chemical potential of Internal Medium of single Sex cell (sSC) (μ_{intsSC}) is subjected to chemical potential of External Medium of single Sex cell (sSC) (μ_{extsSC}), i.e. mother's uterus chemical potenial (μuterus). Therefore haploid primitive division cells via Meiosis 1 due to initial obtained energy from both parents in single Sex cells (sSC) receive supplementary energy from mother's uterus of stem cells system that exert shift Meiosis I into Meiosis II for advance haploid primitive division cells that form germ as a primitive organism with minimization gain of fluctuating middle Entropy according Prigogine theorem and Boltzmann theory [5, 7, 27, 28]. However the forming germ requires supplemental energy for further division germ's cells via cellular cycle. But insufficient energy of mother's uterus as External Medium chemical potential of germ's cells (μ_{gcell}) does not give possibility for development germ's cells' cellular cycles through genomic inheritance from parents' genes pathways. Hence mother's uterus External Medium chemical potential of germ's cells (μ_{gcell}) is become insufficient energy for the further development haploid cellular cycle via Meiosis, and it is required energy for more wide and big External Medium of germ's cells (μ_{gcell}). This requirements through resonance waves of germ's cells cellular capacitors exert forming new tissue of placenta tissue which forms External Medium of germ's cells' chemical potentials (μ_{gcell}) in placenta tissue forming Embryo which External Medium is mother organism's placenta tissue Internal Medium with its chemical potential ($\mu_{plac.tissue}$) [7, 8, 26, 27, 28]. Thus the main embryonic pathway direct into following development of sequence [single Sex cell (sSC) → Embryonic stem cells (ESC) → Basic stem cells] going via Meiosis which

share out the small parts of energy between Meiosis I and Meiosis II. Just both Meiosis I and Meiosis II show efficient expendable energy via further divided cell through Karyokinesis I and Cytokinesis I as well as through Karyokinesis II and Cytokinesis II respectively. In the beginning Meiosis I, the energy 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 DNAs (homologous recombination). 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 of alleles which may be beneficial combination. 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 the half number of chromosomes as well as the parent sex cell - gamete, i.e. gamete is a biologic alive formation having lack energy for minimization gain of fluctuating middle Entropy in its activity. But nonhomologous chromosome Y and chromosome X remain as unjoined chromosomes although in prophase of Meiosis I, it happens primary rearrangement genomic organization in chromatids of chromosome X and chromosome Y. However this primary rearrangement genomic organization is insufficient in Meiosis I due to formed two haploid cells having the half number of chromosomes including nonhomologous either chromosome Y or chromosome X. Therefore Meiosis I is considered as reduced division. During Prophase II of Meiosis II, also homologous second chromosomes, are paired and exchange with DNAs (homologous recombination). It results in chromosomal crossover. Also during Meiosis II, the cohesion between sister chromatids is realised and they segregate from one another, as well as during Mitosis. Just Meiosis II is an equational division analogous to Mitosis, in which the sister chromatids are segregated, creating four haploid daughter cells (1n, 1c) [7, 8, 26, 27]. However in prophase of Meiosis II it happens repeated rearrangement genomic organization of chromosome X and chromosome Y which transform nonhomologous chromosome Y and chromosome X into two homologous chromosomes. Therefore twofold rearrangement genomic organization in chromaids of chromosome X and chromosome Y in Meiosis I and Meiosis II forms two haploid cells having half number of homologous chromosomes, as well as during Mitosis. The next steps after Meiosis II of development these haploid cells are further advance of Cytokinesis via receiving supplementary energy from mother's placenta stem sells that exerts Karyokinesis mechanisms causing transition haploid cells into diploid cells named Zygotes which preserve received from mother energy into its cells. Maybe Zygotes are the initial cells of Basic stem cells (neurons) which preserve stores Basic Internal Energy of expectant organism. Just Zygotes has diploid cellular cycle via Mitosis which leads to forming multicellular human organism via exerting by sequence stem cells: Basic stem cells → Totipotent stem cells → Pluripotent stem cells → Multipotent stem cells → Oligopotent stem cells → Unipotent stem cells → type cells. Mitosis is shared into Prophase, Prometaphase, Metaphase, Anaphase, Telophase. Thus Meiosis II uses some energy obtained from mother's stem cells [Basic stem cells → Totipotent stem cells → Pluripotent stem cells → Multipotent stem cells → Oligopotent stem cells → Unipotent stem cells] and transits into Mitosis receiving supplementary energy from stem cells of mother organism which is preserved in Zygotes. Thus energy, preserved in Zygotes, forms balance of middle disintegrated microstates & middle integrated microstates of eukaryotic cells in open thermodynamic system reflecting balance catabolic exergonic processes & anabolic endergonic processes in normal Stationary State of an open thermodynamic system of an organism via minimization gain of fluctuating middle index Entropy according Prigogine theorem and Boltzmann theory [6,18,19,27,28]. Besides the whole processes of transiting Meiosis into Mitosis are directed by flow energy which was received from male's and female's energy of DNA molecular bonds as inheritant energy from parents. Also there are received mother's stem cells energy and the Surroundings foods' energy through mother's organism which organized Embryonic stem cells preserve molecular bond's energy for building different organ's tissues via sequence stem cells [Basic stem cells → Totipotent stem cells → Pluripotent stem cells → Multipotent stem cells → Oligopotent stem cells → Unipotent stem cells → type cells] because of breaking up energy into many parts for making multicellular organ for storing energy how Basic Internal Energy into Basic stem cells [neurons] in brain. Thus the obtained inherited energy both from parents and supplementary energy from mother's placenta stem cells exert driving mechanism of advance development single cell → germ → Zygote → Embryo through minimization fluctuating middle gain Entropy according Prigogine theorem due to balance of middle disintegrated microstates & middle integrated microstates of thermodynamic system, according Boltzmann theory which lead to balance catabolic exergonic processes & anabolic endergonic processes in normal Stationary State of thermodynamic system of an organism. The mechanisms forming multicellular organ occur due to different chemical potential between Embryonic cells and Environment ($\mu_{cell} \neq \mu_{environment}$) via forming Foetus showing "absent contact inhibition of cell propagation" by using Theorell equation. Foetus at the end of 9 months pregnancy and baby at first moment after birth have similar characteristic of thermodynamic system according Glansdorff and Prigogine theory, reflecting interactions between force energy and flow energy: $\sum J_k dX_k/dt = 0$ and $\sum X_k dJ_k/dt = 0$ [J – Flow, X – Force, t – Time]. Also Foetus at the end of 9 months pregnancy and Baby at first moment after birth obtain 100% Basic Internal Energy from their parents which is preserved in Basic stem cells [neurons] in brain of Central Nervous System. Then the organism of born baby after opening lungs' respiration begins to maintain stability Internal Energy of its open thermodynamic system of an organism due to appearance catabolic aerobic exergonic processes [aer$\sum X_k dJ_k/d_t$]. Catabolic aerobic exergonic processes [aer$\sum X_k dJ_k/d_t$] induce expression catabolic anaerobic exergonic processes [anaer$\sum X_k dJ_k/d_t$] causing balance catabolic aerobic exergonic processes & catabolic anaerobc exergonic processes, i.e. balance aer$\sum$XkdJk/dt & anaer$\sum X_k dJ_k/d_t$ [5, 13, 14, 26, 27]. Balance catabolic aerobic exergonic processes & catabolic anaerobc exergonic processes exert balance catabolic anaerobic exergonic processes & anabolic anaerobic endergonic processes, i.e. balance $\sum X_k dJ_k/d_t$ & $\sum J_k dX_k/d_t$, which is subjected to HIF exertion of cellular cycle [7, 8, 14, 23]. Thus haploid distribution chromatids in chromosomes via Meiosis I [Prophase I, Metaphase I, Anaphase I, Telophase I] and Meiosis II [Prophase II, Metaphase II, Anaphase II, Telophase II] reflects many microstates due to great distribution energy. However diploid distribution chromatids in chromosomes via Mitosis [Prophase, Prometaphase, Metaphase, Anaphase, Telophase] reflects decreased microstates due to considerably distribution its energy. Hence haploid division causes some increased Entropy being subjected to greater cells' apoptosis, and diploid divission causes decreased Entropy being subjected to considerably lesser cells' apoptosis, corresponding to Boltzmann equation. Also just diploid cellular division in Mitosis phases cellular cycle lead to minimization gain fluctuations of Entropy during life of an

eukaryotic open thermodynamic system of an organism's cells causig maintenance stability Internal Energyof cells' thermodynamic system of according Prigogine theorem. Just driving mechanisms of maintenance stability Internal Energy of basophilic chemical potential of cytoplasms ($\mu_{cytopl.}$) of all cells induce stability Internal Energy as stability chemical potential of an organisn (μ_{org}) [7, 8, 14, 23] (Figure 4 and Figure 5). Moreover it is formed three levels of biochemical mechanism regulation stability Internal Energy and Internal Medium of Stationary State an organism as open non equilibrium thermodynamic system of an organism [1,2,3,4,27,28] (Figure 2). Just thermodynamic mechanism maintenance stability open non equilibrium thermodynamic system via minimization gain fluctuation Entropy was proved by famous Prigogine theorem [5]. Besides open non equilibrium thermodynamic system of an organism is characterized also as non linear pathway of its development according to Glansdorff and Prigogine theory [5, 6]. Hence there are the two mechanisms of maintenance stability o an open non equilibrium non linear thermodynamic system of an organism: cellular mechanism and biochemical mechanism [1]. The duration of life an open non equilibrium non linear thermodynamic system of an organism depends on the store of Basic Internal Energy in Basic stem cells (neurons) [6].

Driving Mechanisms of Differences Cellular Cycles in Different Tissues of Different Organs in An Organism from The Point of View of Thermodynamics, Biophysics and Biochemistry

The embryogenesis is subjected to the inherited genomic of development single sex cell's DNA which determines forming as different organes of an organism containing different tissues with different cells' properties [27,28]. Also these different cells' properties have differed cellular cycles activity. However driving mechanisms of differed cellular cycles activity subjected to thermodynamic laws as well as to influences thermodynamic mechanisms of an open non equilbrium non linear thermodynamic system of an organism. Just the genes encode proteins synthesis, named cyclins, and cyclin-dependent kinases (CDKs) which support exertion of advance cellular cycles of different tissues' cells types determining different cells' division cycles, e.g. supporting by cdc 20 or cdc 25 [29-33]. The inherited from parents Basic Internal Energy is the driving mechanism of all cells' cellular cycles which causes building mechanisms of all chemical processes in cellular cycles. Thus, the neurons (as Basic stem cells) share Basic Internal Energy between cells of different tissues through stem cells in following sequence [7,27,28]:

1. Basic stem cells (neurons) keep inherited from parents Basic Internal Energy (E_{basic}) and share this energy through sequence: Basic stem cells → Totipotent stem cells → Pluripotent stem cells → Multipotent stem cells → Oligopotent stem cells → Unipotent stem cells → Type cells. Basic stem cells (neurons) carry out role of driving mechanisms of cells' cellular cycles for building mechanisms of all chemical processes in cellular cycles creating by Basic Internal Energy. Besides Basic stem cells (neurons) create human mental works [Feelings, Memory, Mentality, Thought and so on] due to Basic Internal Energy inducing intracellular chemical potentials (μ_{neuron}) of neurons which interact with all cells and tissues of an organism and also with Environment through resonance waves of cells-neurons' cellular capacitors as well as via connections between both an organism's chemical potential (μ_{org}), neurons' chemical potentials (μ_{neuron}) and all tissues' chemical potentials (μ_{tissue}) of an organism causing nerve electro impulse through nerve fiber and nerve receptors [7,27,28].

2. Totipotent stem cells' is shared obtained energy as for their cellular cycle as well as provide all further stem cells of all tissues with energy exerting all phases of celluler cycles, i.e. these stem cells can build an organism. Also Totipotent stem cells' energy support intracellular maintenance stability Internal Energy of cytoplasms' basophilic chemical potentials ($\mu_{cytopl.}$) causing interactions between intracellular mediums (inner cell) and extracellular mediums (outer cell) of common balances anabolic endergonic anaerobic processes & catabolic exergonic anaerobic processes of oxidative phosphorilation & catabolic exergonic aerobic processes of oxidative respiration which mechanisms exert stability Internal Energy of an organism via organism's chemical potantial (μ_{org}) of mechanisms supporting by HIF-1α activity and interactions between cells and on organism causing by resonance waves of cellular capacitors operations [23, 29 – 33] (Figure 4 and Figure 5).

3. Pluripotent stem cells' energy is shared as for their cellular cycle as well as provide with energy certain family cells' cellular cycles, e.g. connective tissues cells, muscle tissues cells, eye's tissues cells, ear's tissues cells, blood different cells and so on, exerting cellular cycle for development further sequence stem cells till their type cells. Inducing by Pluripotent stem cells' energy, the cells' cellular cycles of each tissue have different frequency cells' cellular cycles of some tissue from frequency cells' cellular cycles of the other tissue due to different cells' division cycles supporting by different cyclin-dependent kinases (CDKs), e.g. cdc 20 or cdc 25 or inducing by different cells growth factors (EGF, IGF, TGF etc) [29-33]. For example, epithelial cells proliferation frequency due to their cellular cycles are differed than intestinal cells proliferation frequency due to their cellular cycles or than trombocytal cells proliferation due to their cellular cycles and so on. Pluripotent stem cells' energy stabilize cells' Internal Energy of cytoplasms' basophilic chemical potentials ($\mu_{cytopl.}$) of intracellular medium via interactions between intracellular mediums and extracellular mediums in hypoxic condition promoting by HIF-1α activity. Just the interactions between intracellular mediums and extracellular mediums cause interactions between intracellular balance anabolic endergonic anaerobic processes & catabolic exergonic anaerobic processes of oxidative phosphorilation and extracellular balance anabolic endergonic anaerobic processes & catabolic exergonic anaerobic processes of oxidative phosphorilation which induce balance intracellular chemical potential ($\mu_{intracel}$) & extracellular chemical potential ($\mu_{extracel}$) causing cytoplasms' basophilic chemical potentials ($\mu_{cytopl.}$) and mutual influences between cells' chemical potentials (μ_{cell}) and theirs tissues chemical potentials (μ_{tissue}) as cells' extracellular mediums ($\mu_{extracell}$).

4. Multipotent stem cells' energy is shared for their cellular cycle as well as provide with special energy of spacial cells' cellular cycles in organs of an organism: cells of hormonal organs [thyroid gland, hypophysis, pancreas insulin production cells, suprarenal glands' cells and so on], digestive glands of stomach and of other gland digestive system, immuno systems T- cells and B-cells. Thus Multipotent stem cells' energy is shared as for its carrying out activities as well as defensive immune role of an organism aganist strange agents due to resonance waves causing by cellular capacitors of T-cell and B-cells that leads to regulation of T cells functions via T memory, T helper and T killer because of interactions between proteins like CTLA-4, PD-1 and CD-28, CD-80 (B-7-1), CD-86 (B-7-2) [7]. Besides Multipotent stem cells' energy exerts enzymatic mechanisms of metabolic biochemical processes as well as Hormonal mechanisms regulation of cells activities in metabolic processes via influence on cellular capacitors of cells' wall.

5. Oligopotent stem cells' energy is shared as for their cellular cycle as well as into only a few cell types, such as either lymphoid stem cells or myeloid stem cells or epidermal stem cells and so

on. Thus Oligopotent stem cells' energy is shared in mechanisms certain stem cells' resonance waves of their cellular capacitors operation for exerting works of different functions as in different tissues as well as in different organs of an organism which cause maintenace stability Internal Energy of different organs' different cells of different tissues via balane anabolic endergonic anaerobic processes & catabolic exergonic anaerobic processes causing by HIFα activity [23-26].

6. Unipotent stem cells' energy is shared as for their cellular cycle as well as only one cell type, their own, but have the property of self-renewal, which distinguishes them from non-stem cells (e.g. progenitor cells, which cannot self-renew). Thus Unipotent stem cells preserve expenditure energy in activity type cells for more efficient cells operation in maintenance stability Internal Energy of an organism.

7. Type cells use obtained energy as for their cellular cycle as well as for their destination causing maintenance stability Internal Energy and Internal Medium of an open non equilibrium non linear thermodynamic system of an organism [1,2,7,23,24].

Driving Mechanisms Cellular Cycles Causing Defensive Immune Mechanisms, Autoimmune Mechanisms and Autophagy Promoting Maintenance Stability Internal Energy From the Point of View of Thermodynamics, Biophysics and Biochemistry in Norm

Autophagy, autoimmune mechanism and humoral immune mechanisms with cellular immune mechanisms generating by reticulo-endothelial system (RES) are supplementary mechanisms maintenance stability Stationary State of an organism [6,33]. All cells of an organism are advanced through aging processes which leads to cell death due to increased apoptotic processes via expending Basic Internal Energy (E_{bas}) through sequence Basic stem cells (neurons) → Totipotent stem cells → Pluripotent stem cells → Multipotent stem cells → Oligopotent stem cells → Unipotent stem cells → and then type cells [2, 7, 8].

Autophagy is the process causing the bulk degradation cytoplasmic components of dead cells which are enclosed by double-membrane structures known as autophagosomes which are subjected to delivery them to lysosomes due to operation resonance waves of macrophages' cellular capacitors with lysosomes' capacitors on autophagosome substances corresponding to the Schroedinger equation of the method of the molecular orbitals – a linear combination of atomic orbitals (MO LCAO) [5, 7, 8]. Thus Lisosomes' enzymes lyse the autophagosomes of dead cells and release a lot of decomposing proteins named autophagy-defective mutants (apg) [6,34-38]. Decomposed substances were subjected to metabolic processes resulting in H_2O, CO_2 and the other waste products which should be excreted from an organism's tissues by autophagy cells (macrophages, monocytes) into blood and then excreted into Environment (Figure 1). But the some proteins named autophagy-defective mutants (apg) remain in cells-macrophages and in blood as the Products of Autophagy. These proteins are conjugated to one anothers in processes degradations due to Lysosome enzyme operation causing Apg5/Apg12 conjugations [6]. Then Apg16 protein is added forming Apg12p–Apg5p–Apg16p conjugations [7, 8, 34 – 38]. Also these cytoplasmic components react with waste products of Autophagy including into Apg12p–Apg5p–Apg16p conjugations of 350-KDa Complex (5). Apg7 is a ubiquitin-E1-like enzyme which takes part in Autophagy [7, 8, 34 - 38]. Besides Apg12p-Apg5p conjugation reaction is mediated by Apg7p, a ubiquitin activating ubiquitin-E1-like enzyme, and Apg10p, suggesting that it is a ubiquitination-like system [6,34-38]. Ubiquitination is the well known modification system, which is involved in selective protein degradation, endocytosis, etc [6]. Considering termination of each cell's life via Apoptosis and Autophagy, clearance from degradation components, are indispensable processes for maintenance stability Internal Energy and Internal Medium of an organism. Just insufficient processes of Autophagy leads to heavy diseases due to violation local mechanism or whole mechanism maintenance stability Internal Energy and Internal Medium of tissues or of an organism [39,40]. Therefore there are suggested to exert Autophagy in treating some diseases [39]. Besides there were appeared some microRNAs as fragments of dead cells' nuclear genomes [41-45] which can contain as nuclear fragments of normal dead cells as well as dead cells' nuclear fragments affected with pathologic genome, e.g. microRNAs with v-oncogene strands. Also decomposed dead cells release a lot of microRNAs, thereby creating DNA-MicroRNA Complex which should be excreted into the Environment [6] (Figure 1). All of these microRNAs regulate the function of target genes at the post-transcriptional phase due to reaction resonance waves of autophagy cells' cellular capacitors on waves function of these microRNAs molecules corresponding to the Schroedinger equation of the method of the molecular orbitals – a linear combination of atomic orbitals (MO LCAO) [18]. Besides forming DNA-MicroRNA Complex create cell reprogramming of the generation induced pluripotent stem cell (iPSC) [7, 41 – 45]. Just the lives of able-bodied cells and pathologic cells lead to Apoptosis both normal dead cells and pathologic dead cells. All dead cells should be destroyed and eliminated from tissues by cells of autophagy operation. Therefore there are arisen the autophagy as links which make clearance Internal Energy (temperature 36,4°C – 36,9°C by which all enzymes operate etc.) and Internal Medium (stable concentration substances in blood and neurolymph) of an organism from dead cells and their waste substances. The balance forming autophagy products & clearance autophagy products causes balance pro-apoptotic factors [BCL-2 family proteins] & anti-apoptotic factors [BH3, BAX, BAK, BOK], which are the links of supplement mechanism maintenance stability Internal Energy (U) of an organism as Internal Works (W_{int}) according first law of thermodynamics [40,41,1]. Also there are occurred reverse reactions: DNA-MicroRNA Complices → induced pluripotent stem cells (iPSCs) [7, 46 – 50]. These reverse reactions transit into normal right regulative developments inducing pluripotent stem cells [iPSC] which substitute Unipotent stem cells: Basic stem cells (neurons) → Totipotent stem cells → Pluripotent stem cells → Multipatent stem cells → Oligopotent stem cells → induced pluripotent stem cells (iPSCs)[DNA-MicroRNA Complex] → type cells. Then the conjugations DNA-MicroRNA Complices are broken up into DNA and MicroRNAs. Both DNA and MicroRNAs are subjected to metabolic disintegrations [6]. Further type cells in wound are developed by delivering energy through sequence of stem cells via Basic stem cells → Totipotent stem cells → Pluripotent stem cells → Multipotent stem cells → Oligopotent stem cells → Unipotent stem cells → type cells exerting proliferative processes via cellular cycle. On the other hand, an organism resists environmental influences causing maintenance stability Internal Energy (U) of an organism via External Works (W_{ext}) of an organism [3,4,51]. Penetration of strange high-molecular substance from Environment into an organism creates local change of chemical potential (μ) which exert the stimulation, via resonance waves of T cells capacitors, biosynthesis immunoglobulins in G1 phase cellular cycle of B leucocytes [B cells] producing immune antibodies. Humoral immune complements are proteins, which are synthesized in considerable quantity by hepatocytes and are produced also in

fewer quantities by blood macrophages, blood monocytes, some epithelial cells. Complements activate as humoral immune reactions of antibodies creating esterase property with also proteolytic properties as well as exerting cellular immune reactions of phagocytosis. Thus antibodies bind antigens, and complements' both esterase and protease enzymes lyse antigens in humoral immune processes. Also an organism's local change of chemical potential (μ) promotes remote reactions across distance of phagocytes' [macrophages, monocytes etc.] cellular capacitors via resonance waves on common molecular wave of strange high-molecular substance, due to the wave function of any molecule which is determined as the total wave functions of the nuclear orbitals, according to Schroedinger equation of linear combination of atomic orbitals (MO LCAO) [5, 33, 51]. The forming resonance waves cause attraction the immune cells to strange high-molecular substance and create the contact reaction of decomposing the high-molecular substance of the strange objects, ruining bacteria and other strange cells. Just biophysical mechanism of immune cells remote reactions transit into contact biochemical immune reactions for decomposition of the strange oblect [33]. These defensive mechanisms of humoral immune reactions and cellular immune reactions are defensive links of Internal Works (W_{int}) of an organism which are realized by biochemical and biophysical mechanisms maintenance stability Internal Energy (U) of an organism. The environmental influences on an organism's processes fluctuate from positive influences how e.g. inducing production of some Vitamins [Vitamin D etc.] to negative influences causing some allergens. Just development of both an organism and cells of an organism through aging processes are subjected to under the permanent influences of various environmental allergens. The negative influences, causing by some allergens, damage the respiratory link of electron transport chain [one from five Complexes] of local tissue's cells causing either violation local tissue's respiratory function or general violation respiratory function of an organism. Violation of organism's general respiratory function causes violation of lung tissue's cells respiratory function inducing violation common catabolic aerobic oxidative processes of an organism [13,14]. Violation of local tissue's respiratory function causes allergic reactions via weak local inflammations because of forming local tissue disbalance of catabolic aerobic processes & catabolic anaerobic processes due to excessive catabolic aerobic processes that causes rhinitis, pharyngitis etc. The violation of lung tissue's cells respiratory function with violation of common catabolic aerobic oxidative processes of an organism causes common pathologic processes, e.g. bronchial asthma. The environmental allergens react with some respiratory link of electron transport chain of local tissue's cells forming strange autoantigens of IgE. The cells of reticulo-endothelial system (RES), both T cells and B cells take part in humoral immune processes due to production immune antibodies by B cells and immune cellular reactions by T cells. The activation immune cellular reactions by T cells occur by immunoglobulins CTLA-4 and PD-1 exerting processes nuclear DNAs transcription and translation of biosynthesis immunoglobulins in G1 phase cellular cycle due to cellular capacitors' resonance waves reactions on autoantigen IgE substances' strange molecular waves, according to Schroedinger equation of linear combination of atomic orbitals (MO LCAO) [5]. Thus autoantigen IgE substances' strange molecular waves are subjected to influences by resonance waves of T cells' cellular capacitors, which realize autoimmune defensive reactions [8, 33, 51]. Just the mechanism of autoimmune reactions are realized by T lymphocytes [T cells] which are regulated by productions opposed mechanisms either producing immunoglobulins CTLA-4 and PD-1 for activation T cells operation or producing immunoglobulins CD-28, CD-80 (B-7-1), CD-86 (B-7-2) for desactivation T cells operation [52-61]. T cells are formed by thymocytes of RES in thymus and carry out various immune functions like: T helper cells stimulate autoimmune reactions of some immune cells [T lymphocytes and B lymphocytes] influencing by resonance waves of variable cellular capacitors located in the cells' walls and in their receptors. T killer cells, being exerted by T helper via their resonance waves of cellular capacitors, destroy some autoantigens of IgE (including some viral antigens coupled with autoantigens) via producing proteases and esterase enzymes [8, 42-44]. T memory cells learn and remember to encounter antigens and via their resonance waves of cellular capacitors exerting T helper cells through interactions between relative resonance waves of T memory cells and resonance waves of T helper cells [7]. So, defensive autoimmune reactions caused by alarm exerting T cells and B cells promote production the immunoglobulins CTLA-4 and PD-1. The production the immunoglobulins CD-28, CD-80 (B-7-1), CD-86 (B-7-2) by RES cause suppression function all T cells in norm. Thus fluctuating balance of these immunoglobulins maintains stablity Stationary State of an organism in norm.

Role of Basic Internal Energy in Influences of Driving Mechanisms Cellular Cycle on Both Cells Development and an Organism Development

Considering the role of Basic Internal Energy in development of both cells and an organism, it should be appreciated the role of Glansdorff and Prigogine theory in explanation development of an open non linear non equilibrium thermodynamic system of human organism (2). Taking into account Prigogine theorem corresponding to minimization of gain entropy as mechanism maintenance stability an open thermodynamic system of an organism, Glansdorff and Prigogine theory has expanded minimum production entropy into non linear field causing minimization of gain entropy for stability Stationary State of an organism [2, 5, 7, 8, 27, 28]. They divided local production Enropy into two data which reflects stability in non linear development open thermodynamic system of a human organism via such formula:

$d\beta / dt = d/dt (\sum J_k X_k) = \sum J_k dX_k/dt + \sum X_k dJ_k/dt$ [β – Entropy, t – time, X – Force, J - Stream]

The stability system shows following formula: $d\beta/dt = \sum dJ_k dX_k/dt = d_x\beta/dt$, if $dJ_k/dt = 0$; Hence stability thermodynamic system defines Force (X).

Thus the minimization gain entropy shows: $d_x\beta/dt \leq 0$, i.e. negative fluctuation entropy. It is meant that it is far away from equilibrium of open thermodynamic system although the sign of equality defines Stationary State thermodynamic system of an organism.

Just state stability Stationary State is arisen so: If $d_x\beta = \sum dJ_k dX_k / dt > 0$ [If $dJ_k/dt = 0$], it corresponds to positive fluctuations entropy ($+\Delta x\beta$). However the positive fluctuations entropy ($d_x\beta > 0$) are fast disappeared in such situation of Stationary States thermodynamic system due to principle the minimization gain entropy in Stationary State. Thermodynamic system must return to initial state. But there arise negative fluctuations enropy ($d_x\beta < 0$) ($-\Delta_x\beta$) which transits thermodynamic system into new Stationary State of decreased entropy $\Delta S_x < 0$ (ΔS_x is the gain entropy) (Figure 7). Thus Glansdorff and Prigogine theory explains mechanism development of a human organism during its life as open non equilibrim non linear themodynamic system. 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 G_0/G_1/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 fluctuation entropy ($\Delta S_x < 0$), i.e. minimization gain entropy according Prigogine theorem. Thus $\sum dJ_k dX_k/dt$ is meant exchanged such manifestations entropy in following modes: manifestation Force which is meant manifestation anabolic endergonic processes $\sum J_k dX_k/dt$, then manifestation Stream which is meant manifestation catabolic exergonic processes $\sum X_k dJ_k/dt$ [2,5,27,28].

For example, there are development an organism through its aging: Foetus at the end of 9 months pregnancy and baby at first moment after birth have similar equations: $\sum J_k dX_k/dt = 0$ and $\sum X_k dJ_k/dt = 0$. Therefore foetus at the end of 9 months pregnancy and baby at first moment after birth have 100% basic energy obtained from their parents which is condensed in Basic Internal Energy being situated in neurons named Basic stem cells. Then the organism of born baby after opening lungs' respiration begins to maintain stability Internal Energy of its open thermodynamic system due to appearance catabolic aerobic exergonic processes [aer$\sum X_k dJ_k/dt$]. Catabolic aerobic exergonic processes [aer$\sum X_k dJ_k/dt$] induce expression catabolic anaerobic exergonic processes [anaer$\sum X_k dJ_k/dt$] causing balance catabolic aerobic exergonic processes & catabolic anaerobc exergonic processes, i.e. balance [aer$\sum X_k dJ_k/dt$] & [anaer$\sum X_k dJ_k/dt$] [6, 7]. Balance catabolic aerobic exergonic processes & catabolic anaerobc exergonic processes exert balance catabolic exergonic processes & anabolic endergonic processes, i.e. balance [$\sum X_k dJ_k/dt$] & [$\sum J_k dX_k/dt$] [2, 3, 14]. Thus it is formed three levels of mechanisms regulation stability Internal Energy and Internal Medium of an open non equilibrium thermodynamic system as Stationary State an organism [2, 3, 4, 6, 7] (Figure 2). Just thermodynamic mechanism maintenance stability an open non equilibrium thermodynamic system of an organism via minimization gain Entropy was proved by famous Prigogine theorem [2, 7, 8]. But an open non equilibrium thermodynamic system of an organism is characterized also as non linear pathway of its development according to Glansdorff and Prigogine theory. The development an open non equilibrium non linear thermodynamic system of an organism depends on the store of Basic Internal Energy which is situated in Basic stem cells (neurons). On the one hand, the Basic stem cells, as the store of energy, provide with energy as specific differentiations of the next generations stem cells till type cells as well as the proliferation of all cells which operate in different tissues of an organism being derived from stem cells. There are the specific differentiations of the stem cells:

1. Basic stem cells are cells which store Basic Internal Energy (U_{basic}) [$d\beta/dt = \sum dJ_k dX_k$ /dt (100% energy)] which is expended during life of an organism causing lifetime of an organism and maintaining stability Internal Energy of an organism as Highest level regulation [3,4] (Figure 2).
2. Totipotent (or omnipotent) stem cells [$d\beta/dt = \sum dJ_k dX_k$ /dt (100% energy)] can differentiate into embryonic and extraembryonic cell types. Such cells can construct a complete viable organism. These cells are produced from the fusion of an egg and sperm cell. Cells produced by the first few divisions of the fertilized egg are also totipotent [27,28].
3. Pluripotent stem cells are the descendants of totipotent cells and can differentiate into nearly all cells, i.e. cells derived from any of the three germ layers with common balance catabolic aerobic exergonic processes [aer$\sum X_k dJ_k/dt$] & catabolic anaerobc exergonic processes [anaer$\sum$XkdJk/dt] & anabolic endergonic processes [$\sum J_k dX_k/dt$] [27, 28].
4.Multipotent stem cells can differentiate into a number of cell types, but only those of a closely related family of cells, each of them has common balance catabolic aerobic exergonic processes [aer$\sum X_k dJ_k/dt$] & catabolic anaerobc exergonic processes [anaer$\sum X_k dJ_k/dt$] & anabolic endergonic processes [$\sum J_k dX_k/dt$] [27,28].
5. Oligopotent stem cells can differentiate into only a few cell types, such as lymphoid or myeloid stem cells each of them has common balance catabolic aerobic exergonic processes [aer$\sum X_k dJ_k/dt$] & catabolic anaerobc exergonic processes [anaer$\sum X_k dJ_k/dt$] & anabolic endergonic processes [$\sum J_k dX_k/dt$] [27,28].
6. Unipotent cells can produce only one cell type, their own, but have the property of self-renewal, which distinguish them from non-stem cells (e.g. progenitor cells, which cannot self-renew) each of them has common balance catabolic aerobic exergonic processes [aer$\sum X_k dJ_k/dt$] & catabolic anaerobc exergonic processes [anaer$\sum X_k dJ_k/dt$] & anabolic endergonic processes [$\sum J_k dX_k/dt$] [27, 28].

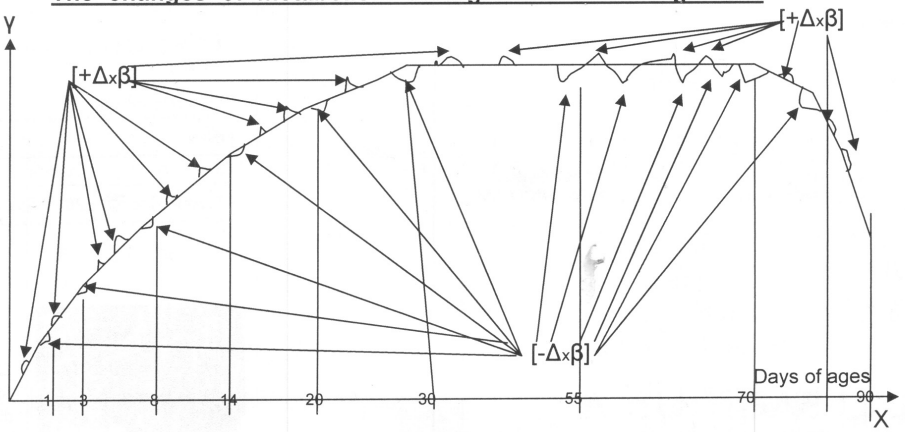
Also the Type cells of each tissue in each organ have common balance catabolic aerobic exergonic processes [aer$\sum X_k dJ_k/dt$] & catabolic anaerobc exergonic processes [anaer$\sum X_k dJ_k/dt$] & anabolic endergonic processes [$\sum J_k dX_k/dt$].

Parental inherited Basic Internal Energy (U_{basic}) store energy in Basic stem cells [neurons] for development an organism during its life. Also Basic Internal Energy (U_{basic}) realizes Central nervous system's Highest level regulation mechanism maintenance stability Internal Energy of an organism via expending stored electric energy and stimulating both High level regulation and Low level regulation of mechanisms maintenance stability Internal Energy of an organism [3,4] (Figure 2). The metabolic biochemical processes in each tissue form extracellular chemical potential ($\mu_{extracell}$) which induce charges on external cellular membranes of tissue's cells walls. Internal cellular membranes of these cells' walls are charged via inducing by cytoplasmic basophilic chemical potentials ($\mu_{cytoplsm}$) via staining cells. Thus there are formed cellular capacitors of tissues' cells which relative resonance waves with tissue chemical potentials determine mechanisms maintenance stability Internal Energy of tissue. Just cytoplasmic basophilic chemical potentials of Central nervous System's cells (neurons) also named Basic stem cells form electric charges on cellular inner membranes of neurons. Central nervous system's neurons are bound through nerve fibers with neurotransmitter of receptors in each tissue. Thus neurotransmitter of receptors present cytoplasmic chemical potentials of neurons (μ_{neuron}), and special tissue cells' membrane receptors are charged being induced by neurotransmitter receptors' chemical potentials. Just there are such special tissue cells' membrane receptor proteins being induced by such neurotransmitter receptors: heat-sensitive membrane, photo-sensitive membrane, osmo-sensitive membrane, mechano-sesitive membrane, chemo-sensitive membrane, pain-sensitive membrane. Mutual influences between three activities as relative resonance waves of cellular capacitors tissue's cells, neurotransmitter receptors' charges with various sensitive membranes and tissue's chemical potential determine mechanism maintenance stability Internal Energy of tissues [e.g. skin, connective tissue, muscular tissue, neuroglia etc (Figure 1). Besides the charged nervotransmitter receptors of Basic stem cells (neurons) transmit energy of electric charge sharing it through the sequence of the other pluripotent stem cells and then to various type cells. Basic stem cells supply next generations of stem cells with energy of Basic Internal Energy (E_{basic}) which expends this energy during life of an organism (Figure 7). Moreover Basic stem cells (neurons) retain Basic Internal Energy (E_{basic}) in genes of their chromosomes displaying specific human capabilities, i.e. memory, musical talents, artistic talents, mathematical talets, scientific talents, constructor talents and the other gifts. These parts of Basic internal Energy (E_{basic}) are inherited capabilities from mother's and father's chromosomes. Also Basic stem cells (neurons) are divided very rarely as

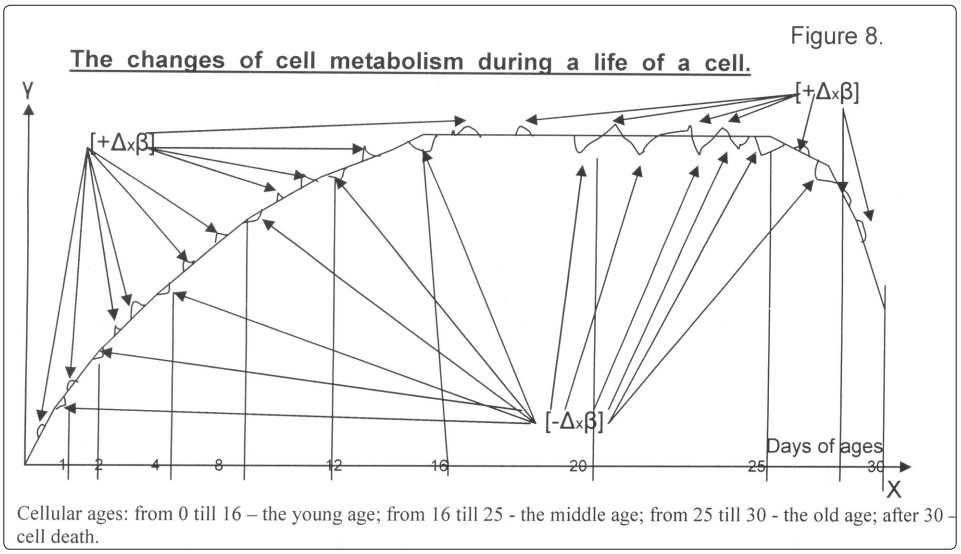
compared with the other stem cells due to defining aging of an organism. Basic stem cells expend the stored energy as for development of an aging organism as well as for development of all cells considering terms of each cell's life, i.e. driving mechanisms cellular cycle, apoptosis, autophagy etc. The other stem cells expend their energy for advance cellular cycles of type cells of various tissues [1, 2, 6, 7, 8, 27, 28]. Just the ageing processes during life of an organism expend some Basic Internal Energy (E_{basic}) from Basic stem cells exerting cellular internal Works ($W_{int\ cell}$) via expression some cellular metabolic processes with inflow and outflow (excretion) substances and energy in order to maintenance stability cellular Internal Energy as stable basophilic cytoplasm's chemical potentials via staining cells as well as stable Internal Energy of an organism (Figure 7). Besides the Basic stem cells, as the store energy of Basic Internal Energy, are some replenished with the energy by inflow energy with food products through gastrointestinal tract (Figure 1). However the replenishing energy of the Basic stem cells occurs in different ages of an organism differently, reflecting aging of an organism. Totipotent (or omnipotent) stem cells are the next step differentiation of stem cells after Basic stem cells. Totipotent (or omnipotent) stem cells induce initial development all cells of an organism. Also Totipotent (or omnipotent) stem cells are divided considerably rarer than next stem cells. Next sequence differentiated generations of stem cells are Pluripotent stem cells, Multipotent stem cells, Oligopotent stem cells and the last Unipotent stem cells which cells operate differently in different tissues of organs bringing differentiations of Unipotent stem cells nearer to differentiations of type cells certain tissues of an organism. Thus growth of an organism requires supplementary energy for Internal Works ($W_{int\ org}$) and External Works ($W_{ext\ org}$) for maintenance stability Internal Energy of an organism (temperature 36,4°C – 36,8°C by which all enzymes operate and the other indices) [1]. The Internal Works of an organism ($W_{int\ org}$) exert heart's cells works, lung's cells works and works of the cells of other organs and tissues. The driving mechanisms of cells' cellular cycles in different organs are the driving mechanisms of Internal Works of all organs and tissue of an organism ($W_{int\ org}$) which promote mechanism maintenance stability Internal Energy of an organism via normal metabolism of an organism forming as balance catabolic anaerobic exergonic processes & catabolic aerobic exergonic processes as well as balance catabolic exergonic processes & anabolic endergonic processes [13,14]. The External Work of an organism ($W_{ext\ org}$) resists harmful influences of Environment and also accepts useful energy and subtances from Environment. The Internal Works ($W_{int\ org}$) exerting the growth of an organism by spacific hormones was limited by driving mechanisms cellular genetic inheritance and depend on male or female inheritance. Just Glansdorff and Prigogine theory explains mechanism development of a human organism as open non equilibrim non linear themodynamic system from its birth to death, which Graphic shows changes positive fluctuation entropy ($+\Delta_x\beta$) into negative fluctuation entropy ($-\Delta_x\beta$) during life of an organism [2, 7, 27, 28] (Figure 7). However the ageing organism is depended on driving mechanisms of ageing all cells of an organism via driving mechanisms sharing energy through ageing of all stem cells and type cells. The genetical inherited energy into the genes bonds of the stem cells [Basic stem cells → Totipotent stem cells → Pluripotent stem cells → Multipotent stem cells → Oligopotent stem cells → Unipotent stem cells] sharing between type cells were limited for each cell causing increased expenditure energy and remaining decreased alive energy leading as to expression growth via positive fluctuation entropy ($+\Delta_x\beta$) in cellular young age, further as stop growth showing exchanges positive fluctuation entropy ($+\Delta_x\beta$) and negative fluctuation entropy ($-\Delta_x\beta$) in cellular middle age as well as decreased growth via negative fluctuation entropy ($-\Delta_x\beta$) in cellular old age that determine lifetime of each stem cell and each type cell [27,28] (Figure 8). Thus it is occurred the expenditure Basic Internal Energy (E_{basic}) of Basic stem cells (neurons) which is the store retention energy during life of an organism reflecting mechanism minimization of gain entropy for maintenance stability Internal Energy of an organism (temperature 36,4°C - 36,8°C by all enzymes operate and the others indices) according Prigogine theorem [2,18]. Thus the expenditure Basic Internal Energy (E_{basic}) via growth of an organism happens through born organism, then there appear babyhood from 0 to 1 year, childhood from 1 to 3 years, young age from 3 to 14 years, juvenile age from 14 to 18 – 20 years, middle age from 18 – 20 years to 30 years, full age from 30 years to 55 years, elderly age from 55 years to 70 years, old years after 70 years [2, 7, 27] (Figure 7). Thus develpment of an organism from born organism to old years is subjected to stored energy of Basic Internal Energy from Basic stem cells (neurons) expending for development driving mechanisms of cells' cellular cycles during life of an organism.

Figure 7.

The changes of metabolism during a life of an organism.



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.



Cellular ages: from 0 till 16 – the young age; from 16 till 25 - the middle age; from 25 till 30 - the old age; after 30 – cell death.

Driving Mechanisms of Cancer Cellular Cycle From the Point of View of Thermodynamics, Biophysics and Biochemistry

There are arised different viruses causing different diseases how influenza viruses, HIV virus, viral oncogens [v-oncogens] etc. [62]. The viral oncogens affect human cell's nuclear DNAs causing cellular DNA genome transmutation which exert viral accelerated cellular cycle in cancer cells' cellular cycle [7, 8,13,62]. Viruses have no own respiratory systems. Therefore viruses use the human cells' electron transport chain for its cellular oxidative processes. The cancer cells' DNAs been intruded by viral DNAs exert accelerating cancer cellular cycle resulting in increase of cancer cells' proliferative processes. However consumption energy for building new cells via cellular cycle are different by different viruses because different viruses obtain human Basic Internal Energy [molecular bonds energy] on different levels of an organism. For example, influenza viruses obtain energy of human Basic Internal Energy [molecular bonds energy] from Type cells being light separated by an organism, but v-oncogenes intrude in deep level human Basic Internal Energy [molecular bonds energy] of cellular genome, maybe on levels either Oligopotent stem cells or Unipotent stem cells or even Multipotent stem cells transmutating also mitochondrial oxidative processes of affected cells [6, 7, 8, 14 - 17]. The affected by viral DNA [v-oncogene], the human cells' DNAs are subjected to viral accelerated cellular cycle via forming cancer combined Meiosis-Mitosis phase of cancer accelerated cellular cycle which are arisen by shift balance anabolic anaerobic endergonic processes & catabolic anaerobic exergonic processes into the excessive anabolic anaerobic endergonic processes of increased biosynthesis of proteins in G_0 and G1 phases cellular cycles which cause abundance consumption energy and acetyl coenzyme A [Acetyl-CoA] leading to overloaded "nodal point of bifurcation anabolic and catabolic processes [NPBac]" because of insufficient energy and Acetyl-CoA and causing partial suppression catabolic anaerobic exergonic processes of Krebs tricarboxylic acid cycle [TCA] [13,14,20] (Figure 6). Just excessive quantity Lactic acids accumulate energy for excesive anabolic processes in cancer metabolism (Figure 6). The overloaded "nodal point of bifurcation anabolic and catabolic processes [NPBac]" because of insufficient energy and Acetyl-CoA and partial suppression catabolic anaerobic exergonic processes of Krebs tricarboxylic acid cycle [TCA] create obstacle for excretion from cancer cells of waste high-molecular substances as products of excessive anabolic biosynthetic processes. Therefore cancer cells via their resonance waves of cellular capacitors find healthy tissues without overloaded "nodal point of bifurcation anabolic and catabolic processes [NPBac]" and move due to remote reactions between cancer cells and this tissue causing attraction into these tissues forming metastases [11, 12, 19, 20] (Figure 6). The suppression catabolic anaerobic exergonic processes of Krebs tricarboxylic acid cycle [TCA] leads to shift balance catabolic anaerobic exergonic processes & catabolic aerobic exergonic oxidative processes into expression catabolic aerobic exergonic oxidative processes. Thus it forms both excessive anabolic anaerobic endergonic processes and expression catabolic aerobic exergonic oxidative processes. The excessive anabolic anaerobic endergonic processes and expression catabolic aerobic exergonic oxidative processes display Warburg effect mechanism of , aerobic glycolysis in cancer tissue" versus Pasteur effect of „incompatibility glycolysis and aerobic oxidation in healthy tissue" [12, 13, 19, 20] (Figure 9). Also excessive anabolic anaerobic endergonic processes are supported by expression excessive HIF-1α factors with excessive prolyl hydroxylases domains activity [PHD]. Then expression catabolic aerobic exergonic processes occur due to some inhibition HIF-1α by ubiquitination of excessive HIF activity causing by arisen excessive von Hippel-Lindau (VHL) protein in cancer tissues in which excessive FIH-1 takes part as jointed link in transition excession HIF-1α into expression VHL due to some inhibited HIF-1α in cancer driving mechanism [21,22]. Just further exerting accelerated cancer cellular cycle causes also Meiosis-Mitosis phases cancer cellular cycle by leading to shift complex balance anabolic anaerobic endergonic processes & catabolic anaerobic exergonic processes & catabolic aerobic exergonic processes into excessive anabolic anaerobic endergonic processes that results in shift balance inner chemical potential cells ($\mu_{inner\ cell}$) & outer chemical potential cells ($\mu_{outer\ cell}$) into excessive outer chemical potential cells ($\mu_{inner\ cell}$) causing inflow substances into cells corresponding to Theorell equation: $dn/dt = -UcA\ d\mu/dx$; (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). Thus it occurs the expression HIF-1a due to inhibition VHL leading to expression excessive anabolic endergonic processes through inflow substances from extracellular medium into cell inducing Karyokinesis and Cytokinesis of forming new cancer cells. Also it occurs excessive increased biosynthesis of proteins in G1 and G2 phases cellular cycle because of the shift balance anabolic endergonic processes & catabolic anaerobic

exergonic processes [Krebs tricarboxylic acid cycle (TCA)] into excessive anabolic endergonic processes causing partial suppression catabolic anaerobic exergonic processes [Krebs tricarboxylic acid cycle (TCA)] in G1 and G2 phases cancer cellular cycle which induce shift balance inner chemical potential cells ($\mu_{inner\ cell}$) & outer chemical potential cells ($\mu_{outer\ cell}$) into excessive inner chemical potential cells ($\mu_{inner\ cell}$) causing outflow enzymatic substances from cell into cancer tissue due to Theorell equation: $dn/dt = -UcA\ d\mu/dx$ in which interaction between VHL and HIF-1a causes mechanism of Warburg effect in such mode: The excessive anabolic endergonic processes and expression aerobic exergonic processes in complex balance anabolic endergonic processes & catabolic anaerobic exergonic processes & catabolic aerobic exergonic processes of cancer tissue metabolism display "Aerobic Glycolysis" of Warburg effect because anabolic endergonic processes and catabolic anaerobic exergonic processes are both derived from Glycolysis anaerobic reaction, and the fluctuating changed excessive anabolic anaerobic endergonic processes and expression catabolic aerobic exergonic oxidative processes exert driving mechanism of cancer cellular cycle into excessive proliferative processes in S, G2 phases and then transiting into combined Meiosis-Mitosis phase of cancer cellular cycle. The combined Meiosis-Mitosis phase of cancer cellular cycle occur via arisen anaerobic state, inducing by increased excessive Hypoxia-inducible factor 1 alpha (HIF-1α) with excessive prolyl hydroxylases domains activity [PHD], and suppression HIF-1α by von Hippel-Lindau (VHL) protein activity in Meiosis-Mitosis phase of cancer cellular cycle also causing Karyogenesis and Cytogenesis. Besides both the excessive increased biosynthesis proteins and the excessive proliferative processes are exerted by excessive quantity Free Radicals because partial suppression catabolic exergonic anaerobic processes of Krebs cycle (TCA) leads to prevailing excessive aerobic processes [12,13,14] (Figure 9). Moreover transmutation mitochondria causes excessive aerobic processes too [14,15-18] resulting in very great quantity superoxide [O*] because lack Hydrogen ions don't neutralize whole great quantity oxygen (O_2) due to stable respiratore index (RI) in an organism [$RI = CO_2 : O_2 = 0,8 – 1,0$]. The very great quantity superoxide [O*] form very great quantity ROS/H_2O_2/free radicals due to adding electron to surplus oxygen (O_2) which is produced by transformings NAD↔NADH and FAD↔$FADH_2$ in Electron Transport Chains of both Complex I and Complex II : $n[O_2] + n[e-] \rightarrow n[O_2*]$. Superoxide ($O_2^*$) induces complex ROS/$H_2O_2$/Free radicals [12,13]. Thus Free radicals intrude into nuclei DNA genomes of cancer cells exerting excessive proliferative processes due to realizing great quantity 2nDNA [14-18]:

$*OH + H_2$-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 process irrepressible DNA replication occurs in S phase cancer cellular cycle via accelerated cancer cellular cycle caused by cancer viral oncogenes with supported by excessive quantity Free Radicals due to mitochondrial transmutation [14,15] (Figure 9). Increased accelerated cancer cellular cycle leads to state of Resistance Apoptosis of cancer cells. Also excessive expression aerobic exergonic oxidative processes via transmutation of mitochondria induce expression the von Hippel-Lindau (VHL) propteins with inhibition HIF-1α via ubiquitination of excessive HIF activity causing irrepressible cancer cells' DNA replications in S, G2 phases cancer cellular cycle. Just it occurs shift complex balance anabolic anaerobic endergonic processes & catabolic anaerobic exergonic processes & catabolic aerobic exergonic processes into excessive catabolic aerobic exergonic processes leading 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 [12,13,19, 20] (Figure 6 and Figure 9).

Genetic Mechanisms of Cancer Cellular Cycle From The Points of Views of Thermodynamics, Biophysics and Biochemistry

Considering that all organisms, both prokaryotic and eukaryotic organisms, are subjected to thermodynamic laws, the genetic mechanisms cancer cellular cycle must be considered via comparison of difference between mechanism of viral haploid cellular cycle and human diploid cellular cycle which 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 due to complete increased Entropy which reflects complete increasing disorganization of thermodynamic system according Boltzmann formulation.

It is meant that, firstly, dissipating disintegrated microstates from macrostate thermodynamic system reflect break up of thermodynamic system via complete increased Entropy. Secondly, complete integrated microstates into macrostate thermodynamic system reflects 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 a human organism due to minimization gain of fluctuating middle characteristic Entropy according Prigogine theorem [3,4, 5,18]. Thus eukaryotic human cell shares diploid division cellular cycle in Mitosis phase of cellular cycle through 5 phases via Prophase → Prometaphase → Metaphase → Anaphase → Telophase 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 an eukaryotic human organism's cell. But haploid primitive 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 Meiosis I division. The new combinations of DNA is created during crossover which is 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 divisions 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. But meiotic haploid cells with half 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 flows energy and substances 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 initial viral prokaryotic cell because of also absent viral cells' electron transport chain for their cellular oxidative processes [6,7,18]. 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.

However cancer virus (how v-oncogene) affects the stem cells intruding in deep level Basic Internal Energy [molecular bonds energy] of cellular genome, maybe on levels either Unipotent stem cells or Oligopotent stem cells or even Multipotent stem cells showing sequence Basic stem cells → Totipotent stem cells → Pluripotent stem cells → Multipotent stem cells → cancer stem cells → cancerous type cells. Besides affecting by viral oncogenes the nuclear DNAs of some an organism's cells were subjected to viral accelerating cellular cycles which consume abundance energy from an organism for great anabolic processes in /G_0/ G1/S phases cancer cellular cycle exerting excessive proliferative processes of tumor growth (19). 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) [2]. Besides cancer cells use also electron transport chain of five Complexes and mitochondrial oxidative processes of an organism's cells that give cancer cell possibility form binding in genome for exerting Karyogenesis and Cytogenesis in cancer cellular cycle. The 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. Just 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. Therfore the some of these chromosomes are inherited viral haploid division via Meiosis, the other chromosomes are inherited human diploid division via Mitosis forming integrated Meiosis/Mitosis phase of cancer cellular cycle in which Meiosis phase comsume huge quantity energy for cancer accelerating cellular cycle and Mitosis phase comsume huge quantity energy for huge anabolic endergonic biosynthetic processes increased proliferative processes in cancer cellular cycle leading to sift balance anabolicic processes & catabolic processes into excessive anabolic processes [19]. Thus integrated Meiosis/Mitosis phase of cancer cellular cycle creates Apoptosis Resistance of cancer cells' property. The excessive anabolic endergonic processes in cancer tissue is formed by great oxidative phosphorilation processes of increased Glycolysis which make 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 [13,14,19] (Figure 6). Just excessive quantity Lactic acids accumulate abundance energy for huge anabolic endergonic processes of cancer metabolism in Warburg effect mechanism [19] (Figure 6). 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" [12,13] (Figure 9). Besides partial suppression catabolic exergonic anaerobic processes of TCA Krebs cycle leads to forming great 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 [15,16]. 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 6). 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 [12,19]. Thus cancer disease disseminates via metastases into an organism in order to absorb great quantity energy, especially from Basic Internal Energy. Besides cancer disease absorbs great quantity substances especially fat substances resulting in cachexia of an organism via exhausted also cellular energy via metastasis which are received as from Internal Works [W_{int}] and External Works [W_{ext}] of an organism as well as from Basic Internal Energy [12,19] (Figure 6 and Figure 9). 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. Furthermore viral accelerating cellular cycles of cancer cells occur because of prevailing absorption energy by viral genomic mechanism [Meiosis] over normal cellular facilitated process than Mitosis according Boltzmann theory 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 (see above): [Meiosis phase of haploid energy shares into Meiosis I which is shared into Prophase I, Metaphase I, Anaphase I, Telophase I then into Meiosis II which 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 normal sequence stem cells [Basic stem cells → Totipotent stem cells → Pluripotent stem cells → Multipotent stem cells → Oligopotent stem cells → Unipotent stem cells] than viral chromosomes. Therefore the initial absorbed energy goes 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 integrated Mitosis/Meiosis phase of cancer cellular cycle shows balance increased Entropy & decreased Entropy. However partial suppressed 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] versus moderate quantity production of Superoxide / Hydrogen peroxide /Free Radicals [O*/H_2O_2/*OH in healthy cells (see above). Great 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 [14-18]:

*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

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

Thus cancer cells‘ nuclear genomes increase quantity summarized haploid/diploid chromosomes and mitochondrial abundance quantty Free Radical causing supplementary mechanism of 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 causing Resistance Apoptosis 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.

Discussions Driving Mechanisms Cellular Cycle

Semenza et al. have noted (20,21,22) : It is not known what determines the battery of genes that are activated by HIF-1 in response to hypoxia in a given cell type and whether this response will lead to adaptation or apoptosis. Because HIF-1 activity is induced by hypoxia in all cell types, the interaction of HIF-1 with other proteins is likely to play a major role in determining its biological activity [21,22]. Because of the important role played by HIF-1 in cancer and ischemic cardiovascular disease of interacting proteins may also provide novel therapeutic targets [20,21,22].

Author’s explanation: Just fluctuating balance HIF-1 activity & HIF-1 suppresion is exerted by biophysical mechanisms of an open non equilibrium non linear thermodynamic system of a human organism which is subjected to thermodynamic laws [1,2]. According first law of thermodynamics, stability Internal Energy (U) of a human organism is supported by Internal Works (W_{int}) and External Works (W_{ext}) of an organisms which determine expenditure Energy (Q) in interactions between an organism and Environment [1,2] (Figure 1). Just these interactions between an organism and Environment display fluctuations hypoxic state and oxidative state in an organism causing fluctuating balance HIF-1 activity & HIF-1 suppresion which form mechanism maintenance stability common balance anabolic anaerobic endergonic processes & catabolic anaerobic exergonic processes & catabolic aerobic exergonic processes in norm causing minimization gain entropy according famous Prigogine theorem and Glansdorff and Prigogine theory in norm [5,11-19]. Besides the fluctuating balances HIF-1 activity & HIF-1 suppresion are depended on interactions between intracellular medium ($Cell_{inner}$) and extracellular medium ($Cell_{outer}$) causing stable balance of inner cellular balance catabolic processes & anabolic processes and outer cellular balance catabolic processes & anabolic processes which induce stable balance inner cellular chemical potential ($\mu_{c.uner}$) & outer cellular balance chemical potential ($\mu_{c.outer}$) determining stable Internal Energhy of a cell due to stable basophylic chemical potential of cytoplasm (μ_{cell}) in able-bodied cell [5,13,14,18,19].

Semenza et al. have noted [20,21,22]: From these results it was not clear whether HIF-1α protein overexpression was sufficient to activate target gene transcription in renal clear-cell-carcinoma [RCC] lines, whether other mutations in these cells eliminated the O_2-dependent negative regulation of HIF-1α transactivation, or whether VHL also regulated transactivation [20, 21,22].

Author’s explanation: Just the O_2-dependent negative influetion of HIF-1α transactivation due cells mutations into cancer cells occurs due to mitochondria transmutation causing cells affecting by v-oncogene which results in HIF-1α transactivation via supplementary VHL influences for target gene transcription in any cells‘ cancer mutation because transition of HIF-1α expression into VHL expression leads to expression oxidative processes causing increased Superoxids (O*) and ROS/H_2O_2/Free Radicals and increased replicative processes in nuclear DNA via realizing of 2nDNA reaction [15-18].

Semenza et al. have noted [20,21,22]: phosphatidylinositol-3-kinase (PI3K)/AKT/FRAP signaling stimulated by receptor tyrosine kinases such as HER2 induces HIF-1α protein expression by increasing its rate of synthesis rather than by decreasing its rate of degradation“ [20,21,22].

Author’s explanation: The phosphatidylinositol-3-kinase (PI3K)/AKT/FRAP kinases transfer phosphate group from 3-phosphatidylinostol of high energy side to low energy side, i.e. PI3K maintains stability balance intracellular chemical potential ($\mu_{inner\text{-}cell}$) & extracellular chemical potential ($\mu_{outer\text{-}cell}$) causing by fluctuations balance of inner cellular balance catabolic processes & anabolic processes and outer cellular balnce catabolic processes & anabolic processes [23,26]. Also AKT protein kinase, HER2 receptor tyrosine kinases, FRAP kinases and others kinases support phosphatidylinositol-3-kinase (PI3K) in its activity. Just fluctuating balance intracellular chemical potential ($\mu_{inner\text{-}cell}$) & extracellular chemical potential ($\mu_{outer\text{-}cell}$) determines interactions cells‘ chemical potentials (μcell) and an organism’s chemical potential (μ_{org}) as extracellular chemical potential ($\mu_{outer\text{-}cell}$) which promote interactions between cells‘ Internal Energy and organism’s Internal Energy causing by resonance waves of cellular capacitors as biophysical mechanism maintenance stability Statationary State of an organism in norm. Thus phosphatidylinositol-3-kinase (PI3K)/AKT/FRAP operations induce maintenance stability balance intracellular chemical potential ($\mu_{inner\text{-}cell}$) & extracellular chemical potential ($\mu_{outer\text{-}cell}$) causing by fluctuations balance of inner cellular balance catabolic processes & anabolic processes and outer cellular balance catabolic processes & anabolic processes via HIF-1α protein operation which exerts anabolic processes of transcription for proteins biosythesis in G1 phase cellular cycle in norm [1,2,6,7,19] (Figure 4, Figure 5). As concerning cancer pathology, the shift intracellular balance catabolic processes & anabolic processes into excessive anabilic processes causing overloaded „nodal point of bifurcation anabolic and catabolic

processes [NPBac]" and partial suppression catabolic processes [TCA] and resulting in inflow substances into cells, according Theorell equation, which causes expression intracellular chemical potential ($\mu_{inner\text{-}cell}$) over extracellular chemical potential ($\mu_{outer\text{-}cell}$) exerting excessive HIF-1α protein expression due to arisen excessive anabolic anaerobic endergonic processes [20] (Figure 6).

Semenza et al. have noted : activation of the MAP kinase pathway has been reported to increase HIF-1 transcriptional activity without affecting HIF-1α protein expression [25,26], and it will be interesting to determine whether this effect is mediated via decreased binding of FIH-1" [20, 21, 22].

Author's explanation: Really, MARK kinase takes part in S, G2 and M phases of cellular cycle exerting cell proliferation, cells differentiations, cells death, causing influence on forming either intracellular chemical potential ($\mu_{inner\text{-}cell}$) or extracellular chemical potential ($\mu_{outer\text{-}cell}$) in these phases of cellular cycle for operations of cellular capacitors, nuclear capacitors, mitochondrial capacitors, organella' capacitors via their resonance waves operation. Just all these phases of cellular cycle are created in exchanging hypoxic condition and oxidative condition therough interactions between MARK, HIF-1α, HIF-1β the one side of hypoxic state and VHL the other side of oxidative state, and FIH-1 proteins how transferor of energy. Just interactions between MARK, HIF-1α, HIF-1β the one side of hypoxic state and VHL the other side of oxidative state with link FIH-1 proteins induce fluctuating common balance anabolic anaerobic endergonic processes & catabolic anaerobic exergonic processes & catabolic aerobic exergonic processes between hypoxic state and oxidative state. Thus activities of each protein-kinase depend on requirement of development cellular cycle which is detemined by resonance waves influences causing by all these capacitors operations. As concerning cancer pathology, the shift intracellular balance catabolic processes & anabolic processes into excessive anabilic processes causing partial suppression catabolic anaerobic processes of TCA due to overloaded „nodal point of bifurcation anabolic and catabolic processes [NPBac]" with expression catabolic aerobic oxidative processes occurs also either in excessive hypoxic condition of MARK, HIF-1α, HIF-1β or in excessive oxidative condition of VHL with link FIH-1 proteins inducing excessive increased replicative processes in nuclear DNA via realizing of 2nDNA reaction [15-18].

Kaelin et al. have noted : Fibronectin coimmunoprecipitated with wild-type von Hippel-Lindau protein (pVHL) but not tumor-derived pVHL mutant. Whether pVHL play a role in control of transcriptional elongation in vivo is not known [22,23,24]. Over produce hypoxia-inducible mRNA (via cell lacking pVHL) is the vascular endothelial growth factor (VEGF) under normooxic condition. The available data, however, suggest that the effect of pVHL on hypoxia-inducible mRNA is mediated largely at the level of transcriptional elongation.

Kaelin WG and Retcliffe PJ have noted: Concerning Prolyl Hydroxylase Domains, which are inducing hydroxylation HIFα, PHD1 is exclusively nuclear, PHD2 is mainly cytoplasmic, and PHD3 is found in both the cytoplasm and nucleus. But a fourth enzyme (P4-TM) is located in the endoplasmic reticulum, and more closely related to the procollagen prolyll hydroxylases than the PHDs, can also hydroxylate HIFα in vitro. A connection to the HIF pathway is supported by the effect of P4-TM via siRNA and P4-TM overexpression on HIF1α levels (induction or reduction, respectively), although it is possible that these effects are indirect, and that the true substrate has not yet been indentified [22,23].

Kaelin WG and Retcliffe PJ have noted: PHD1 is induced by estrogen in breast cancer cells and can stimulate proliferation in vitro. Whether this effect reflection an HIF-independent PHD1 function is not known. Many of proteins will be hydroxylated by FIH. However significante FIH1-mediated hydroxylation of IkBs and Notch receptors is unclear [22, 23].

Author's explanation: The driving mechanisms of cellular cycle are subjected to first law thermodynamics. Cellular cycle provides maintenance stability Internal Energy of cells via stability of cytoplasm basophylic chemical potential (μ_{cell}) [7,8].

The stability cytoplasm basophylic chemical potential (μcell) forms through exchanged fluctuating shift balance catabolic anaerobic exergoniic processes & anabolic anaerobic endergonic processes either into moderate expression anabolic anaerobic endergonic processes or into moderate expression catabolic anaerobic exergonic processes. So these exchanged fluctuating processes exert corresponding to either biosynthetic processes of fusion proteins production via transcriptionand and translation processes causing by HIF-independent PHD1 function in G1, G2 and also in M phases [via Karyogenesis and Cytogenesis] providing the effect of pVHL on the level of transcriptional elongation in G1 and G2 phases cellular cycle or division processes of fission DNA replicative processes in S phase cellular cycle and cell division in M phase cellular cycle causing DNA proliferation. Really, all these fluctuating processes occur in hypoxic condition via supporting by HIF-1α are inducing hydroxylation by Prolyl Hydroxylase Domains [PHD] and exerting their exchanges by expression VHL which are induced by driving mechanisms proliferative processes of S phase cellular cycle. Thus driving mechanism of cells' cellular cycles are exerted by mechanism maintenance stability Internal Energy of an organism (U) due to interactions between Internal Works (W_{int}) and External Works (W_{ext}) of an organism causing resistance influences of Environment via exchanges inflows and outflows Subtances and Energy as between an Organism and Environment as well as between each cell's membranes forming an organism's chemical potential ($\mu_{organism}$). Also it occurs inflows and outflows substances and energy through cellular wall's two membranes between Exracellular Medium and Intracellular Medium causing inner cellular chemical potentials (μ_{inner}) and outer cellular chemical potentials (μouter) which are induced via supporting by HIF-1α being hydroxylated by Prolyl Hydroxylase Domains [PHD]. Also it occurs inflows and outflow energy and substances through nuclear shell's two membranes between Exranuclear Medium and Intranuclear Medium causing inner nuclear chemical potentials ($\mu_{inner\ nuc}$) and outer nuclear chemical potentials ($\mu_{outer\ nuc}$) which are induced by HIF-1α being hydroxylated either by PHD1 (exclusively nuclear) or by PHD3 (found in both the cytoplasm and nucleus). Also it occurs inflows and outflows substances and energy through mitochondrial shell's two membranes between Exramitochondrial Medium and Intramitochondrial Medium causing inner mitochondrial chemical potentials ($\mu_{inner\ mit}$) and outer mitochondrial chemical potentials (μouter mit) which are induced by HIF-1α being hydroxylated by PHD2 (mainly cytoplasmic and possible also mitochondrial). Also it occurs inflows and outflows substances and energy through each organella's two membranes between Exraorganella Medium and Intraorganella Medium causing inner organella chemical potentials ($\mu_{inner\ org}$) and outer organella chemical potentials ($\mu_{outer\ org}$) which are induced by fourth enzyme (P4-TM) located in the endoplasmic reticulum, and more closely related to the procollagen prolyll hydroxylases than the PHDs, can also hydroxylate HIFα. Thus there are formed each tissue's complete chemical potential (μ_{tissue}) how extracellular complete chemical potentials ($\mu_{tissue.extracell}$),

as well as cell's chemical potentials (μcell), nuclear chemical potential (μ_{nucl}), mitochondrial chemical potential (μ_{mitoch}), organella's chemical potential ($\mu_{organel}$). Just interactions between all these mechanisms due to inflows and outflows Substances and Energy form cellular capacitors, nuclear capacitors, mitochondrial capaciters, all organella's capacitors which resonance waves' interactions are the driving mechanisms of cellular cycle due to supporting hypoxic condition by HIF-1α activity and exerting exchanges energy between HIF-1α and VHL.

Kaelin et al. have noted: Increased HIFα levels have been documented in many solid tumors [30]. Highly aggressiveness of cancer are more likely to outgrow their blood supply, and hence become hypoxic it occurs over production both HIF-1α and HIF- 2α, but eliminate HIF- 2α by VHL in renal cancer and induce suppression tumor. Many HIF-responsive gene products are suspected of playing role in cancer, including VEGF, PDGF, TgFα, TgFß, SDF-1, CXC4, and MMP1 [28,29].

Author's explanation: The driving mechanism of cancer aggresiveness via tumor growth showing expression above mention Factors occurs in hypoxic condition supported by over production both HIF-1α and HIF- 2α causing excessive anabolic biosynthetic processes of production proteins and the other substances in G1, G2 phases cellular cycle and in Cytogenesis of Mitotic (M) phase cellular cycle. But advance cellular cycle are exerted due to interrupting hypoxic condition by expression oxidative processes of catabolic aerobic processes in mitochondria which are supported by VHL of ubiquitin ligase complex operation causing both HIF-1α and HIF- 2α inhibition that advance cellular cycle through replicative processes in S phase cellular cycle and also in Mitotic phase (M) cellular cycle of Karyogenesis [14,15]. Just transition hypoxic state in Glycolysis and Krabs cycle of trichloroacetic acid (TCA) metabolic processes supporting by HIFs factors into oxidative state of catabolic aerobic oxidative processes supporting by VHL of ubiquitin ligase complex corresponding to Warburg efect mechanism of „aerobic glycolysis" in meabolism of cancer tissue [12,13,14,19].

Acknowledgments

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

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