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Biophysical and biochemical mechanisms disturbance of cellular genome leading to transmutation benign neoplasm into cancer

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ABSTRACT. It was considered processes transmutation of genome mechanism from the point of view of thermodynamics, biophysics, and biochemistry. Just it was explained mechanisms maintenance stability Internal Energy of Stationary State an able-bodied organism according first law of thermodynamics. Besides it was considered some negative influences on an organism of solar radiation causing germination viruses. Hence it was described mechanisms normal development of an organism reflecting activity of cellular genomes via generating cellular divisions. The links between genomic mechanisms and mechanisms maintenance stability Internal Energy of an organism and cells of an organism exert activity stem cells which induce cells types division in healthy tissues. The local violation these links due to viral affection causes local tissue transitions normal genomic cycle into genomic cycle of benign neoplasm, i.e., the transition of genomic link due to viral affection of cellular genomic link leading to forming benign neoplasm. The mechanism of these transformations in cellular genome was described from point of views of thermodynamics, biophysics, and biochemistry. Also, it was elucidated the cause that genomic mechanism of benign neoplasm don't break Stationary State of an organism. Furthermore, it was described the viral affecting genomic link of cells in benign neoplasm causing mechanism transmutation benign neoplasm into cancer with forming Warburg effect mechanism. The forming cancer metabolism creates Quasi-Stationary State of cancer disease organism.

Key words: Basic stem cells; Totipotent stem cells; Pluripotent stem cells; Multipotent stem cells; Oligopotent stem cells; Unipotent stem cells; Cells types; Benign neoplasms; Malignant neoplasms; Warburg effect.

INTRODUCTION

These were studied genomic mechanisms of normal Stationary State of an able-bodied organism and an organism with benign neoplasm as well as genome mechanism of Quasi-stationary pathologic State a cancer disease organism. The activity cellular genomics of an organism was described considering mechanism maintenance stability Internal Energy of an organism from the point of view of thermodynamics, biophysics and biochemistry. Besides it was studied genomic mechanism of cellular cycle from the point of view of thermodynamics, biophysics, and biochemistry. Just the activity of cellular cycle influences on stability Internal Energy of cells which induce stability Internal Energy of Stationary State of an organism.

The stability internal energy of stationary state of an organism's tissue shows "incompatibility aerobic oxidation and Glycolysis" in normal tissue metabolism according to Pasteur effect. The stability Internal Energy of Stationary State of an organism's tissues promotes stability internal energy of stationary state of an organism.

Investigating transition normal cellular cycle of an organism's cells into pathologic cellular cycle of benign neoplasm cells, there was described the target of genomic link affected by viruses leading to forming cells of benign neoplasm. The cells of benign neoplasm are not subjected to regulative mechanisms of an organism, but an organism preserve stable Internal Energy and stationary state despite of having benign neoplasm.

Transmutation cellular cycle of benign neoplasm into cancerous cellular cycle of malignant neoplasm was considered describing viral affected link of cellular cycle that cause irrepressible proliferative processes with irrepressible tumor growth, metastasis, invasive capability, Apoptosis Resistance etc. Thus, development of malignant neoplasm leads to Quasi-stationary state of an organism.

RESEARCH METHODOLOGY

Genetic mechanism of cellular cycle in norm

Human organisms have normal mechanisms maintenance stability Internal Energy: stable temperature 36.3°C to 36.8°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. (Ponizovskiy M.R, 2013 & 2017).

The stability Internal Energy (ΔU) of an organism is maintained by three lever regulations: Highest level regulation – Central Nervous System; High level regulation - Equilibrium Constants of ionic metabolism, Equilibrium Constants of acid – alkaline metabolism, Equilibrium Constants of oxidative – reductive Potentials of metabolism, Equilibrium Constants of coagulating system of a blood; Low level regulation - Equilibrium Constants of endergonic and exergonic processes, Equilibrium Constants of anabolic and catabolic processes (Ponizovskiy M.R, 2013 & 2017) (Figure 1).

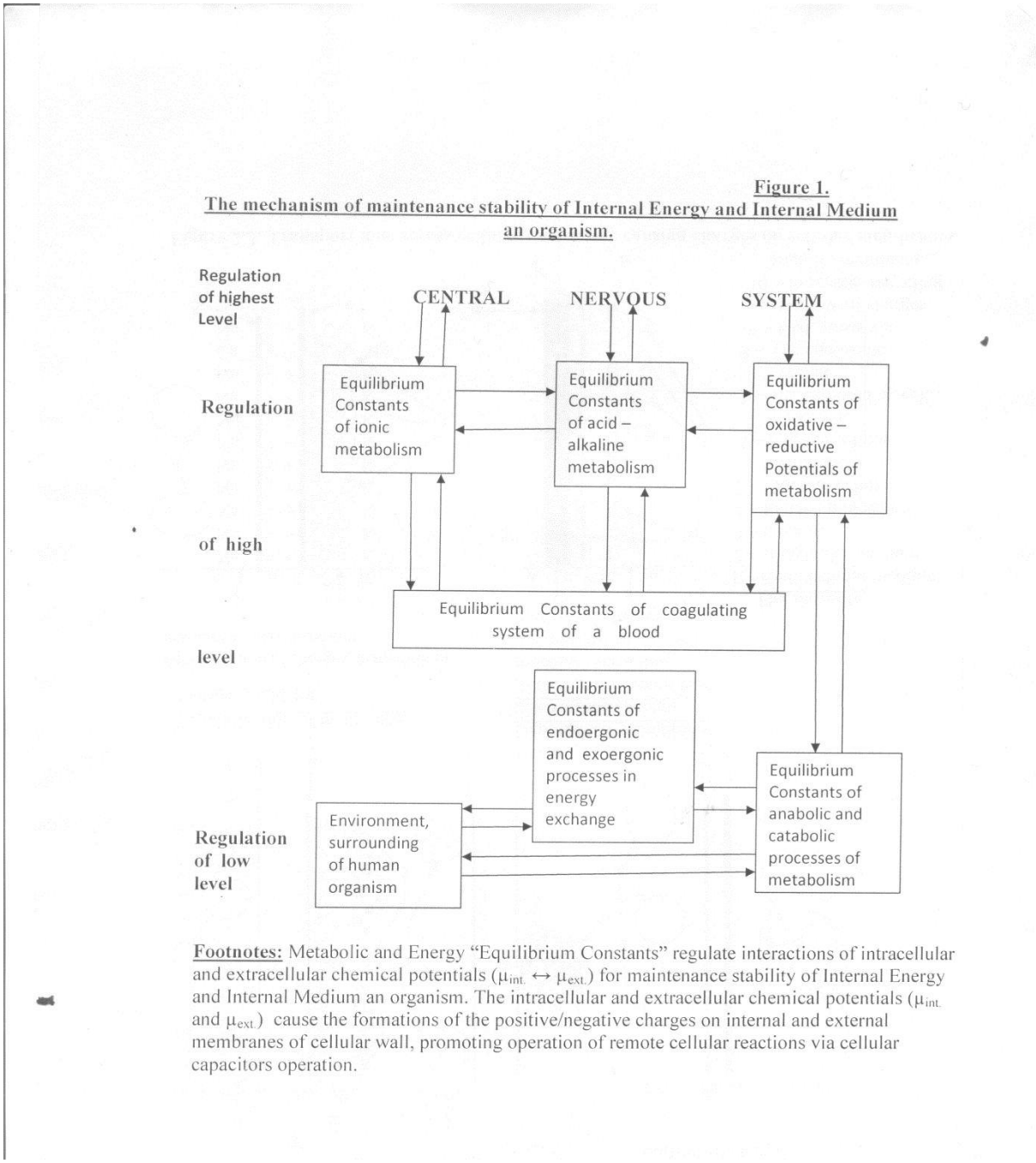

Figure 1. Mechanisms maintenance internal energy stabilities

Besides human organisms have stable Internal Medium displaying normal concentrations substances in blood and neurolymph which is induced by stability Internal Energy (ΔU) of an organism (Ponizovskiy M.R, 2013, 2017). Mechanism maintenance stability Internal Energy (ΔU) of an organism creates common balance catabolic aerobic exergonic processes and catabolic anaerobic exergonic processes and anabolic endergonic processes (Ponizovskiy M.R, 2013, 2016, 2017). Besides the all cells of an organism have normal mechanisms maintenance stability cellular Internal Energy (U_{cell}) of their cytoplasmic basophilic chemical potentials ($\mu_{cytoplasm}$) via staining cells (Ponizovskiy M.R, 2000, 2011, 2015). Thus human eukaryotic organism is the open non equilibrium non linear thermodynamic system.
This is the equation of common Energy (E_{common}) of thermodynamic system according formula of first law of thermodynamics:

$E = \Delta U + W_{int.} + W_{ext.}$ [E- common Energy (E_{common}); ΔU – Internal Energy; $W_{int.}$ – internal work of system; $W_{ext.}$ – external work of system].

The common Energy (E_{common}) of open non equilibrium non linear thermodynamic system of an organism contains stable Basic cellular Internal Energy (U_{basic}) which is included into fluctuating stable Internal Energy (ΔU) of an organism. Stability Internal Energy (ΔU) of an organism is supported by organism's Internal Works ($W_{org\ int.}$) and organism's external Works ($W_{org.\ ext.}$) forming Stationary State of an organism according first law of thermodynamics (Ponizovskiy M.R, 2000, 2014). Basic cellular Internal Energy (U_{basic}) of an organism is the store energy keeping expending energy (Ponizovskiy M.R 2017). Therefore Basic cellular Internal Energy (U_{basic}) is formed obtaining energy from organism's parents during germination of an organism and has 100% energy after birth of an organism Ponizovskiy M.R 2017. Basic cellular Internal Energy (U_{basic}) is found in cells of central nervous system (neurons) which are named Basic stem cells Ponizovskiy M.R 2017. Just Basic stem cells (neurons) distribute Basic cellular Internal Energy (U_{basic}) among the other stem cells in sequence [Basic stem cell → Totipotent stem cell → Pluripotent stem cell → Multipotent stem cell → Oligopotent stem cell → Unipotent stem cell] which distribute obtained energy among cells types of different tissues Ponizovskiy M.R 2017. All stem cells and cells types divide via Mitosis in eukaryotic organisms. Mitosis in "M phase cellular cycle" is asexual reproduction. There are two broad types of stem cells: embryonic stem cells, which are isolated from the inner cell mass of blastocyst, and stem cells of an organism, which are found in various tissues. All cells of born organism have in their nuclei 22 pairs chromosome and two sex chromosomes for a total of 46 chromosomes, i.e. diploid cells having homologous pair chromosomes. Females have two X sex chromosomes; males have X sex chromosome and Y sex chromosome (Ponizovskiy M.R 2017). All cells of an organism proliferate through G_0, G1/S, G2, M (Mitosis) phases of cellular cycle showing diploid proliferative processes (Ponizovskiy M.R 2017). Just M phase cellular cycle consists of two processes: karyokinesis and cytokinesis. Karyokinesis processes display division cellular nucleus via division chromosomes. Cytokinesis processes display division cell's cytoplasm with all its organelles forming two daughter cells. Cell's divisions are vital process in which cells of tissues are renewed, i.e. skin's cells, blood cells, and cells of internal organs. After cell division, each of the daughter cells begins the new interphase, i.e. G_0, G1, S, G2 phases, and then begins M phase of a new cellular cycle (Table 1).

Table 1. Phases of cellular cycle.

Phase	Description development cellular cycle via cellular phases
G_0	A phase where the cell has left the cycle and has stopped division.
G1	Cells increase in size in G1 [Gap1]. The G1 checkpoint control mechanism ensures that everything is ready for DNA synthesis. In G1 phase, there occurs production as enzymes as well as the proteins for development further phases.
S	DNA replication occurs during this phase.
G2	During the G2 [Gap 2] between DNA synthesis and mitosis, the cell will continue to grow. The G2 checkpoint control mechanism ensures that everything is ready to enter the M (mitosis) phase.
M	Cell growth stops at this stage and cellular energy is focused on the orderly division into two daughter cells.

The G_0 phase cellular cycle is characterized as cell's quiet state in which it occurs RNA translation and transcription for biosynthesis of proteins.

The G1 phase cellular cycle is characterized via preparing of DNA synthesis. It is also called the growth phase. During this phase, it continues the biosynthetic activities. In this phase, the cell increases its supply of proteins, enzymes, increases the number of organelles (such as mitochondria, ribosome, lysosome and the others), and grows in size.

The S phase cellular cycle starts when DNA synthesis begins, and then DNA replication occurs. Thus, during this phase, the amount of DNA in the cell has effectively doubled. Rates of RNA transcription and protein synthesis are very low during this phase. An exception to this is histone production, most of which occurs during the S phase.

The G2 phase cellular cycle occurs after DNA replication and is a period of protein synthesis and rapid cell growth to prepare the cell for mitosis. During this phase microtubules begin to reorganize to form a spindle.

The M phase cellular cycle via Mitosis is the process by which an eukaryotic cell separates the chromosomes in its nucleus into two identical sets creating two nuclei via prophase, metaphase, anaphase and telophase. During the process of mitosis the pairs of chromosomes condense and attach to fibers that pull the sister chromatids to opposite sides of the cell. After mitotic karyokinesis is immediately followed cytokinesis, which divides the nuclei, mitochondria, cytoplasm, organelles and cell membrane into two cells containing roughly equal shares of these cellular components. Mitotic karyokinesis and cytokinesis together define the division of the mother cell into two daughter cells, genetically identical to each other and to their parent cell (De Souza C.P, 2007).

There are the specific differentiations of the stem cells

Basic cellular Internal Energy (U_{basic}) in Basic stem cells is divided into two parts: The first part of Basic Cellular Internal Energy (U_{basic}) takes part in mechanism maintenance stability Internal Energy of an organism via exchanges with its energy and substances via their inflows and outflows according to famous Prigogine theorem Ponisovskiy M.R, 2011. Secondary parental inherited part of Basic Cellular Internal Energy (U_{basic}) store energy for cells' divisions causing cellular development during their lives. Both parts of Basic Cellular Internal Energy (U_{basic}) are situated in nervous cells of central nervous system (neurons) which are also named Basic stem cells (Figure 1). Thus, Basic cellular Internal Energy (U_{basic}) realizes Central nervous system's activity of Highest level regulation causing mechanism maintenance stability Internal Energy (ΔU) of an organism via expending stored electric energy and stimulating both High level regulation and Low-level regulation in mechanism maintenance stability Internal Energy (ΔU) of an organism (Ponisovskiy M.R, 2016, 2017) (Figure 1).

Depending on metabolic biochemical processes in tissue, each tissue has extracellular chemical potential ($\mu_{extra\ cell}$) which induce charges on external cellular membranes of tissue cells' walls. Internal cellular membranes of tissue cells' walls are charged due to inducing charge by cytoplasmic basophilic chemical potentials ($\mu_{cytoplsm}$) via staining cells. Thus, there are formed cellular capacitors of tissue cells. Just relative resonance waves of tissue cells' cellular capacitors determine supplementary mechanism maintenance stability Internal Energy of tissues of an organism as well as an organism. Also, cytoplasmic basophilic chemical potentials ($\mu_{cytoplsm}$) of cells central nervous system (neurons), named Basic stem cells, form electric charges of cellular inner membrane.

Neurons of central nervous system are bound via nerve fibres with neurotransmitter receptors in each tissue. Thus, neurotransmitter receptors' chemical potential membranes ($\mu_{neurotrans\ receptor}$) are charged by charges of cytoplasmic chemical potentials of neurons ($\mu_{cytoplsm}$). Hence tissue cells' membranes are also charged via supplementary being induced by charges of neurotransmitter receptors. Just there are such sensitive membranes of neurotransmitter receptors: heat-sensitive membrane, photo-sensitive membrane, osmo-sensitive membrane, mechano-sensitive membrane, chemo-sensitive membrane, pain-sensitive membrane. Mutual influences between three activities as relative resonance waves of cellular capacitors of tissue's cells, neurotransmitter receptors' charges with various sensitive membranes and tissues' charges due to their chemical potentials determine mechanism maintenance stability Internal Energy as tissues [skin, connective tissue, muscular tissue, neuroglia etc.] as well as of an organism (Figure 2).

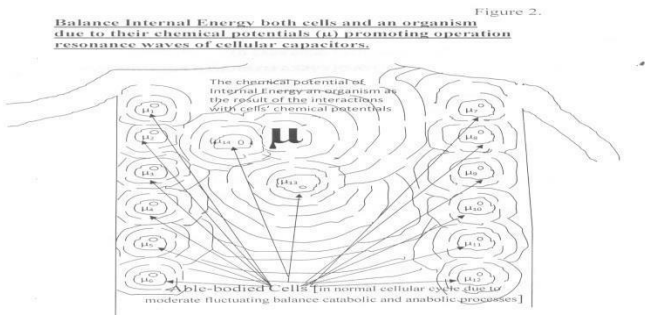

Figure 2. Interaction cells and an organism

Just cells of central nervous system (neurons), also named basic stem cells, store energy and create bio current via negative charge causing stimulation mechanical reactions, tactile reactions, painful reactions and the other reaction of an organism. Besides the charged neurotransmitter receptors of neurons [Basic stem cells] transmit energy of bioelectric charges sharing it through the sequence of the stem cells [Basic stem cell → Totipotent stem cell → Pluripotent stem cell → Multipotent stem cell → Oligopotent stem cell → Unipotent stem cell] and then to various cells types. Basic stem cells supply next generations of stem cells with energy from Basic Cellular Internal Energy (U_{basic}) which expends this energy during life of an organism (Figure 3).

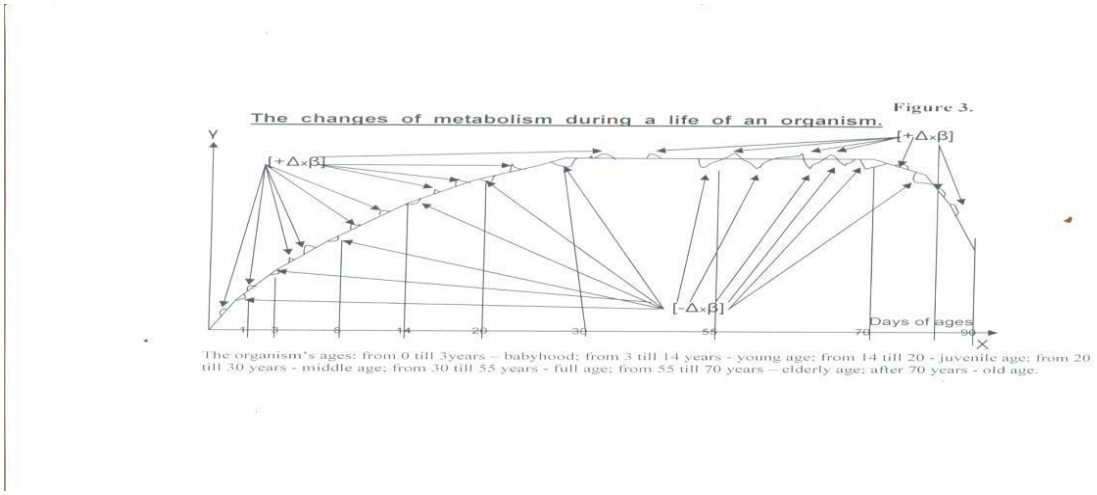

Figure 3. Changes metabolism during life of an organism

Moreover, Basic stem cells retain some Basic Cellular Internal Energy (U_{basic}) in some genes of their chromosomes displaying specific human capabilities, i.e. memory, musical talents, artistic talents, mathematical talents, scientific talents, constructor talents and the other gifts. These parts of Basic Internal Energy (U_{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 determining aging of an organism. Basic stem cells expend the stored energy through sequence of stem cells for development of an aging organism via development of all cells types of various tissues considering terms of each cell's life, i.e. various quantity cellular cycles, apoptosis, autophagy etc. Thus, all stem cells expend their substances and energy for advance cells types of various tissues of an organism (Bernstein H, et al. 2011, Bernstein H, 2010, Tsutsumi M, 2014, Brunet S, 2010, Rosenbusch B, 2006). Just the ageing processes during life of an organism expend some Basic Cellular Internal Energy (U_{basic}) from Basic stem cells exerting cellular internal Works ($W_{int\ cell}$) via expression some cellular metabolic processes with inflow and excretion substances to maintenance stability cellular Internal Energy (U_{cell}) as stable basophilic cytoplasm's chemical potentials ($\mu_{cytoplsm}$) via staining cells as well as stable Internal Energy (ΔU) of an organism (Ponizovskiy M.R, 2013). (Figure 3). Just this expending Basic Cellular Internal Energy (U_{basic}) induces the change of an organism's state from babyhood and childhood to old age in processes of an organism's ageing (Ponizovskiy M.R, 2017). On the other hand, the Basic stem cells, as the store of energy, are replenished with some energy by inflow energy with food products through gastrointestinal tract. Moreover, Basic stem cells are replenished with the energy due to accepting some solar rays' quanta energy. Just long-lived persons live considerably more among mountains as dwellers than persons among flat ground as dwellers because solar rays are considerably more in mountains than in flat ground. Therefore, the Basic stem cells retain more Basic Cellular Internal Energy in mountains than in flat ground. However, most of the replenishing energy through food products are used in both Internal Works of an organism ($W_{int.org}$) [heart works, lung works, liver works, kidneys work etc.] and various External Works of an organism ($W_{ext.org}$) for maintenance stability Internal Energy of an organism (ΔU). But most of Basic Cellular Internal Energy (U_{basic}) in neurons expend energy for growth of an organism due to cells' divisions and for aging an organism due to exhaustion Basic Cellular Internal Energy (U_{basic}). However, it occurs in different ages of an organism differently exhaustion basic cellular internal energy (U_{basic}) leading to aging of an organism.

The 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. However Totipotent (or omnipotent) stem cells operate differently in male organism and in female organism, e.g. in female organism Totipotent (or omnipotent) stem cells differentiate initial cells into embryonic and extraembryonic cell types as well as initial cells of female secondary sexual characters and initial cells of different tissues' type cells; in male organism Totipotent (or omnipotent) stem cells differentiate initial cells of male secondary sexual characters and initial cells of different tissues' type cells. 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 Unipotent stem cells which bring differentiations of stem cells nearer to differentiations of specific cells types certain tissues of an organism.

Furthermore common balance catabolic aerobic exergonic processes and catabolic anaerobic exergonic processes and anabolic endergonic processes stimulate regulatory mechanisms cellular cycles of different tissues' cells types basing on the obtained bioelectric energy from the stored energy of Basic cellular Internal Energy (U_{basic}) in the genome's molecular bonds of Basic stem cells' (neurons) chromosomes due to molecular orbital energy of linear combination of atomic orbitals (MO, LCAO) according to Schreodinger equation. This energy was shared via sequence through basic stem cells (neurons), totipotent stem cells, pluripotent stem cells, multipotent stem cells, oligopotent stem cells, unipotent stem cells into cells types. The genes encode protein synthesis, named cyclins, and cyclin-dependent kinases (CDKs) which advance cellular cycles of different tissues' cells types determining different cells' division cycles (CDC), e.g. CDC 40 or CDC 55.

Also results from the study dynamics group of nine genes (E2F) coding transcription factors at the single-cell level prove that the role of cyclin-CDK (Cyclin-dependent kinases complex) activities in G1 phase cellular cycle, in particular cyclin D-CDK4/6, create the timing rather than the inducing cell cycle entry in S phase cellular cycle (Nigg E.A, 1995, Spellman P.T, 1998). But cyclin-CDK complex promotes expression of transcription factors which are stimulated by Hypoxia-induced aFactor (HIFa) and Hypoxia-induced c-Factor (HIFc) (Nigg E.A., 1995). Further active cyclin S-CDK complex phosphorates proteins that prepare pre-replication complexes in G1 phase cellular cycle for DNA replication in S phase cellular cycle. These different cellular division cycles are finished with Mitosis (M phases) of kariokinesis and cytokinesis. Energy of the genome's molecular bonds determine different cells' lifetimes via creating different their cycle times. Thus, considering the average quantity 50 times of each cell's divisions, the obtained energy from the genome's molecular bonds determines the lifetime of a cell. Just single chromatid is decondensed in chromosome. Therefore, after DNA is copied, chromosome consists of two sister chromatids connected by proteins [cohesins]. Two sister chromatids are tightly connected at the centromere region condensing chromosome. Chromatids are pulled apart. Each of these two chromatids can be considered as own chromosome. The driving mechanisms of these transformations in nucleus are provided by cellular energy which is expended in cellular cycle for anabolic endergonic biosynthetic processes. The moderate expression anabolic endergonic processes lead to moderate shift balance anabolic endergonic processes and catabolic anaerobic exergonic processes into moderate expression anabolic endergonic processes with moderate partial suppression Krebs tricarcoxilic acids cycle (TCA). Just partial suppression Krebs tricarcoxylic acids cycle (TCA) in mitochondria leads to lack Hydrogen ions (H+) which are produced in Krebs tricarboxylic acid cycle. The lack Hydrogen ions (H+) don't neutralize whole oxygen (O_2) which come from lungs and is carried by systems of Hemoglobin and Cytochromes. Therefore, there are formed surplus Superoxide (O_2*) via adding electron by surplus oxygen (O_2) which is produced by transforming NAD+↔NADH and FAD↔$FADH_2$: n[O_2] + n[e-] → n[O_2*]. Superoxide (O_2*) induces forming ROS/H_2O_2/Free radicals Ponizovskiy M.R, 2013, Furda Amy Marie, 2011. Free radicals (*OH) react on nuclear DNA [nDNA] in G1/S phases cellular cycle and moderate induce process replication via realizing of 2nDNA.

*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, moderate process replication nuclear DNA occurs in S phase cellular cycle. The process replication in S phase cellular cycle induces expression catabolic aerobic exergonic respiratory processes of link [from lungs O_2 → oxyhaemoglobin → Mitochondrial system cytochromes] which interrupts anabolic processes via temporarily suppression expressed anabolic endergonic biosynthetic processes. Thus, catabolic aerobic exergonic respiratory processes carry much energy and exert catabolic anaerobic exergonic processes which induce metabolic oxidative processes causing oxidative excretion waste substances via CO_2 and H_2O into Environment. Such oxidative excretion waste substances via expression aerobic processes eliminate metabolic blocking anabolic endergonic processes. The replication in S phase cellular cycle is finished when energy is decreased in the molecular bonds of nucleus. Then catabolic aerobic exergonic processes are suppressed by expressed anabolic endergonic processes causing transition into G2 phase cellular cycle which receive supplementary energy via link [Basic stem cells (neurons) → sequence of stem cells → tissue's cells types]. The expressed anabolic endergonic processes of G2 phase cellular cycle induce biosynthesis of proteins and other substances preparing to Mitosis (M phase cellular cycle) of karyokinesis and cytokinesis. Transition G2 phase cellular cycle into M phase cellular cycle occurs due to decreased supplementary energy received via link [Basic stem cells (neurons) → sequence of stem cells → tissue's cells types].

Further in the mitotic M phase cellular cycle each portion of the cell's genome is divided once and only once via expending of obtained stored portion energy. Thus, daughter cells touch on all parts of crucial genes of cell's genome only once. Mitosis (M phase cellular cycle) receives supplementary energy also via link [Basic stem cells (neurons) → Totipotent Stem Cells → Pluripotent Stem Cells →Multipotent Stem Cells → Oligopotent Stem Cells → Unipotent Stem Cells → tissue's cells types]. During mitosis, the chromosomes condense and attach to spindle fibres that pull one copy of each chromosome to opposite sides of the cell (Maton A, 1997). As the result, there are formed two genetically identical daughter nuclei. Thus, during the Mitotic phase, the chromosomes are condensed in two new nuclei. Mitosis is often accompanied by cytokinesis, which divides the cytoplasm, organelles and cell membrane into two new cells containing roughly equal shares of these cellular components (Maton A, 1997). The rest of the cell may then continue to divide by cytokinesis to produce two daughter cells (Maton A, 1997). Mitosis and cytokinesis together define the mitotic (M) phase of cell cycle, i.e. the division of the mother cell into two daughter cells genetically identical to each other. The process of mitosis is divided into stages corresponding to the completion of one set of activities and the start of the next set of activities. These stages are named prophase, prometaphase, metaphase, anaphase, and telophase. Prophase: During prophase the cell prepares to divide by tightly condensing two chromosomes and initiating mitotic spindle formation, this process is called chromosome condensation. After prophase, each chromosome has two chromatids, i.e. the diploidy of the cell is occurred. The two chromatids are joined at a place called centromere (Prasanth K.V, 2003, Ribeiro K.C, 2002).

Prometaphase

At the beginning of prometaphase in cells, phosphorylation of nuclear lamina creates the nuclear envelope via disintegrating into small membrane vesicles. As this happens, microtubules invade the nuclear space. In late prometaphase, kinetochore microtubules begin to search to attach to chromosomal kinetochore (Chan G.K, 2005). Kinetochore is a proteinaceous microtubule-binding structure that forms the chromosomal centromere during late prometaphase (Chan G.K, 2005). (Cheeseman I.M, 2008). Number of polar microtubules find and interact with corresponding polar microtubules from the opposite centrosome to form the mitotic spindle (Winey M, 1995). The polymerisation and depolymerisation of microtubules provides the pulling force necessary later to separate the chromosome's two chromatids (Maiato H, 2004).

Metaphase

After the microtubules have located and attached to the kinetochores in prometaphase, the two centrosomes begin pulling the chromosomes towards opposite ends of the cell. The resulting tension, the chromosomes align along the metaphase plate or equatorial planer creating an imaginary line which is centrally located between the two centrosomes (at approximately the midline of the cell) (Winey M, 1995). In order to ensure equitable distribution of chromosomes at the end of mitosis, the metaphase

checkpoint guarantees that kinetochores properly are attached to the mitotic spindle and that the chromosomes are aligned along the metaphase plate (Chan G.K, 2003). If the cell successfully passes through the metaphase checkpoint, it proceeds to anaphase.

Anaphase

During anaphase A, the cohesions bind sister chromatids together, and then they are cleaved, forming two identical daughter chromosomes (Fitz Harris G, 2012). Shortening of the kinetochore, microtubules pulls the newly formed daughter chromosomes to opposite ends of the cell. During anaphase B, polar microtubules push against each other, causing the cell to elongate (Miller K.R, 2000). In late anaphase, chromosomes also reach their overall maximal condensation level, to help chromosome segregation and the re-formation of the nucleus (Zhou J, 2002).

Telophase

Telophase is a reversal of prophase and prometaphase events. At telophase, the polar microtubules continue to lengthen, elongating the cell even more. If the nuclear envelope has broken down, a new nuclear envelope forms using the membrane vesicles of the parent cell's old nuclear envelope. The new envelope forms around each set of separated daughter chromosomes (though the membrane does not enclose the centrosomes) and the nucleolus reappears. Both sets of chromosomes are surrounded by new nuclear membrane and begin to "relax" or decondense. Mitosis is completed. Each daughter nucleus has an identical set of chromosomes. Cell division may or may not occur at this time depending on the organism. Maybe cytokinesis is either a telophase of mitosis or rather a separate process necessary for completing cell division (Glotzer M, 2005, Albertson R, 2005).

All these sequences operations in G_0, G1, S, G2 and M phases cellular cycles of cells types are stimulated by capacitors' resonance waves of identical cellular cycles by inflow gene's molecular bonds energy of sequences from unipotent stem cells, from oligopotent stem cells, from multipotent stem cells, from pluripotent stem cells, from totipotent stem cells, from basic stem cells.

The genetic mechanisms of forming benign neoplasms and mechanisms of their transmutations into cancer

The genetic mechanisms of forming benign neoplasms

Cells of all tissues and free cells are divided permanently via G_0, G1, S, G2 and M phases of cellular cycle displaying asexual mitotic cellular division of eukaryotic organisms in norm. Each type cell creates average 50 times divisions being exerted by corresponding stem cells due to obtained energy through row of these stem cells: Basic stem cell → Totipotent stem cell → Pluripotent stem cell → Multipotent stem cell → Oligopotent stem cell → Unipotent stem cell.

1. Basic stem cells, named neurons, are cells which store Basic Cellular Internal Energy (U_{basic}) which is expended during life of an organism causing aging of an organism via aging all cells of an organism and maintaining stability Internal Energy (ΔU) of an organism as Highest-Level Regulation causing Stationary State of an organism.
2. Totipotent (or omnipotent) stem cells can differentiate as into embryonic and extraembryonic cell types as well as in next sequence of stem cells. Such cells can construct a complete viable organism (Mitalipov S, 2009). These cells are produced from the fusion of an ovum and sperm cells. Cells produced by the first divisions of the impregnated ovum are also initial totipotent stem cells (Mitalipov S, 2009).
3. Pluripotent stem cells are the descendants of totipotent cells and can differentiate into next stem cells for nearly all cells (Thomson J.A, 1998) i.e. cells derived from any of the three germ layers (Thomson J.A, 1998).
4. Multipotent stem cells can differentiate into next stem cells for each number of cell types, but only those of a closely related family of cells (Ying Q. L, 2008).
5. Oligopotent stem cells can differentiate into next stem cells for only a few cell types, such as

e.g. lymphoid cells or myeloid cells etc. (Ying Q. L, 2008).

6. Unipotent cells can produce only one cell type, their own (Ying Q. L, 2008) but have the property of self-renewal, which distinguishes them from non-stem cells (e.g. progenitor cells, which cannot self-renew).

Thus, primary type cells' divisions transit to last layer cells' divisions entering either into rejected cells or into keratinizing cells of epidermic keratoid layer, nails, hairs and so on (Gomes N.M, 2011, Gibellini Lara, 2010) (Figure 4).

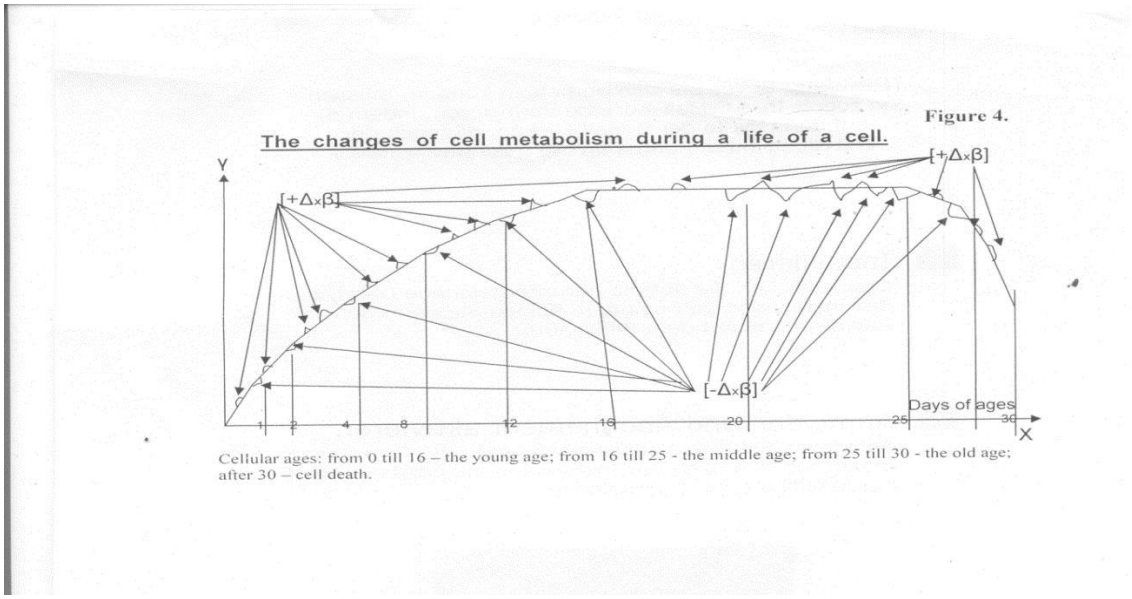

Figure 4. Cell metabolism during cell life

The rejected cell subjected to Apoptotic death and Autophagy (Figure 4). Therefore, the cells types expend energy, received from stem cells, during their life, and each next cellular cycle of 50 cellular cycles will be less efficient defensive, i.e. cellular wall more permeable for viral antigens. The intruded viral agents bring supplemental energy for old cells inducing cellular moderate haploid division via meiosis creating benign neoplasms [nevus, wart, different benign adenomas, benign polyp etc.]. The sister chromatids are segregated to separate daughter cells for producing a total of four haploid cells. Meiosis or reductive cellular division occurs via division cell's nucleus of eukaryotic cells with decreasing chromosomes in two times.

It occurs in two steps as reductive step and equational step of meiosis. The decreased chromosomes, as the result of meiosis, reflect transition diploid phase to haploid phase. Thus, it occurs local moderate proliferative processes where old cells are divided via meiosis with forming local benign neoplasms [nevus, wart, different benign adenomas, benign polyp] creating some resistance to apoptosis due to slow supplementary permanent proliferation without rejection of benign cells. Just haploid division creates more stepped division via Prophase I, Metaphase I, Anaphase I, Telophase I, Prophase II, Metaphase II, Anaphase II, Telophase II as compared with diploid division via Prophase, Prometaphase, Metaphase, Anaphase, Telophase. Therefore, meiosis of haploid division expends less energy than mitosis for diploid division, and meiosis is more economic division than mitosis. Thus, neoplasms are formed when viral agents affect only M phase cellular cycle [Mitosis], i.e. last superficial phase of cellular cycle "M phase" of old cells in last layer cellular divisions.

Taking into account that viruses cannot live out of organisms, we suppose that the ray's quanta from solar thermonuclear synthesis generate by short wavelength solar rays some viral non-living organisms [as well as also beetles, flies and the other insects at spring]. These viral non-living organisms were transformed into living organisms [viruses] due to intruding in organism's genome. Such viral intruding into a living human organism is promoted by influences of local solar radiation on an organism's tissue

with influences of surroundings' conditions, e.g. different carcinogens, inheritance susceptibility to these influences or weak barrier and so on. A foetus and an embryo are defended from viruses by transplacental barrier. Therefore, only almost all adult organisms are subjected to be affected by moderate viruses. As concerning to benign adenomas into an organism and benign polyps into intestine, maybe some moderate viruses can also be diffused by blood into internal organs of an organism. Therefore, chemical potentials of benign neoplasm tissue's cells are differed from chemical potentials of able-bodied tissues' cells exhibiting retarded cellular cycle and slowed down proliferative process without apoptotic processes. However, driving mechanism of cellular cycle, G1/S/G2 phases, is not touched by viruses in benign neoplasm's tissue because "M" phase cellular cycle is last superficial phase cellular cycle. Although chemical potentials of benign neoplasm tissue's cells are differed from chemical potentials of able-bodied tissues' cells, resonance waves of cells in able-bodied tissues of an organism are not strange to benign neoplasm's tissue due to identical biochemical structures of substances in cells of both benign neoplasms' tissue and in able-bodied tissues. Also, benign neoplasm tissue's cells are not subjected to regulative processes of an organism's cells due to unrelated resonance waves of benign neoplasm's cells and an organism's cells. Thus, benign neoplasm tissue exhibits autonomic development.

The moderate expression anabolic endergonic processes and moderate suppression catabolic exergonic anaerobic processes with moderate expression catabolic aerobic exergonic processes promote oxidative excretion products of biochemical reactions via CO_2 and H_2O, in benign neoplasm's cells. Moreover moderate expression anabolic endergonic processes and moderate suppression catabolic exergonic anaerobic processes with moderate expression catabolic exergonic aerobic processes don't produce great quantity superoxide O_2* in benign neoplasm's cells. Besides the moderate expression anabolic endergonic processes and moderate suppression catabolic anaerobic exergonic processes with moderate expression catabolic aerobic exergonic processes don't produce great surplus Lactic acids, i.e. marker of Glycolysis, in common balance anabolic endergonic processes and catabolic anaerobic exergonic processes and catabolic aerobic exergonic processes in benign neoplasm. Thus, metabolism of benign neoplasm's tissue is also determined via "incompatibility aerobic oxidation and Glycolysis" according to Pasteur effect. Hence a human organism retains normal Stationary State despite benign neoplasm in it.

The mechanisms of transmutation benign neoplasm into cancer causing mechanism metastasis into the other inner organs (Lung, liver, kidney, cerebrum etc.)

Just benign neoplasm into internal organ is often mutated into malignant neoplasm being affected by viral oncogenes. Viruses as viral oncogens are generated by the quanta rays of short wavelength from solar thermonuclear synthesis with influences of different carcinogens. These viruses exhibit malignant property how capability translocation into inner organs causing metastasis etc. Also, it appears assumption that viral oncogenes arise in the inner organs of an organism because viruses cannot live out of organisms. However as compared with viral affected mitotic "M" phase for causing benign neoplasms, cancer v-oncogene affects driving mechanism of S /C2 phases cellular cycle exerting excessive processes replications. Affected by cancer v-oncogene, nuclear DNA of tissue's cells are subjected to accept accelerating viral cellular cycle which requires abundance energy and Acetyl-CoA for anabolic endergonic processes in G1/S and G2 phases for excessive processes replications in accelerating cellular cycle. Excessive processes replications in accelerating cellular cycle change normal cellular chemical potentials of able-bodied cells due to changed chemical potentials of nuclei ($\mu_{can.nucl.}$) and mitochondria ($\mu_{can.mitoch.}$). These cancerous chemical potentials of nuclei ($\mu_{can.nucl.}$) and mitochondria ($\mu_{can.mitoch.}$) change permeability nuclei and mitochondria membranes creating chemical potentials of cancer cells' cytoplasm's ($\mu_{can.cytopl.}$).

The excessive processes replications in accelerating cellular cycle lead to excessive shift cellular balance anabolic endergonic processes and catabolic anaerobic exergonic processes of oxidative phosphorylation (Krebs tricarboxylic acids cycle) into excessive abundance anabolic endergonic processes. Just the requiring supplementary abundance energy and Acetyl-CoA for excessive anabolic endergonic processes in G1/S and G2 phases, the cancerous anabolic endergonic processes consume huge quantity energy and Acetyl-CoA that cause overload of "Nodal point of bifurcation anabolic processes and catabolic anaerobic processes [NPBac]" with partial suppression catabolic anaerobic processes of oxidative phosphorylation (Krebs cycle), remaining some catabolic anaerobic processes for cellular survival (Ponisovskiy M.R, 2010, Lopez-Lazaro Miguel, 2010). (Figures 5 and 6). Thus, also it occurs in mitochondria of cancer cells shift cellular balance catabolic aerobic oxidation and catabolic

anaerobic oxidative phosphorylation into excessive catabolic aerobic oxidation due to partial suppression catabolic anaerobic oxidative phosphorylation of Krebs tricarboxylic acids cycle (TCA).

The excessive shift balance catabolic aerobic oxidation and catabolic anaerobic oxidative phosphorylation into great expression catabolic aerobic oxidation in cancer tissues leads to situation that stable quantity oxygen (O_2), obtained via systems oxyhaemoglobin and Cytochrome c/Cytochrome-c-oxidase due to stable organism's respiratory index [CO_2: O_2 = 0,8 average], don't find sufficiently hydrogen ions (H^+) in cancer cells for forming water (H_2O) because of partial suppressed Krebs tricarboxylic acids cycle (TCA). Hence it is produced the great quantity of mitochondrial superoxide [O_2*], due to adding electron [e^-] to oxygen (O_2). The superoxide [O_2*] does not lead to final products CO_2 and H_2O. The superoxide [O_2^{*-}] reduces Ferric iron [Fe^{3+}] into Ferrous iron [Fe^{2+}] and forms supplementary oxygen:

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

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

$$2O_2^{*-} + 2H^+ = H_2O_2 + O_2$$

The concentration of superoxide [O_2*] is grown higher in mitochondrial matrix than in cytoplasm and nucleus. Thus, it happens Haber –Weiss reaction of catalysed iron production via superoxide transformations which pass into Fenton reaction with forming abundance free radicals Ponizovskiy M.R, 2013, Furda Amy Marie, 2011.

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

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

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

The huge formed complex ROS/H_2O_2 with free radicals (*OH) pass through mitochondrial membranes and cytoplasm into nucleus, owing to changed permeability nuclei and mitochondria membranes. Free radicals (*OH) react on nuclear DNA [nDNA] and induce supplementary exertion of excessive processes replications via realizing of 2nDNA in cancer cells Ponizovskiy M.R, 2013, Furda Amy Marie, 2011.

$$*OH + H_2\text{-nDNA-DNA} \longrightarrow H_2O + H^{\bullet}\text{-nDNA-DNA};$$

$$O^{*} + 2H_2O \longrightarrow 2H^{\bullet} + 2OH^{-};$$

$$2H^{\bullet}\text{-nDNA-DNA} + 2H^{\bullet} \longrightarrow 2\text{nDNA-}H^{\bullet} + 2\text{nDNA-}H^{\bullet};$$

$$2\text{nDNA-}H^{\bullet} + 2{*}OH \longrightarrow 2\text{nDNA} + H_2O$$

Thus, excessive processes replications with accelerated viral cellular cycles induce nuclear cancerous accelerated cellular cycles which stimulate mitochondrial excessive production of huge quantity free radicals (*OH) that advance exertion of irrepressible proliferative processes of cancer cells.

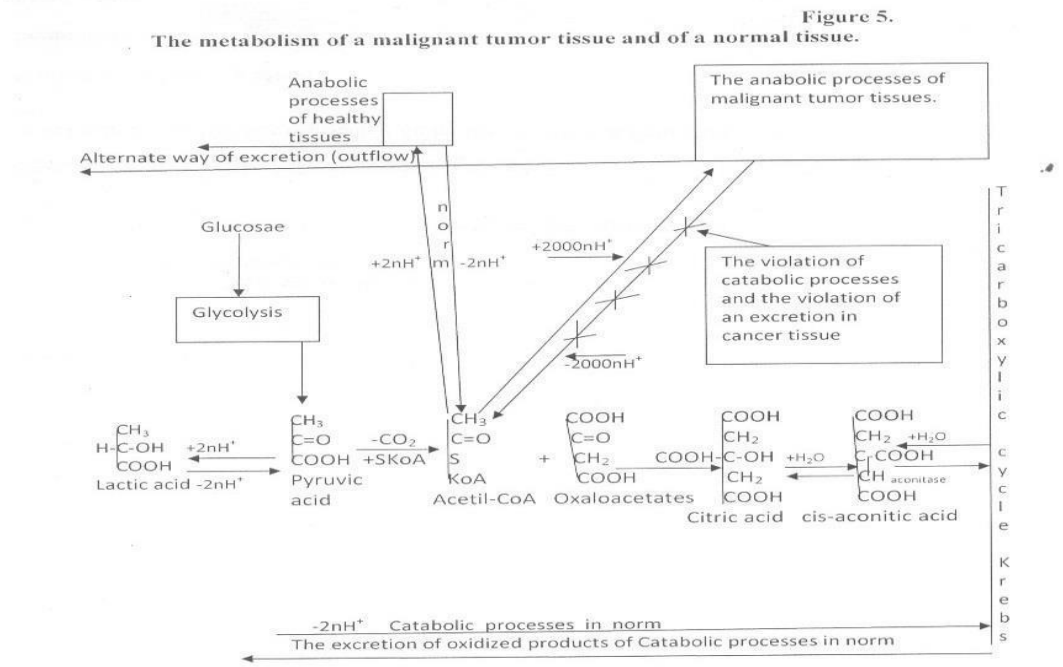

Figure 5. Warburg effect in cancer metabolism

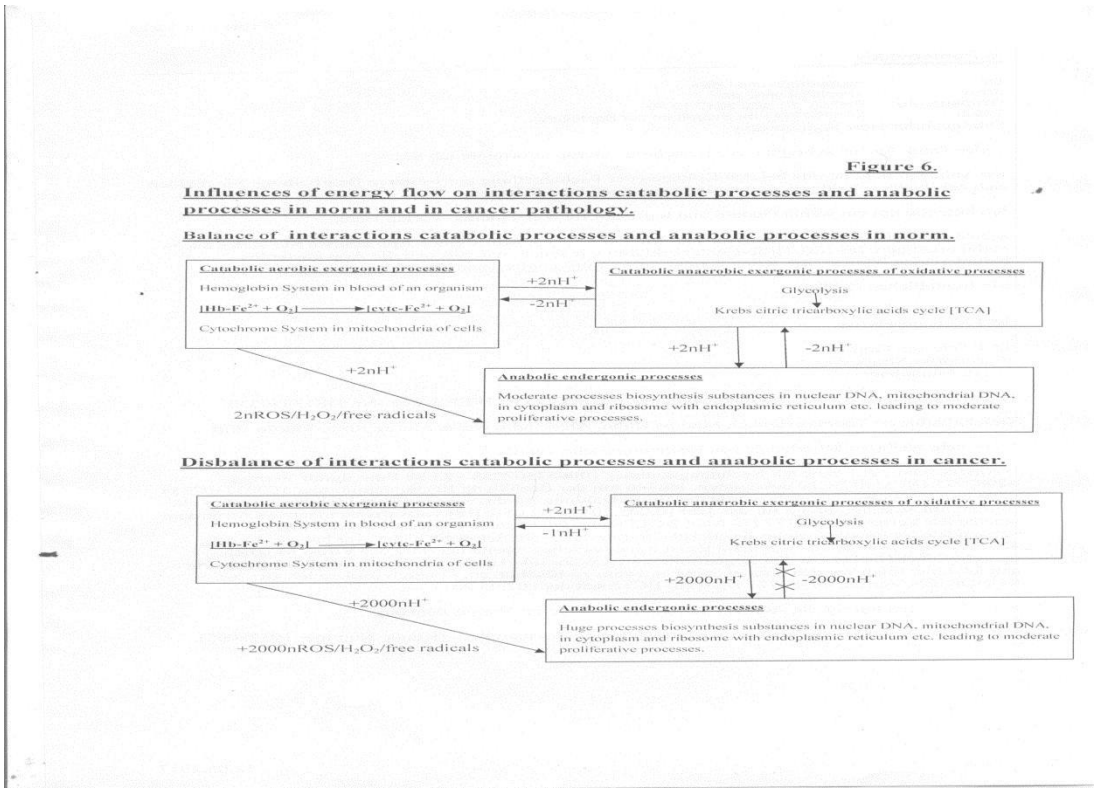

Figure 6. Energy flow in norm and cancer pathology

But transition normal balance anabolic endergonic processes and catabolic exergonic anaerobic processes into excessive anabolic endergonic processes with expression catabolic aerobic oxidation create Warburg effect of Aerobic Glycolysis. Aerobic Glycolysis arises because Glycolysis is driving mechanism both excessive anabolic endergonic processes and partial suppressed catabolic exergonic anaerobic processes which arises expression catabolic aerobic exergonic oxidative processes. Besides great increased Lactic acids, being marker of glycolysis, define aerobic glycolysis in cancer metabolism because lactic acids accumulate energy for excessive anabolic endergonic processes in condition of expression aerobic oxidative processes of cancer metabolism (Ponisovskiy M.R, 2010) (Figure 5). As compared with Warburg effect in cancer tissue, in able-bodied tissue the both balance anabolic endergonic processes and catabolic anaerobic exergonic processes and balance catabolic aerobic exergonic oxidative processes and catabolic anaerobic exergonic oxidative phosphorylation processes demonstrate incompatibility aerobic oxidation and Glycolysis according to Pasteur effect because energy and Acetyl-CoA, produced by Glycolysis, are shared between anabolic endergonic processes and two catabolic exergonic processes (Ponisovskiy M.R, 2010). (Figures 5 and 6). But the two identical catabolic pathways [aerobic and anaerobic pathways] together take more energy and Acetyl-CoA than one anabolic endergonic pathway in norm. Therefore, the Lactic acids as marker of Glycolysis don't increase in common balance anabolic endergonic processes and catabolic anaerobic exergonic processes and catabolic aerobic exergonic processes showing "incompatibility Glycolysis and aerobic oxidation in able-bodied tissue" according Pasteur effect (Ponisovskiy M.R, 2010). Also, the mechanism of Warburg effect leads to forming metastasis and unhealed cancer wounds in following mode: The overload of "Nodal point bifurcation anabolic and catabolic processes" [NPBac] due to great consumption energy and Acetyl-CoA by excessive anabolic endergonic processes causes partial suppression catabolic anaerobic processes due to lack energy and Acetyl-CoA for catabolic processes (Figure 5 and Figure 6).

Partial suppression catabolic anaerobic exergonic oxidative phosphorylation impedes oxidative decomposing synthesized high-molecular substances leading to excretion these high-molecular substances within separated cancer cells. These separated cancer cells with high-molecular substances in them move to healthy tissue without overload of "Nodal point bifurcation anabolic and catabolic processes" [NPBac] forming metastasis (Ponisovskiy M.R, 2010). Also, cancer cells are not subjected to regulative processes of an organism's cells due to unrelated resonance waves of cancer cells and an organism's cells and are also not subjected to regulative processes of an organism, creating autonomic development of cancer cells (Ponisovskiy M.R, 2010). Besides some cancer cells with the high-molecular substances in them fall out into environment that forms cancerous unhealed wound (Ponisovskiy M.R, 2010). Thus, spreading metastasis in an organism causes consumption great quantity energy and substances for excessive huge anabolic processes of cancer metabolism leading to Quasi-Stationary State of an organism which can leads to cancerous cachexia and to an organism's death.

Highlights of cancer metabolism

As outcome of v-oncogenes operation the excessive anabolic processes cause huge consumption of energy and Acetyl-CoA and partial suppression catabolic anaerobic processes in cancer tissue due to lack Acetyl-CoA for catabolic anaerobic processes in cancer metabolism. Just great quantity Lactic acids accumulate energy for excessive anabolic processes in condition great glycolysis metabolism in cancer tissue. Partial suppression catabolic anaerobic oxidative phosphorylation of link Glycolysis - Krebs tricarboxilic citric acids cycle causes excessive shift balance Aerobic oxidative respiratory processes and anaerobic processes of oxidative phosphorylation into prevalence of Aerobic oxidative processes. Partial suppression of Anaerobic processes oxidative phosphorylation in cancer cells induces forming excessive quantity of ROS/H_2O_2/Free radicals in mitochondria which exert excessive accelerating replications in S/G2 phases cellular cycle via realizing of excessive 2n DNA replication process. Affected by viral oncogenes and accepted their accelerating cellular cycle, cancer cells display excessive processes replications in accelerating cellular cycle causing cancer cells' irrepressible proliferative processes and cancer tumor irrepressible growth. Thus, cancer metabolism shows Aerobic Glycolysis metabolism according to Warburg effect.

DISCUSSION

Transmutation of benign neoplasms into cancer

There was considered affected by virus of able-bodied tissue's cells causing genomic mechanism transition normal cells into benign neoplasm's cells which don't subjected to regulatory mechanism of an organism, and an organism preserves stabile Internal Energy of its Stationary State. Just benign polyp and benign adenomas are most often subjected to transmutations into cancer than other benign neoplasms, although it was also known transmutation wart and the other neoplasms into cancer. However biophysical and biochemical mechanisms of all these transmutations are identical reflecting mechanism transmutation cellular cycle of benign neoplasm into malignant neoplasm due to identical mechanism of affected target by viral oncogene. Moreover, considering that viruses cannot live outside organism, we suppose that the quanta of short wavelength solar rays from solar thermonuclear synthesis generate both living organisms (e.g. different insects in spring) and non-living organisms being generated via haploid genomic mechanism into some viral organisms which are transformed into living viruses due to influences of carcinogens in condition of a human organism. Just the viruses use eukaryotic organisms for their vital activity intruding in an organism's genome. The transmutation benign neoplasm into malignant neoplasm occurs via different affecting tissues of an organism's organs. However, the biophysical and biochemical mechanism transmutation benign neoplasm's cells into cancer cells differ from transition able-bodied cells into benign neoplasm's cells. The target of moderate viral activity by transition normal cells into benign neoplasm's cells is "M" phase cellular cycle causing transition mitosis into meiosis. The target of viral oncogene is driving mechanisms of S /G2 phases cellular cycle which are additionally induced by free radicals causing supplementary stimulating replicative processes for exertion excessive proliferations.

CONCLUSION

Transmutation cellular cycle of benign neoplasm into cancerous cellular cycle of malignant neoplasm causes irrepressible proliferative processes with irrepressible tumor growth, metastasis, invasive capability, Apoptosis resistance etc., which leads to Quasi-stationary state cancerous cachexia and death of an organism.

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