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A systemic evolutionary approach to cancer: Hepatocarcinogenesis as a paradigm

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ABSTRACT

The systemic evolutionary theory of cancer pathogenesis posits that cancer is generated by the de-emergence of the eukaryotic cell system and by the re-emergence of its archaea (genetic material and cytoplasm) and prokaryotic (mitochondria) subsystems with an uncoordinated behavior. This decreased coordination can be caused by a change in the organization of the eukaryote environment (mainly chronic inflammation), damage to mitochondrial DNA and/or to its membrane composition by many agents (e.g. viruses, chemicals, hydrogenated fatty acids in foods) or damage to nuclear DNA that controls mitochondrial energy production or metabolic pathways, including glycolysis. Here, we postulate that the two subsystems (the evolutionarily inherited archaea and the prokaryote) in a eukaryotic differentiated cell are well integrated, and produce the amount of *clean* energy that is constantly required to maintain the differentiated status. Conversely, when protracted injuries impair cell or tissue organization, the amount of energy necessary to maintain cell differentiation can be restricted, and this may cause gradual de-differentiation of the eukaryotic cell over time. In cirrhotic liver, for example, this process can be favored by reduced oxygen availability to the organ due to an altered vasculature and the fibrotic barrier caused by the disease. Thus, hepatocarcinogenesis is an ideal example to support our hypothesis. When cancer arises, the pre-eukaryote subsystems become predominant, as shown by the metabolic alterations of cancer cells (anaerobic glycolysis and glutamine utilization), and by their capacity for proliferation and invasion, resembling the primitive symbiotic components of the eukaryotic cell.

Introduction

The prevailing theory of cancer development (carcinogenesis) attributes its primary cause to mutations of nuclear DNA, such as oncogenes and tumor suppressor genes [1,2]. Standard chemotherapeutic treatments in medical oncology are based mostly on this genetic mutation assumption. However, this theory, which is often presented as dogma in textbooks of oncology, is in crisis [3]. Building even more elaborate genetic models of carcinogenesis has been linked to adding epicycle models to the pre-Copernican Ptolemaic paradigm of planetary motion in order to explain discrepancies in astronomical data without postulating that the earth revolves around the sun. The description of the motion of each newly discovered planetary body had to be retrofitted to Ptolemy's theory of "planetary perfection" [4]. A change of paradigm, from the genetic theory of cancer origin to a new theory, is therefore needed.

Prevailing theories of cancer

Several "theories of cancer" or groups of theories have been proposed over the last decades. For example, a group of five theories includes mutational, genome instability, non genotoxic and Darwinian, tissue organization [5]. Another group includes mutational, genome instability, Darwinian, epigenetic, tissue organization field theory, a based on ontophylogenesis [6]. A summary group of three theories is represented: by tissue organization field, the cancer stem cell and the intrinsically disordered proteins theory [7]. However, a simple grouping into two main groups: (a) cellular theories of cancer and (b) tissue theory of cancer [8,9] summarize all these different points of view. The cellular theories include different subgroups that are updates of the initial somatic mutation theory of cancer, and are determined by new research

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findings: mutational standard theory, selection theory of cancer cell (Darwinian theory of cancer), mutator genes-chromosomal instability theory, epigenetic theory. The original mutational theory of cancer states that very few driver mutations in somatic cells are able to generate a cancer cell, and was initially based mainly on epidemiological and experimental studies [10], then supported by molecular biology studies with the discovery of oncogenes and cancer suppressor genes [2]. This theory has been modified to explain the heterogeneity of cancer cells, not only between different types of tumors or in the same type of tumor between different patients, but even within the same tumor in the same patient [11,12]. To the somatic mutation theory of cancer pathogenesis (mutations generated in many different ways: x-rays, chemical substances, viruses, etc.) was added the concept of selection of the cancer cells that were most fit to compete with other cells to adapt to the environment [13]. Then, a new update of the somatic mutation theory was determined by the arrival of genomic data on cancer that showed that mutations in cancer cells are not few, but actually a huge number, so the theory was changed to include the concept of "mutator phenotype" resulting in a heterogeneous cell population. Cells harboring mutated genes that cause many contemporaneous or successive mutations, with chromosomal instability as a variant of this theory [14]. Finally, another change of the somatic mutation theory known as the epigenetic theory of cancer occurred. This theory was proposed after the description of cancers without genetic mutations and with only variation of intensity of gene expression or gene silencing, caused by the methylation or acetylation of histones or direct methylation of nuclear DNA [15]. A different theory of cancer is the tissue organization field theory, in which the cause of cancer is proposed to be a disturbed communication between different types of cells within their tissue of residence, caused mostly by chronic inflammation [16,17]. The theory of the pathogenesis of cancer cells as a consequence of a stem cell that does not evolve [18] can be considered in a certain way, as a subgroup of the field theory of cancer, or a compromise between the field theory and the somatic mutation theory. The updates to the somatic mutation theory and to the field theory, signal the fact that both theories probably are incomplete descriptions of cancer pathogenesis and a new theory is needed to help in explaining several unexplained aspects of cancer. For example, there are certain facts in cancer that are not explained by these theories of carcinogenesis, indicated as paradoxes in carcinogenesis [4]. The spontaneous regression of cancer is one of these paradoxes in carcinogenesis. Furthermore, there are the findings from nuclear to cytoplasmic transfer experiments that contrast with the somatic mutation theory of cancer origin [19]. We think that both the somatic cell mutation theory and the tissue organization field theory of carcinogenesis can be included in a new theory, namely a "systemic evolutionary theory of cancer pathogenesis", which can better explain the conundrum of data on this disease.

Fundamentals for a new theory of cancer

There are some concepts from cellular evolution and systems biology that can be very useful to build a new theory of carcinogenesis.

Cellular evolution

A growing body of scientific evidence supports the idea that the formation of the eukaryotic cell is an exceptional event, due to the endosymbiosis of an archaea and a prokaryote more than two billion years ago [20–22]. These two very different types of bacteria started to collaborate, with the archaea engulfing the prokaryote. The collaboration became so strict at a certain point that most of the genes of the prokaryote were transferred to the DNA of the archaea, saving a lot of energy of the primitive eukaryote [23]. The archaea (genetic material and cytoplasm) were able to metabolize glucose to pyruvate through the process of anaerobiosis, generating a small amount of energy as ATP. However, the prokaryote (mitochondrion) was able to metabolize pyruvate to H_2O and CO_2, thus producing a major increase in quantity of energy per gene than the original pre-eukaryote, utilizing chemi-osmotic coupling and oxygen [24,25]. The important aspect about this endosymbiotic model is, not only the enormous increase of energy production per gene (that allowed an increase in protein synthesis, energetically more expensive than gene reproduction), but also the efficient elimination of metabolic waste. Instead of the lactic acid produced by the primitive archea, the eukaryote produces the easily eliminable H_2O and CO_2, a very efficient way to eliminate the waste generated by an increased consumption of energy (Fig. 1A). This is a wonderful system design of the eukaryote cell that could also allow for multicellularity [26,27].

However, the inefficient elimination of metabolic waste and the production of *unclean* energy postulated in the primitive protists are features that recur in transformed or de-differentiated cells (Fig. 1B).

Systems biology

The eukaryote can be conceptualized as an emergent system made by two subsystems [28]. One subsystem produces information and little energy (the *old archaea*, now the nucleus and cytoplasm) whereas the other one produces energy and little information (the *old prokaryote*, now mitochondrion) with the waste coming from the first subsystem (i.e. lactate), which is managed by the second subsystem to become CO_2 and H_2O, in an almost perfect system design [26,27]. This way of looking at the cell from the systemic point of view, using the concepts of boundaries, hierarchy of systems and emergence, is quite different from the concept of a cell as a network (a reductionist way of thinking

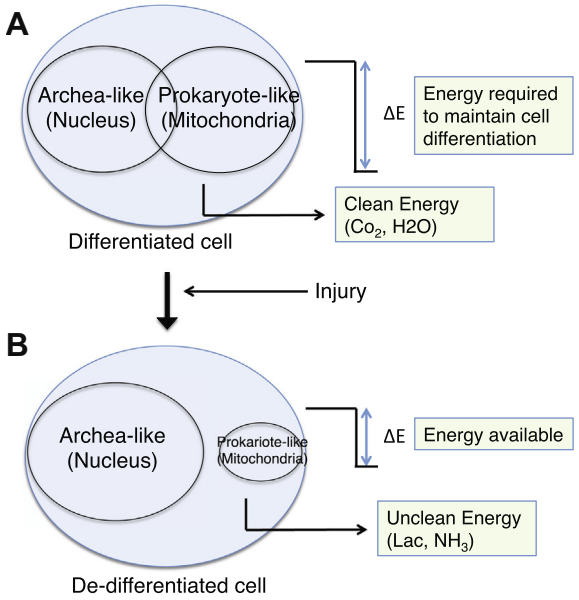

Fig. 1. A constant energy budget (ΔE) as well as a functioning balance between the two subsystems of the eukaryotic cell, the ancestral "archaea" (now the nucleus) and the ancestral "prokaryote" (now the mitochondria), are both required to maintain the status of differentiated cell. The transition from differentiated (A) to de-differentiated cell as a consequence of a protracted injury (B) is accompanied by reduced energy budget, decreased mitochondrial activity (with prevalence of fermentative glycolysis) and the passage from the *clean* to *unclean* energy.

about systems) shown in many textbooks of systems biology of the cell [29]. The field theory of carcinogenesis [30] uses a systems thinking approach, but it is applied to tissues, while our new theory starts from the cell itself before considering tissues. The two subsystems of the eukaryote, the informative and the energetic one work in series, even though the energetic subsystem is made from many copies of the same unit (the mitochondrion) that work in parallel to safeguard the energy production for the cell. However, the plurality of mitochondria can be considered as a single subsystem with its own boundary from our modeling point of view. The eukaryotic cell as a complex adaptive dynamical system thus emerges from the symbiogenesis (endosymbiosis) of these two subsystems, the archaea and the prokaryote, in a new boundary (the cell membrane). This endosymbiosis generates a non-linear change of the merged activities: concentration of information, multiplication of energy, and wastes that are more manageable from the environmental point of view. All these characteristics open the way to the evolution of the primitive eukaryote to a complex adaptive dynamical system, completely different from the previous single archaea and prokaryote, even though including them.

A systemic evolutionary theory of cancer

The systemic evolutionary theory of cancer pathogenesis states that cancer is generated by the de-emergence of the eukaryotic cell system and by the reappearance of its archaea and prokaryotic subsystems, with autonomous, or at least uncoordinated, behaviors; a hypothesis suggested by very few authors [31,32]. This de-emergence of the eukaryote generates problems at cell and tissue level, and eventually it can threaten the survival of the whole organism. A first step in cancer pathogenesis can be represented by a decreased coordination between the two subsystems of the eukaryotic cell, the archaea (now nuclear DNA and cytoplasm) and the prokaryote (now mitochondria) that begin to work independently (Fig. 2). This decreased coordination can be caused by a change in the organization of the eukaryote environment, mainly chronic inflammation [33], by damage to mitochondrial DNA and/or to its membrane composition [34] caused by viruses, chemicals, hydrogenated fatty acids in foods, etc. and by damage to nuclear DNA that control mitochondria energy production or metabolic pathways like glycolysis [35]. In all these cases, the final result is the de-emergence of the eukaryote, with the re-appearance of its old sub-systems, the archaea and the prokaryote, which now work separately. This systemic change allows the de-emerged cell to survive, but at the expense of the surrounding cells and the organization of the tissue and eventually of the whole organism. There are quantitative and qualitative changes in the de-emerged eukaryote, mainly in its way of producing energy, eliminating waste, and interacting with other cells [36], which make the cell assume "atavistic" characteristics. These phenotypic changes can be determined by the somatic mutation of single genes in series, one after the other, or by the simultaneous change of many genes caused by a driver-mutator gene. However, this change of functions (reappearance of the old gene organizations present in the ontophylogenesis of the organism) is better determined by the simultaneous and coordinated change of many gene networks under the pressure of the de-emerged eukaryotic cell struggling to survive in a new cell organization and/or environment. The hallmarks of cancer, the Warburg effect, cancer glutaminolysis, the adaptations of the cells surrounding the cancer cell metabolizing lactic acid, a sort of eso-symbiosis to substitute the failed endo-symbiosis are all characteristics of the cancer cell [37–40]. This could be re-interpreted in the light of the de-emergence of the eukaryotic cell (in the light of evolution) and its association with changes in many nuclear gene networks. They are consequences of the uncoordinated functioning within the cell membrane boundary of the nucleus-cytoplasm subsystem (the atavic archea) and of the mitochondrial subsystem (the atavic prokaryote). The second step of cancer pathogenesis, including

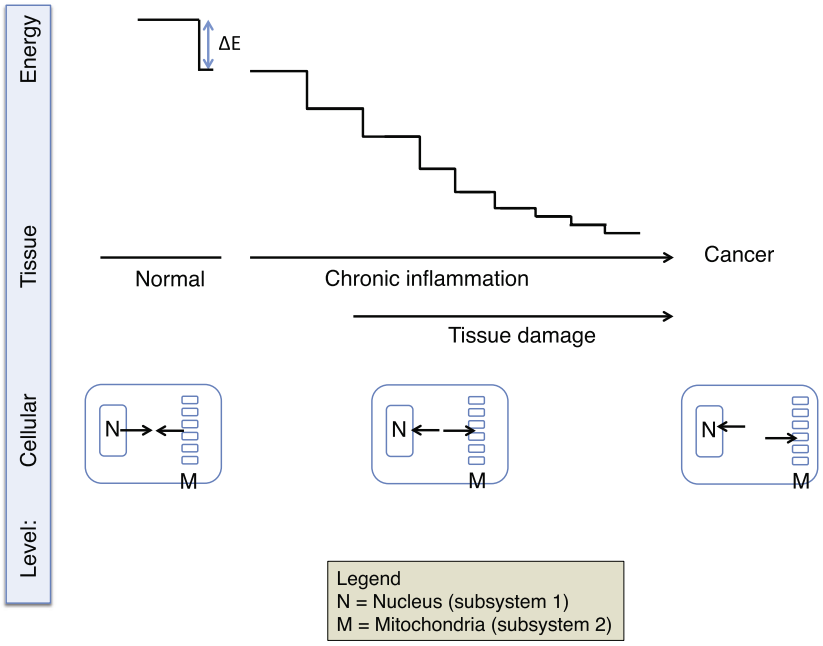

Fig. 2. An energy package is constantly required by the normal cell (e.g. hepatocyte) to maintain its differentiated status. Normally, in the absence of tissue alterations, this is constantly guaranteed and the energy flow works properly, so the two subsystems (the ancestral "archaea", now the nuclues N and the ancestral "prokaryote" now the Mitochondria M) are perfectly integrated with no prevalence of one system on the other. In the case of chronic injury (e.g. multi-year inflammation as in liver cirrhosis), the energy package (amount of energy) necessary to maintain the cell differentiation can be reduced, and this may cause over time a gradual decoupling of the two subsystems. When the energy package becomes constantly insufficient, the two subsystems get completely uncoupled and this may represent a first step in cancer pathogenesis, characterized by a decreased coordination between the two subsystems of the eukaryotic cell, the archaea and the prokaryote, which begin to work independently.

dissemination of cancer cells and formation of metastases, may be supported by a decrease in mitochondrial functionality below a certain threshold, in association with a simultaneous increase in the activity of the anaerobic part of the eukaryotic cell namely the nucleus-cytosol [41,42]. Genetic mutations affecting the nuclear and/or mitochondrial genes and chronic tissue inflammation can determine the neoplastic transformation of the eukaryotic cell, but the final explanation of the pathogenesis of cancer (the prime cause of cancer, as in the words of Otto Warburg) is a systemic change at the cellular level: the de-emergence of the eukaryote cell and its division into the old archaea and the old prokaryote within the same boundary, with consequent changes in the management of energy and waste as well as in the relationship with other cells. These cellular changes cause modifications at the tissue level and then at the organism level [43]. It is the de-emergence of the eukaryotic cell as the primary cause of cancer, that makes many gene networks change at the same time. The systemic evolutionary theory of cancer can explain the transformation of a normal cell, a complex adaptive dynamical system, into a cancerous cell, another complex adaptive dynamical system, but selfish and uncoordinated towards the other cells in the tissue of origin. Afterwards, the proliferation of cancer cells can be specifically stimulated by modern diets, rich in carbohydrates and animal proteins, that feed anaerobic glycolysis with sugar and mitochondrion with proteins [44].

Thermodynamics, stability, disturbances and control mechanisms in cells as complex adaptive dynamical systems, and their importance for cancer causation

In our theory of cancer causation, we refer to general causes, in the sense that so far the various proposed theories of the causes of cancer refer to local causes, without a glimpse of the possible fundamental relationship that binds all local causes, or most of them, to the genesis of cancer. It is time for a common view that unifies the different theories, accepting the suggestion of the famous theoretical physicist Richard Feynman: "take the world from another point of view" [45]. In our theory, there is more attention to the evolution of the cell, how this dynamic complex adaptive system was formed and to the endosymbiosis between two subsystems with their specific flows of energy and information. What are the conditions to be met by a differentiated normal cell, to survive? Given that the cell is a living organism, a coherent complex system with a program [46], it is necessary to obtain useful (privileged) energy to be converted into chemical bonds and various types of work or to be partly degraded as heat, usable at the nanometer level by molecular motors (e.g. kinesins and myosins) [47–50]. It goes without saying that the laws of thermodynamics must be respected in this process of energy conversion, considering the cell an open system that exchanges matter and energy. The functioning of a complex system such as the cell is certainly hierarchical and controlled by a regulation system with positive and negative feedbacks. Therefore, we should first examine a well-functioning emergent differentiated cell, the "emergence", and then try to figure out how a "de-emergence" represented by a cancer cell takes place. The proper functioning of a differentiated cell is influenced deeply by an efficient use of energy and is regulated by an appropriate system of control in a hierarchical organization. Essentially, there are thousands of coupled sequences of enzymatic reactions, with enzymes and enzyme systems as biological catalysts, wherein the signaling pathways are crucial information. In a mammalian emergent eukaryotic cell, the main flows of matter and energy are *chemical transformation*, *transport through the cell membrane, and transition from mechanical to chemical energy*. These interactive sequences of enzymatic reactions and transmission of information signals (pathways) require a definite budget of free-energy that is indispensable for any differentiated cell, an optimum energy budget value ($\Delta G^{\max}$). The most important part of this complex mechanism of energy production and flow is generated by the endosymbiosis between the two subsystems present in the cell, the residual archaea and the prokaryotes, respectively the nucleus with cytoplasm and the mitochondria. The crucial question is what happens to a differentiated cell when this optimal budget of energy is altered. There are several possible causes of perturbation (generally injury- or inflammation-related) with variation in amplitude, duration and frequency. How does the cell, a complex dynamical adaptive system, react to such disturbances? The theory of the stability of open systems examines some possible behaviors of perturbed systems [51]. To work properly, a complex system (our body cells) is equipped with a redundant control system (the opposite of an engineering network that is designed optimally), because the more the system is complex, the more the errors are frequent. In fact, one of the most interesting and still largely unresolved questions in the context of complex systems is the puzzle of their stability. The question now is if we should continue to deal with the local causes and the infinite possibilities of fluctuations that can undergo the system (i.e. interactive sequences of enzymatic reactions, interactive transmission sequences of signals, etc.), as it is done actually in cancer research from a reductionistic point of view. In our new theory of cancer, instead of researching these thousands of possible fluctuations and local causes that can destabilize the system and lead to cell de-differentiation and possibly cancer, we start with the evolution of the eukaryotic cell to identify the primary cause of the fluctuations that can become critically destabilizing because they are no longer controlled by regulatory systems. We propose focusing on two parameters which are determinant for cell resilience: (i) the minimum package of energy needed for cell survival, and (ii) the symbiotic relationship between the two cell subsystems, in constant and effective relationship. These two cell features decrease the percentage of fluctuations that can destabilize the system (de-emergence), with an increase in the possibility of neoplastic transformation, a chaotic bifurcation in which the system falls into a new attractor, different from that of the normal differentiated cell [52,53]. From this systemic point of view, it can be useful to describe the behavior of a cell to define in a quantitative way a coefficient of endosymbiosis. A tentative equation for the efficiency of repair mechanism could be the following:

$$R = kI_{ES}$$

where

$$I_{ES} = 1/2I_{ES}^{max}\{\exp[-(\Delta G^{\max} - \beta \bullet \Delta G] + \exp[-(\Delta P - \Delta P^{\circ})]\}$$

and

- $\Delta G^{\max}$ = production of free energy of the normal differentiated cell;
- ΔP° = maximum amplitude perturbation that the mechanism of normal repair is able to dampen;
- $I_{ES}^{\max}$ = index corresponding to the maximum symbiosis;
- $\beta = (\Delta P^{\circ}/\Delta P)$.

From the above equation, both the exponentials tend to 1 if everything is working well, whereas they both tend to very low values if the energy production differs from the maximum, and also if the perturbation amplitude is sufficiently large compared with the dampening routine.

Hepatocellular carcinoma as a model of the systemic evolutionary theory of cancer

Hepatocellular carcinoma (HCC) is estimated to become the third leading cause of cancer-related deaths by 2030 in the United States [54]. But incidence and epidemiology apart (illustrated exhaustively elsewhere [55]), HCC is an excellent model for studying the pathobiology of cancer. This is because HCC normally develops in the liver with chronic disease, generally hepatitis and/or cirrhosis. Therefore, HCC is an example of a multistep pathogenesis of cancer where determinant risk factors such as inflammation, regeneration and fibrosis represent the background for HCC development. The fact that hepatocarcinogenesis is strongly related to chronic liver disease has also been largely shown by epidemiological studies [56]. HCC development requires several steps leading to the acquisition of tissue, cellular and molecular alterations necessary for cell transformation. The natural history of disease usually involves a chronic hepatitis (often viral), which represents an important risk factor. The evolution of this condition to a fibrotic or cirrhotic liver, with alteration of the hepatic tissue architecture and vasculature, predispose to dysplastic or pre-neoplastic areas and nodules. These are the hotbeds where HCC develops. This is accompanied or associated with genetic (generally, the frequency of replication errors is low in HCC; by contrast there is a high prevalence of chromosome abnormalities) or epigenetic modifications that seem to have a predominant role during the long pre-neoplastic stage and the early phases of HCC development. However, little attention has been paid to the plasticity of hepatocytes (as an integrated cellular system) during the long and stepwise process of carcinogenesis, considering, for example, the availability of energy and/or oxygen to the hepatocyte during cancer transformation. In other words, when and until when do the two subsystems, the archaea and the prokaryote work as a coupled system? This question offers an important starting point on why hepatocarcinogenesis is a valuable model to support the systemic evolutionary theory of cancer. The availability of energy is a suggestive explanatory link between the multistep development of HCC and the aforementioned theory, because the chronic damage to the liver organization may offer an interesting model for the depletion of energy [57]. Here, we propose that an energy package is constantly required by the hepatocyte to maintain its differentiated status. Normally, in the absence of tissue alterations, this is constantly guaranteed. In particular, we postulate that in normal conditions, when the energy flow works properly, the two subsystems (the archaea and the prokaryote) are perfectly integrated and there is no prevalence of one system on the other. Accordingly, the hepatocyte maintains its differentiated status (Fig. 2). As soon as injury is applied and the liver becomes damaged, the flow of energy is restricted, but still in a condition to recover if the liver damage does not last too long. However, in the presence of long lasting damage (i.e. chronic multi-year inflammation), the energy package (amount of energy) necessary to maintain the cell differentiation can be reduced, and this may cause over time a gradual decoupling of the two subsystems (Fig. 2). When the energy package becomes constantly insufficient, the two subsystems get completely uncoupled, with the pre-eukaryote component becoming predominant in terms of specific metabolism and toxic waste. In the cirrhotic liver, this process can be favored by the alteration of the oxygen availability due to the altered vasculature and the fibrotic barrier. The reappearance of the two uncoupled pre-eukaryote subsystems may explain the metabolic alterations (i.e. aerobic glycolysis or Warburg effect in the cytoplasm with lactic acid as waste, glutamine utilization in mitochondria with waste of amidic groups, and other metabolic pathways) seen in neoplastic cells [58] as well as the capacity for proliferation and invasion, especially towards areas of major oxygen availability (i.e. alteration of blood vessel architecture, arterialization of portal vein, etc.). The scenario proposed here may also explain why tissue integrity is essential to constantly guarantee the availability of a given amount of energy required for maintaining the status of the differentiated cell. Thus, tissue integrity is essential for the proper flow and availability of energy and therefore for the maintenance of cellular homeostatic functions. When integrity is not maintained over time, the balance is broken and the two subsystems become uncoupled, generally resulting in the resurfacing of a prokaryote-like phenotype. In the process of neoplastic transformation, this becomes particularly evident and could be one of the mechanisms that supports hepatocarcinogenesis.

Concluding remarks

The systemic evolutionary theory of cancer pathogenesis opens the way not only to the explanation of cancer characteristics not explained by the other theories of cancer, but also to new approaches for cancer treatment. For example, polyploidy is often an early step in tumor formation [59,60] that is explained neither by the somatic mutation theory nor by the field theory of cancer. However, it could be explained as a systemic evolutionary adaptation of the eukaryotic cell, in the process of becoming a cancer cell, to a decreased energy production using the same mechanisms of scaling up genome copy number as in giant bacteria like *Epulopiscium* or *Thiomargarita* [61]. A new direction for treatment of cancer supported by the systemic evolutionary theory could be, for example, the ketogenic diet [62], which can manage the archaeal subsystem of the cancer cell, the uncontrolled self-reproducing nucleus and the cytoplasmic aerobic glycolysis. Intracellular antibiotics could be added to this type of diet (i.e. macrolides) to control the "prokaryotic inheritance" of the cancer cell, the mitochondria [63]. This new therapeutic approach to cancer treatment could be a test of our systemic evolutionary theory of cancer, the de-emergence of the eukaryote, the "prime cause of cancer" to paraphrase the words of Otto Warburg.

Disclosures

The authors have no potential conflicts of interest to disclose.

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