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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

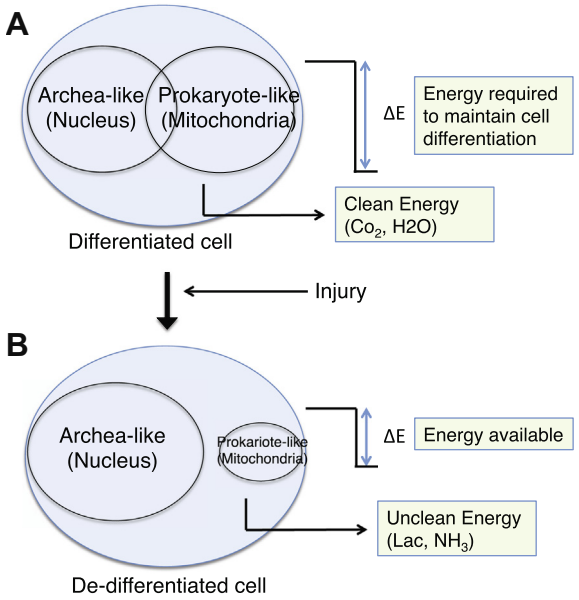

Fig. 1. A constant energy budget (ΔE) as well as a functioning balance between the two subsystems of the eukaryotic cell, the ancestral "archaea" (now the nucleus) and the ancestral "prokaryote" (now the mitochondria), are both required to maintain the status of differentiated cell. The transition from 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.