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Moving the systemic evolutionary approach to cancer forward: Therapeutic implications

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ABSTRACT

We have previously presented a new Systemic Evolutionary Theory of Cancer (SETOC) based on the failure of proper endosymbiosis in eukaryotic cells. Here, we propose that the progressive uncoupling of two endosymbiotic subsystems (*information* and *energy*) inside the cell, as a consequence of long-term injuries, gives rise to alterations (i) in tissue interactions and (ii) in cell organization. In the first case, we argue that the impairment of both the *coherent state* and the synergy between intercellular communications underpins the onset of tissue *dysplasia,* that usually evolves towards cancer development. In the second case, we suggest that the rupture of endosymbiosis drives a sort of cell regression towards a *protist-like* entity represented by the concept of "de-emergence" postulated in our systemic evolutionary approach to carcinogenesis. This conceptual association of the cancer cell with a *protist-like* organism could support the development of novel cancer therapeutic approaches. To this end, we propose a *paradigm shift* in cancer pharmacology since: i) our knowledge of cancer pathophysiology as a complex system is insufficient, despite a vast knowledge of molecular mechanisms underlying cancer; ii) current cancer pharmacology deals only with *microvariables* (e.g. gene or protein targets), which do not account for the integrated pathophysiology of cancer, rather than with *macrovariables* (e.g. pH, membrane potential, electromagnetic fields, cell communications and so on) and *mesovariables* (between *micro* and *macro*), such as the interaction between various cellular components including cellular organelles. This paradigm shift should allow cancer pharmacology to move forward from *molecular treatments* (focusing on single targets) to *modular treatments* that consider cancer-related processes (i.e. inflammation, coagulation, etc.) or even to a sort of *ecosystemic treatment* addressing the whole functioning of the "cancer ecosystem". Examples of ecosystems treatment may be natural plant derivatives that act synergistically or pulsed electromagnetic fields which can act on particular biological processes in cancer cells. In addition, we need different working theoretical models on which to base new anticancer pharmacological approaches. Finally, we examine what value our systemic evolutionary approach could add to cancer treatments, in particular in liver cancer as a paradigm for developing potential applications.

Introduction

We have recently presented a new Systemic Evolutionary Theory of Cancer (SETOC) pathogenesis, based on the failure of the correct *cellular endosymbiosis* between the *ancestral archaea* (now the information component of the cell, chiefly the *nucleus*) and the *ancestral prokaryote* (now the energy component, the *mitochondrion*), which allows the virtuous cell metabolism cycle (that can properly exploit flows of energy, matter, and information) to take place by recycling waste into clean energy production [1]. Accordingly, the acronym SETOC could also mean "Systemic Endosymbiotic Theory of Cancer". In the proposed theory, we have emphasized the importance of the regular energy budget needed to control the cell systems, ensuring the proper functioning of the differentiated eukaryotic cell as a complex adaptive system able to cope with and resist, within certain limits, perturbations (i.e. stress, injuries, damage, etc.) of a certain amplitude. In our view, the effect of prolonged injuries, causing tissue damage and inflammation, for example, as well as impairing the perturbation damping

*Abbreviations:*SETOC, systemic evolutionary theory of cancer

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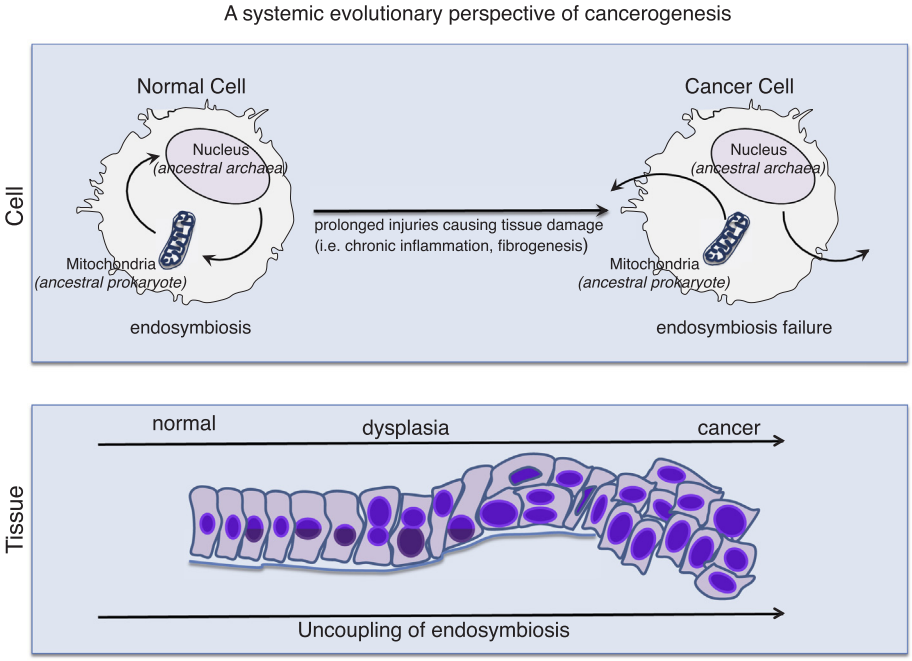

Fig. 1. A schematic model illustrating our proposed systemic evolutionary theory of cancer (SETOC). The condition of eukaryotic cells is maintained by a complex adaptive dynamic system that "emerges" from the endosymbiosis between the ancestral *archea* (now the nucleus and the cytoplasm) and the ancestral *prokaryote* (now the mitochondrion). In this model, we propose that the progressive *uncoupling* of these endosymbiotic subsystems inside the cell, as a consequence of long-term injuries, gives rise to alterations at cellular and tissue level, leading to dysplasia, and over time to cancer. We also propose that the failure of endosymbiosis drives the "de-emergence" of the eukaryotic cell and the reappearance of two endosymbiotic subsystems with autonomous and uncoordinated behaviors, characteristic of transformed cells. This would result in a sort of cell regression, reverting the eukaryotic cell phenotypically closer to a *protist*. Dysplasia would represent a partial de-emergence of eukaryotic cells within a tissue.

function, leading to the failure of the proper endosymbiosis and consequent decrease of the optimal energy budget, are all potential factors underlying tumor initiation and development (Fig. 1). A body of scientific evidence supports the idea that eukaryotic cells evolved from endosymbiosis between *anaerobic archaea* and *aerobic prokaryotes*, with the first engulfing the latter, likely more than two billion years ago [2–4]. According to the *endosymbiotic theory* of the origin of eukaryotic cells, the anaerobic archaea turned into the nucleus and the cytoplasm of future eukaryotes, whereas the aerobic bacteria generated mitochondria. The archaea (nucleus and cytoplasm) retained most of the information of eukaryotic cells but little capacity to produce energy. By contrast, the aerobic bacteria (mitochondria) kept most of the energy generation capacity and retained very little information (mitochondrial genome). We have previously suggested that mitochondria work in series with both the nucleus and the cytoplasm and in parallel with each other, thus maximally protecting the energetic component of eukaryotic cells [1]. From an energy point of view, eukaryotes can be viewed as a circular system [5]. In fact, products of the anaerobic subsystem (i.e. the nucleus and cytoplasm), mainly pyruvate from anaerobic glycolysis, are further catabolized by the aerobic mitochondria into CO_2 and H_2O, that are easily eliminated from the cell and from the body [6]. Our hypothesis about cancer pathogenesis may be considered to some extent as an extension or a continuation of Warburg's hypothesis on the origin of cancer. The German cellular physiologist Otto Warburg hypothesized that multiple factors, mostly acting together, cause cancer, but the final mechanism generating cancer was damage to the mitochondria [7]. We wish to extend the Warburg hypothesis, and propose that the final mechanism is the loss of the balanced endosymbiosis which originated the eukaryotic cell from two different *energy systems*, one aerobic and the other anaerobic. As mentioned above, the causes of cancer are multiple and of different natures (i.e. physical, chemical and biological). A local alteration in tissue architecture due to these causes, leading to chronic inflammation or other damaging processes, is an explanatory example. The interruption of endosymbiosis caused by prolonged exposure to harmful agents generates cells that lose the characteristics of current eukaryotic cells in favor of elements displaying ancestral-like characteristics, in which anaerobic archaea (nucleus & cytoplasm) generally produce energy by catabolizing glucose at high rates (e.g. activity evidenced by PET = *positron emission tomography*) and eliminating lactic acid, whereas the de-emerging ancestral prokaryote (mitochondria) produce energy mostly by catabolizing glutamine and supplying amino acids to the TCA cycle to produce ATP [8]. In cancer cells, the cycle producing energy (ATP) from metabolites and then clean energy no longer occurs. In fact, the nucleus/cytoplasm subsystem generates lactic acid whereas the mitochondria subsystem produces amino-groups. Both catabolites are difficult to eliminate from cells and tissues and from the body, and can be utilized, in a non-finalistic way, as substrates for building cancer cells [8]. In addition to the above energy problems (i.e. abnormalities in energy metabolism), failure of endosymbiosis can result in abnormal or defective cell division and chromosome abnormalities in terms of number (i.e. aneuploidy) or structure (i.e. deletions, duplications, translocations, etc.). Like the two integrated and coupled ancestral subsystems, the two altered processes, namely energy problems and defects in cell division, are obviously linked like two sides of the same coin.

Impairment of endosymbiosis and its consequences

From the biological behavior standpoint, we propose that the progressive uncoupling of two endosymbiotic subsystems (*information* and *energy*) inside the cell eventually gives rise to (i) altered interactions within tissues and (ii) alterations in cell structure (Fig. 1).

Altered interactions within tissues

Tissue damage can be caused by a large variety of injuries and the consequent effects may vary case-by-case, depending on the type of tissue and the harmful factor. Here, we postulate that the loss of endosymbiosis in cells forming a tissue could be the "turning point" generating instability of the integrated structures forming the basis of tissue organization. In physiological conditions, the virtuous feedback systems which guarantee the proper functioning of healthy tissues are based on a continuous intercorrelation between the "tissue field" (a coupling mechanism between mechanical vibrations of polar molecules and electromagnetic fields) and the chemical reactions. This results in a continuous balance, intended to maintain an organizational and non-linear dynamic state far from thermodynamic equilibrium, but capable of generating a sort of overall "coherent state of tissue". This coherent state, in turn, fosters the synergy and virtuous cooperation of the cells that form a tissue, according to several theoretical explanations