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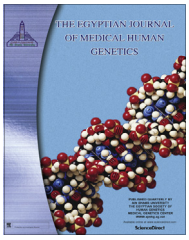

REVIEW

Cancer: Some genetic considerations

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Abstract Malignant transformation of normal cells to cancer cells represents an enigmatic phenomenon because of the many ambiguous controversies embodied within most of its aspects. Within a clinical context, cancer, with very few exceptions, is a dreadful disease that ends lethally. Within a biological context, however, cancer is a peculiar biosystem that has its own rules that regulate the actions/interactions/structure and behavior of its components. Unfortunately, the majority of these rules are, still, unknown.

The current disappointing situation as regards research trials aiming at constructing effective treatments for cancer might be attributed, in part, to incomplete recognition of the significant differences between these two contexts of malignant transformation. Although the peculiar characteristics of cancer as a self-dependent biosystem are well studied and well defined, the basic dilemma of malignant transformation continues to exist: we know, largely, how things happen but we do not know, to any extent, why they happen.

Though the logic that motivates researches aiming at formulating genetic therapies for cancer is quite reasonable, as cancer is primarily a genetic alteration, lack of essential basic knowledge regarding the different aspects of this alteration adjourn successful radical cure of cancer. Till comprehensive disclosure of the underlying mechanisms regulating growth/progression/metastasis and survival of malignant cells is attained, treatments of cancer based on different strategic concepts, viz. proteomic therapies rather than genetic therapies, might, hopefully, be the best approaches available in the fight against cancer in the current as well as in the coming era.

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1. Nature of malignant transformation

Malignant transformation of normal cells to cancer cells represents a radical change in the predefined default programing of the genome. The fate of normal cells is precisely defined according to a dogma that specifies the course of life at the molecular level. The genome of the cell dictates the basic characteristics of the cell within the context of the cell population, tissue or organ as regards essential aspects including growth and differentiation, timing of cell division, synthesis of products needed for mediating physiological functions, interactions with adjacent cells, responses to extracellular stimuli and regulatory mechanisms, and, most important, cell death when the mutation load of the cell causes considerable deterioration of cellular functions and imposes on the cell overburden pressure that drives it into apoptosis.

Transformation of normal cells to malignant cells implies numerous changes involving two main aspects of the cell: cell functions and cell architecture. Functional changes imposed by malignant transformation present as loss of functions, acquisition of new functions and quantitative/qualitative changes of preserved functions. Changes of cell architecture induced by malignant transformation impart to the cell new morphological characteristics that differ greatly from the structural properties of normal cells, and play a detrimental role in defining the natural history of tumor progression and metastasis. The marked deviation of the newly acquired structural and functional characteristics of cancer cells from normal cells constitutes the framework of the malignant phenotype which characterizes each type of malignant tumors.

The marked similarity of the phenotype of malignant cells to that of early embryonic and fetal cells represents an essential clue to understand and interpret the nature of the genetic alterations involved in the process of malignant transformation. This similarity comprises the general cardinal properties of tumor cells including enhanced rate of cell division, mass expression/suppression of large number of genes, resilience and plasticity of the cell cytoskeleton allowing for cell dissemination/migration and metastasis, augmented potential of differentiation/specialization/growth and, most importantly, altered pathways of apoptosis which allow for longer survival of cancer cells with consequent potentiation of the functional profile of the malignant phenotype. This hazardous result of halted or reduced apoptosis in malignant cells plays a critical role in conferring the aggressive behavior upon the cells and in maintaining tumor growth/progression and metastasis, which is the main culprit responsible for the dreadful end of cancer patients.

2. Genomic reprograming of cancer cell

The nature of the malignant transformation of normal to cancer cells is still very far from being completely revealed or properly understood. Many perplexing phenomena of this transformation have no interpretation largely because of lack of sufficient information regarding the underlying mechanisms involved in this mysterious biological behavior of cells. For instance, though some aspects of the malignant phenotype impart many selective advantages to the malignant cell, on the whole cancer represents the most disadvantageous fate of the genetic material that initiates and maintains this phenotype. In direct contradiction to basic concepts of biological evolution, the selective advantages conferred upon the cell by the malignant phenotype paradoxically result in self destruction and final extinction, rather than preservation, of the genome.

Reversion to the early embryonic/fetal state is the most remarkable genomic alteration that characterizes the malignant phenotype. This radical change is reflected, not only in altered cell functions and cell morphology, but also in the behavior of many types of tumors that aim at formation and establishment of a new creature, like malignant teratomas. To a lesser degree, the incongruous formation of incompletely differentiated tissues and incomplete/malformed parts of organs, and the apparently haphazardous transcription and synthesis of products, RNA/proteins/hormones/enzymes/etc., by metastatic tumors, might be considered within the same context. These observations might suggest the preservation of the evolutionary ability of the zygote to develop into a fully-developed organism, by descendant cells, particularly malignant cells. This reversion to the initial original genetic profile suggests the maintenance of the structural and functional phenotype of differentiated normal cells by genomic regulatory mechanisms controlled by master genes, probably through synthesis of mass silencers or suppressor molecules capable of keeping the rest of functionally unneeded genes in differentiated cells in a suppressed state. Disruption of these regulatory mechanisms would result in cessation and removal of mass suppression, with consequent mass reactivation, of non-functioning genes. It might also result in suppression of already functioning genes. These contrasting genetic alterations reflect and represent the actual *reprograming*, or more accurately *deprograming*, process of the genome of normal cells that, probably, paves the way toward the transformation to cancer cells and the establishment/initiation and progression of the malignant phenotype.

3. Genomic involution and hypodiploidy in caner

In view of the complexity of the myriad of interconnected and interacting regulatory mechanisms that control and determine all structural and functional aspects of the cell, it is very difficult to accept the monoclonal theory of oncogenesis that attributes tumor development to a triggering mutational event in