Carcinogenesis as a problem of tissue organization

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For almost one hundred years, carcinogenesis was assumed to be a cellular problem. According to this view, cancer was caused by mutations in the DNA of a single cell. This view and the research program that attempted to unravel the puzzle represent a foremost example of a reductionist approach in biology. The *somatic mutation theory*, currently the prevalent theory of carcinogenesis, is based on those above-mentioned assumptions. Despite aggressive efforts, both in terms of manpower and financial support, data based on this program have fallen short in explaining the causes of cancer and failures in the therapeutic front. More specifically, no mutation or combination of mutations has been able to explain the occurrence of sporadic tumors in humans (representing over 95% of human tumors). The small percentage of human hereditary tumors can be considered inborn errors of development. Furthermore, no therapeutic regime has yet to be designed to reverse the putative mutations that allegedly cause normal cells to become cancer cells.

In the late nineteenth century, pathologists began describing the histological pattern of tumors using the light microscope. This simple realization stealthily suggests that tissue disorganization is at the core of carcinogenesis and neoplasia. For the most part, neoplasms retain the distinctive structures that characterize the organ of origin. Some have considered these patterns as caricatures of the histological structures seen in normal organs.

In contraposition to the *somatic mutation theory*, we adopted a theory of carcinogenesis proposing that neoplasms are due to altered tissue organization; we call it the *tissue organization field theory of carcinogenesis and neoplasia*. A central concept in this theory is that of the persistence of morphogenetic fields during adult life; these fields orchestrate tissue maintenance and regeneration and form microenvironments where each cell interacts with its neighbors, both emitting and receiving positional information. The *tissue organization field theory of carcinogenesis and neoplasia* posits that neoplasms result from a flawed interaction among cells and tissues in a microenvironment that was exposed carcinogens. In addition, the *tissue organization field theory of carcinogenesis and neoplasia* assumes that, at the cellular level of biological hierarchy, the default state of all cells is *proliferation*. This is in sharp contrast with the implicit assumption of the *somatic mutation theory* that the default state of metazoan cells is *quiescence*.

We believe that the effects of carcinogens on the structures and components inside cells, while variably deleterious to each of them, is not directly responsible for the development of a neoplasia. In other words, carcinogens deleteriously act initially on stromal cells. These carcinogen-altered stromal cells would, in turn, affect the adjacent epithelial cells that would become neoplastic. Thus, carcinogenesis and neoplasia would occur entirely through emergent (supracellular) phenomena once the signals that maintain normal organization are disrupted.

It is impossible to predict whether an individual lesion will progress, remain stable, or regress. However, it is clear that the probability of regression decreases as the lesion progresses. During carcinogenesis and even neoplasia, cells may change their repertoire of expressed genes, and consequently change their phenotype. This means that the cells in a neoplasia may preserve a physiologically intact genome, and hence, they may be reprogrammed again to behave like "normal" cells.

We have experimentally vindicated the notion that the stroma is the target of carcinogens using a rat mammary gland experimental model. Using the same model, we have also verified the notion that epithelial tumor cells can reverse their neoplastic capabilities and show a normal phenotype when they are placed in a “normal” microenvironment.

These developments suggest that the cancer phenotype can be reversed and that therapeutic strategies aimed at this outcome bode well to a successful management of this disease in the future.

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