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EDITORIAL

Somatic Mutation Theory/Tissue Organization Field Theory: Has the Premise been Wrong All along?

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INTRODUCTION

Cancer has been considered as a genetic disease and the notion is stated as a stern fact rather than a theory. By not acknowledging that it is a theory, namely the somatic mutation theory (SMT), researchers are limiting exploration in other schools of thoughts and spheres. Since the beginning of the 20th century, researchers with a reductionist spectacle have been unearthing phenotypical differences between normal cells and cancer cells.[1]

A striking alternative to SMT is the tissue organization field theory (TOFT), which is condensed as "development gone astray."[2] According to SMT, cancer starts with a mutation that gives cells a growth advantage, which leads to clonal expansion and successive mutations followed by clonal expansions, in a matter of vicious cycle. There has been a radical increase in the reported number of mutations associated with tumors over the years. In various studies, up to 77 mutations per million base pairs of Deoxyribonucleic acid (DNA) have been reported by investigators; cancers with over 30 mutations, solid tumors averaging up to 66 mutations, and tumors with over 10,000 mutations have also been documented in the literature.[3-8] In another contrasting study, it was reported that only 6% of tumor mutations corresponded to six hallmarks of cancer, and 15% corresponded to apparently no hallmarks of cancer. It has been postulated that only a small number of driver mutations lead to cancer while the remaining passenger mutations play no causal role in carcinogenesis.[3-8] Another conundrum is that some mutations have shown to play both oncogenic and tumor-suppressor roles, depending on the austere ambience. NOTCH1 has shown to act as an oncogene in leukemia and as a tumor-suppressor gene in squamous cell carcinoma.[9] MYC also enacts dual roles of performing as an oncogene and a tumor-suppressor gene.[10] Despite colossal research, no qualitative differences have been ascribed to normal and cancer cells, an assertion extended till the SMT.[11]

Tissue organization field theory[12] states that cancer arises from the disruption of interactions with adjacent tissue, which can be mediated by intercellular chemical signals, mechanical forces, and bioelectric changes. The premises of TOFT is that proliferation is the default state of all cells and carcinogenesis represents a glitch in tissue organization analogous to organogenesis.[12,13] Corollaries stated by TOFT are that carcinogenesis is not the result of mutations, rather genetic instability and is a byproduct of carcinogenesis. Moreover, cancer can commence in tissues that are not affected by carcinogens.[14] In contrast to the current hindrance tackled in SMT, TOFT postulates fascinating candor. Tissue organization field theory involves traits expressed in normal tissue; for instance, rapid proliferation following skin grafts, embryogenesis, etc.[15-17] This suggests that disorder in the microenvironment of the cell leads to cancer and it represents the physical and chemical support by the morphogenetic field which drives epithelial cells toward phenotypical alterations and differentiation. This involves intricate and reciprocal biophysical and biochemical communication between stroma and epithelial cells. In this process, gradients of bioelectric membrane resting potentials play a crucial role. The connection between electrical potentials and morphogenesis depends on the physical fact that electromagnetic fields are produced by flowing currents and the orientation and movement of all charged particles including ion exchange across the membrane is in harmony with the field.[18] Bioimpedance is a well-established method in detecting breast cancer, cervical cancer, prostate cancer, etc. Studies have shown that there are significant differences in electrical impedance between normal tissues and cancerous tissue.[19]

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Through recent years, we have learnt the crucial role stroma plays in the initiation/progression of cancer. Biochemical interactions in the form of cytokines, chemokines, prostaglandins and reactive oxygen, and nitrogen radicals accumulate in the microenvironment of tissues affected by chronic inflammatory reaction. If persistent, these inflammatory factors have the potential to induce cell proliferation and stimulate prolonged cell survival through activation of oncogenes and subsequent inactivation of tumor-suppressor genes. This may result in genetic instability with an increased risk of cancer.[20] Another factor that interferes with the biochemics of the mesenchyme is chronic stress.[21] A number of pathways get triggered during chronic stressful situations; suppression of elements of immune response that are important in responding to malignant cells, stress mediators like epinephrine, norepinephrine, cortisol, etc., causes stimulation of vascular endothelial growth factor, modulation of interleukin 6 (IL6), IL8, increased angiogenesis by direct activation of angiogenesis-promoting molecules, matrix metalloproteinase modulation, impairment of DNA repair, etc.[22] These dynamics have a cumulative effect on the stroma, instigating a distress situation. Disturbed stroma/epithelium interactions are at the core of the TOFT. The plausibility of the TOFT has already been put to a test, and the data collected strongly supports the claim that whole tissues are the targets of carcinogens.

The interaction between cells and their microenvironment, by involving both biochemical and biophysical cues, drives differentiating processes and contributes in a determinant fashion to cancer emergence. Considering cancer as a tissue-based phenomenon implies a profound rewiring of our experimental methodology, by requiring to move from cells and subcellular structures toward higher levels of organization. The TOFT is not disapproved, it's just forgotten.

Thus, a rationale that favors discarding the premises of cancer research, SMT is near the horizon and its time we scope beyond and explore new perspectives.

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