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An Ancient Approach of Understanding Cancer: Atavism Hypothesis

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In cell biology, atavism may denote to the reversion of the evolutionary traits or the recurrence of early-life phylogenetical pathways, which lay encoded and dormant in every cell of the evolved multicellular species.[1] In a simple statement, the'atavistic model' of cancer represents a reversion of these complex genetic evolutionary steps to the original life-form i.e. a self-sustaining single-celled phenotype.[2] Therefore, cancer might represent identity crisis of an individualcell in the hierarchy of a multicellular organism and requires only precise triggering factors to revert back to its aboriginal state.

In the Pre-Cambrian era before the evolution of complex organisms, the early life-forms existed as unicellular, asexual, immortal, non-specialized (not differentiated), exhibited genomic instability and executed simple fermentation (aerobic glycolysis or Warburg effect) for sustenance. They survived in an environment comprising of high radiation, free radicals, low oxygen and, low pH.Eons later, as the environment underwent conducive transitions, it instigated evolutionary changes in the early life-forms to explore the new oxygen-rich atmosphere. It is enthralling to note that in the present environment when a cell is exposed to direct and indirect carcinogens (similar to primitive extreme conditions), the cells attempt to revert back to early-life survival strategies which we term as 'malignant transformation'. The primitive cells, that endured and sustained in a nutrient-deprived and extreme environment, display striking similarities with the hallmark characteristics of a malignant cell.[3-7] It appears as'cancer' is nature's ancient encrypted code embedded in every cell as a life-boat, ensuring the survival of the cell when challenged with hostile conditions.

In the history of the evolution of unicellular to multicellular life-forms,certain key foundations for the proper functioning of the multicellular organisms were established. These include limitation of cell proliferation, programmed cell death, differentiation of cells and division of labour, resource allocation and transport,

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and maintenance of a homeostatic extracellular environment.[8-10] The adaptive mutations which were essential for the survival of a free unicellular organism in an unstable environment, were no longer necessary, as a stable homeostatic environment was established for the cells within the multicellular organisms. Thus several genetic constraints, blocks, and check-points emerged to sustain the functioning of the advancing complex organisms.It is the suppression and downregulation of these genetic check-points that is frequently observed in the malignancies, theoretically supporting the atavistic model.[11-15]

The link between evolution of multicellular organisms and increase in cancer genes is evident by a genomic phylostratigraphy study, in which two strong peaks of cancer-related protein domains were observed; one at the time of the origin of the earliest cells – the caretaker genes and the other around the time of the evolution of the multicellular metazoan organisms – the gatekeeper genes. It is intriguing to note that this phylogenetic progression emulates the ontogenetic progression of tumour development, wherein the mutations in the caretaker genes are thought to precede mutations in the gatekeeper genes.[16] TheRNA sequencing study of drug-resistant multiple myeloma cells revealed that the majority of the expressed genes were biased in age toward the most ancient genes.[17] It is further observed that the ancient genes are capable of re-activating stress-induced mutational response leading to genomic instabilityin the somatic cells, signifying cancer as an atavistic recapitulation of the primitive cell's survival mechanism.[18] The greatest comprehensive molecular evidence of the 'atavistic model' of the cancer was provided by the detailed transcriptome analysis of 3,473 tumour and 386 normal samples. The results indicate that the widespread-shift to preferential expression of genes conserved in primitive, unicellular organisms is a common feature of tumours.[19]

The atavistic model of cancer can introduce novel therapeutic strategies in the management of cancer. This model suggests that instead of targeting the strengths of cancer cells,i.e. the deeply embedded ancient capabilities (e.g. proliferation, survival in hypoxic, low pH conditions, etc.) one should pursue its weakness i.e. the recently-evolved capabilities (e.g. DNA repair mechanisms,adaptive immune system, etc.). For example, the most efficient ancient fundamental capability of a cell is proliferation. But there are multiple redundant and robust drivers for cellular proliferation existing from billions of years. Thus, targeting a single gene is inefficient. Drug cocktails are slightly more effective, nonetheless, the cancer cells have access to other redundant proliferative pathways through mutations. On the contrary, an enhanced adaptive immune response (density of T-cells), which is a relatively newer evolved capability of organisms, is correlated with a good prognosis of many tumours.[20] Thus, according to the atavistic model, immune therapy might prove to be a better treatment strategy in cancer management.

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