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Debating cancer: The paradox in cancer research, Henry H. Heng (World Scientific Publishing Co. Pte. Ltd., Singapore) 2015. 464 pages. Price: US$ 166.00

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The author has proposed a paradigm shift in our understanding of genetics of healthy and diseased conditions including cancer in this book. He has tried to establish a holistic view of the genome as expressed in karyotype instead of reductionism of genes and epigenes. Morphology aberration has been proposed as the most important change that gives rise to many downstream genetic mutations and other changes. However, it is not clear how these can be precisely measured as SKY (Spectral Karyotyping) and interphase FISH (Fluorescence *In Situ* Hybridization) have been mentioned for the present. It is also not clear what statistics will be used to calculate those aberrations. One would probably compare snapshots in discrete time instead of a time series estimation and will probably use linear rather than nonlinearity estimation. Though dynamics, chaos, part, system and fuzzy inheritance have been discussed, there is no mention of nonlinear complexity measures like Lyapunov and fractal dimension calculation. This work gives a fresh lease to the tiresome and less successful subject of oncogene albeit from a non-clinical standpoint.

After reading it for some time it becomes evident that there would hardly be any easier and lucid way to present such a different and difficult proposition. The author has tried to show cause behind cancer and futility of other theories mostly based on a reductionist's viewpoint, however, he starts off using the system approach in linear calculation using mathematical/numerical value of aberration. One might have to wait till it becomes useful clinically and probably diagnostically to begin with. A glimpse of the theory/hypothesis might be of interest to some who are in basic research in medicine.

This book has eight chapters. The first chapter introduces the subject "Why Debate Cancer, and Why Now". The second chapter discusses the gene mutation

theory of cancer. The basis for the gene mutation theory of cancer that dominates current molecular cancer research consists of the belief that gene-level aberrations such as mutations are the main cause of cancers, the concept that step-wise gene mutation accumulation drives cancer progression, and the hallmarks of cancer. While the molecular knowledge of these hallmarks is drastically increasing, the clinical implication remains limited, as cancer dynamics cannot be summarized by a few isolated/fixed molecular principles. Furthermore, the highly heterogeneous genetic signature of cancers, including massive stochastic genome alterations, challenges the utility of continuously studying each individual gene.

Stochastic alterations at various genetic and non-genetic levels are overwhelming. These levels range from gene mutation, copy number variation, transcription regulation, protein degradation, molecular pathway switching/genetic network rewiring, and karyotype changes, to disease progression and therapeutic response. Such a high "noise" level challenges the rationale and strategy of searching solely for the recurrent molecular patterns in the name of understanding bio-specificity-defined mechanisms.

The seemingly random non clonal chromosome aberrations (NCCAs) have long been observed in both normal and disease conditions, and the importance of studying this stochasticity or "noise" at the karyotype level has been vigorously pushed by a few groups. However, the overall response to this effort has been rather limited due to the current cytogenetic practice, in which the main effort is the documentation of recurrent or clonal chromosome aberrations (CCAs). As the karyotype may represents new type of genetic information called the system inheritance, NCCAs might not be only "noise;" rather, they function as the basis of genome heterogeneity, which is the essential form of genomic complexity and one of the pre-conditions for many diseases. The elevated NCCAs and NCCA/CCA cycle may be seen as the key condition for cellular adaptation. The variable karyotype serves as a good model to study fuzzy inheritance. NCCAs can be classified into structural and numerical types. There are increased structural types of NCCAs being reported. Within the punctuated macro-cellular evolutionary phase, massive amounts of NCCAs can be detected, often coupled with complex chromosomal aberrations.

Starting from late 1960s, most cytogenetic methods (*i.e.*, various chromosomal banding, FISH, SKY/m-FISH, and CGH) are designed to identify specific chromosomal abnormalities. Currently, when discussing NCCAs, most researchers refer to non-recurrent chromosomal translocations and aneuploidy. However, there are many more types of chromosomal abnormalities belonging to this category, including defective mitotic figures (DMF), sticky chromosomes, chromosome fragmentations (C-Frag), ring chromosomes and chromosomal bridges, highly diverse chaotic genomes (including unstable giant nuclei, in which a series of transitions occurs, cycling from polyploidy to altered diploid chromosomes through multipolar and bipolar mitoses).

A comparison between *in vivo* samples (using sensitive DNA cytometry methods) and *in vitro* culture (using classical cytogenetic methods) is also needed. It is important to report NCCAs and establish a database. Such a database will serve multiple purposes. First, it will expand the list of types of NCCAs. Second, it will record the frequencies of different types of NCCAs and all types of NCCAs for normal individuals, for specific disease types, and for various tissue types. Third, it will encourage the re-examination of published reports to collect the data, and initiate efforts to examine previous available samples.

This genome system instability is the ultimate link between many diseases and their genetic and environmental contributing factors. The genome serves as the evolutionary platform that links gene/epigene interaction and multiple levels of omics. Using the types and frequencies of NCCAs, and the dynamic relationship between NCCA and CCA, evolutionary potential can be monitored either genetically or environmentally. As all stress responses can be reflected by the level of system instability, this evolutionary mechanism of diseases can unify diverse molecular mechanisms, and reconcile the difficulty of clinical prediction based only on the genetic profile.

Overall, the author's work is laudable in a sense that his baseline work in genetics could reach to such a perfection that he finds many clues in this difficult terrain whereas other would fear as uninitiated suffers from incomprehensibility.

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