BOOK REVIEW

The human genome: better to be dynamic

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Genetic Heterogeneity and Human Disease

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Genome-wide studies have shed light on the unexpectedly high content of wide-spread constitutional (germline) variability. The initial concept of a static and one-dimensional genome has been replaced by a complex and dynamic aggregate of biomolecules arranged in a functional, as well as topological, relationship. Indeed, genome positioning in cells is far from random, and its spatial placement in the nucleus provides additional information.

The authors of this fascinating book go one step further, extending this three-dimensional idea of genome structure to four dimensions, describing the concept of a four-dimensional (4D) genome in which the DNA and the other macromolecular components inside the nuclei vary over time at a somatic level. Expanding on this concept, and significantly shifting the focus of the study of genome variability/instability, the authors take an in-depth look at non-clonal chromosome aberrations, which are often ignored in routine cytogenetics analysis but have potential links to disease conditions. Indeed, several other alterations, such as free chromatin released from interphase nuclei, incompletely packed

chromosomes, fragmentations, genome chaos and so on, are known to contribute to the generation of somatic karyotype heterogeneity over the course of time.

In this context, Liehr *et al* discuss the clinical impact of the small supernumerary marker chromosomes that are often present in a mosaic condition, and frequently emerge in routine cytogenetics testing. The clinical significance of these abnormalities is complicated by the presence of cryptic and tissue-specific mosaicisms, as pointed out in the contribution by Hulten *et al*, who describe the high frequency of low-grade trisomy 21 mosaicism in the general population ('we may all have a touch of Down Syndrome'), and by Iourov *et al* in their discussion on the somatic cell genomics of brain disorders. They point to a greater frequency of neural aneuploidies as a newly identified feature of neurodegenerative diseases, reflecting on other disorders hallmarked by aneuploidy such as chromosome syndromes and cancer.

The book takes into account a wide range of factors, including stochastic elements that produce somatic genetic heterogeneity,

offering insight into the evolutionary nature of intercellular variability, a scenario in which environmental and other interactions, such as virus integration, for example, can act as a substrate for adaptation processes that give rise to new cellular phenotypes.

The authors go on to describe a striking parallelism between the basic mechanisms of species evolution and the development of cancer cells. In cancer evolution, the first non-clonal, or punctuated, phase is driven by a high level of karyotype heterogeneity, whereas the second clonal phase (microevolution) witnesses the evolution of many cells that share similar karyotypes via accumulation of gene mutations. From this perspective, and given the high multiple levels of the genetic/epigenetic heterogeneity that exist in most cancers, genomic heterogeneity can be viewed as the driving force behind many diseases, cancer in particular.

This intriguing vision of a genome broken down into a myriad of elementary particles that form a supermolecular complex, including nucleic acids and proteins, organized in terms of space and time inside each cell and essentially representing 'bioinformation packages', calls for a thorough review of the central dogma of biology, as rightly pointed out by Sgaramella in his contribution that closes the book. Furthermore, the articles in '*Genetic Heterogeneity and Human Disease*' provide an extensive reference 'library' for those who wish to study the specific topics covered in depth, and represent a valuable source of information and clues for a wide audience of professionals in human genetics and biomedicine, highlighting the importance of a large-scale innovative approach to the study of the meaning and implications of a 4D genome. ■

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