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Review

Chromosome instability in neoplasia: chaotic roots to continuous growth

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Abstract

Multiple rearrangements of chromosome number and structure are common manifestations of genomic instability encountered in mammalian tumors. In neoplasia, in continuous immortalized growth in vitro, and in animal models, the accumulation of various defects on DNA repair and telomere maintenance machineries, mitotic spindle abnormalities, and breakage–fusion–bridge cycles, deteriorate the precise mitotic distribution of the genomic content, thus producing various types of chromosomal anomalies. These lesions generate tremendous genomic imbalances, which are evolutionary selected, since they force the function of the whole genome towards continuous growth. For more than a century chromosomal rearrangements and aneuploidy in neoplasia have been discussed and a vast number of genes and pathways, directly or indirectly implicated, have been described. In this review, we focus on the biological mechanisms that generate numerical or structural deviations of the normal diploid chromosomal constitution in epithelial neoplasia. There is growing evidence that chromosomal instability is both an epiphenomenon and a leading cause of cancer. We will discuss the roles of genes, chromosome structure, and telomere dysfunction in the initiation of chromosomal instability. We will explore research strategies that can be applied to identify rates of chromosomal instability in a specimen, and the putative biological consequences of karyotypic heterogeneity. Finally, we will re-examine the longstanding hypothesis of the generation of aneuploidy in the context of telomere dysfunction and restoration.

Keywords: Chromosome instability; Telomeres; Cancer; Aneuploidy; ALT

Abbreviations: ALT, alternative telomere maintenance pathways; APC, anaphase-promoting complex; ATM, ataxia telangiectasia mutated; BFB, breakage–fusion–bridge (cycles); CIN, chromosomal instability in neoplasia; CGH, comparative genomic hybridization; FISH, fluorescent in situ hybridization; ISCN, International System of Human Chromosome Nomenclature; MIN, microsatellite instability; PD, population doubling; PML, promyelocytic leukemia; SCE, sister chromatid exchanges; SKY, spectral karyotyping (multicolor FISH); TERT, telomerase reverse transcriptase; TERC, telomerase RNA component; TRAP, telomeric repeat amplification protocol

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Contents

1. Introduction

Most mammalian cancers derive from a single progenitor cell that acquires the potential for uncontrolled continuous proliferation (Boveri, 1914). Since the time of primitive microscopy at the end of the 19th century it was known that chromosomal instability occurs frequently in neoplasia (Heim & Mitelman, 1994). Abnormalities of chromosome number are the most common genetic aberrations in cancer. The mechanisms regulating the fidelity of mitotic chromosome transmission in mammalian cells are therefore of great interest. Gain and loss of chromosomal material in neoplastic cell populations is considered to be a process of diversification that leads to the survival of the fittest clones (Nowell, 1976).

Chromosomal instability has been considered as an adaptive response of cancer cells to environmental pressure (Jallepalli et al., 2001). It was proposed that virtually all types of human tumors, including their metastatic outgrowths, continue to harbor complex mixtures of several cell types that collaborate to create malignant growth (Hanahan & Weinberg, 2000). During tumor evolution, many cancer cells acquire the ability to synthesize growth factors to which they are responsive, creating a positive signaling feedback loop, termed autocrine stimulation. According to Darwin's theory of evolution, the environment determines on what grounds selection takes place and which characteristics are necessary for better adaptation. Most tumors are composed from genetically heterogeneous cell populations. Although initial differences between cancer cells of the same origin are thought to arise from random mutations due to inefficient checkpoints (Jasin, 2000), selective pressure during continuous growth leads to amplification of oncogenic factors and deletion of oncosuppressors in the evolving genome (Cahill, Kinzler, Vogelstein, & Lengauer, 1999).

Segregation of balanced constitutional chromosomal rearrangements in gametogenesis produces syndromic partial aneusomies usually composed of duplications and/or deletions of small chromosomal segments (Lupski, Roth, & Weinstock, 1996). Affected patients show a phenotype which reflects the clinical components of their isolated partial aneusomies, but at the same time a unique combination phenotype (Lukusa, Holvoet, Vermeesch, Devriendt, & Fryns, 2003). Similarly in cancer cells, simultaneous genomic imbalances can strengthen each other, or act in combination, which may affect other genomic regions that are perfectly balanced. Large genomic alterations in cancer should be expected to affect cell metabolism and function not only by the amplification and/or elimination of chromosomal segments carrying particular genes, but also by altering transcription profiles of many other genes in the genome. Increased or decreased availability of certain transcription factors, RNAi genes or non-genic functional elements can interfere with tightly regulated pathways and activate or inactivate genes without any relevant mutations (Dermitzakis et al., 2002). The impact of various combinations of large genomic imbalances on the overall expression pattern of the cancer genome is illustrated by the intriguing results produced by transcriptome approaches on syndromic trisomies. Dosage imbalance of only 124 genes, in the Ts65Dn mouse model of human trisomy 21, alters the expression of thousands of genes to create a variable trisomic transcriptome (Lyle, Gehrig, Neergaard-Henrichsen,