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Road to the crossroads of life and death: Linking sister chromatid cohesion and separation to aneuploidy, apoptosis and cancer

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Contents

Abstract

Genomic instability, aberrant cell proliferation and defects in apoptotic cell death are critical issues in cancer. The two most prominent hallmarks of cancer cells are multiple mutations in key genes encoding proteins that regulate important cell-survival pathways, and marked restructuring or redistribution of the chromosomes (aneuploidy) indicative of genomic instability. Both these aspects have been suggested to cause cancer, though a causal role for chromosomal restructuring in tumorigenesis has not been experimentally fully substantiated. This review is aimed at understanding the mechanisms of cell cycle (proliferation) and programmed cell death (apoptosis) and chromosomal instability governed by cohesin and other aneuploidy promoters, which will provide new insights into the process of carcinogenesis and new avenues for targeted treatment.

Keywords: Cohesin; Apoptosis; Aneuploidy; Separase; Rad21

1. Introduction

Metazoans comprise of multiple cells that possess distinct features, despite being originated from a single cell with identical genotype. The course of development of a

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multicellular organism from a zygotic single cell revolves around differentiation, a process of becoming phenotypically different while genotypically remaining the same. Such a task is achieved by accommodating changes to the epigenome in each constituent cell of the organism, which in turn results in differential regulation of gene expression. To maintain the organismal homeostasis, the constituent cells must abide by certain norms. That is, the differentiated cells must stay differentiated, and the differentiating cells must strictly follow the exact path of differentiation that the organism needs them to. Alteration in normal gene regulation profile of a constituent cell causes the cell to deviate from this path, resulting in homeostatic imbalance. Such imbalance is detrimental to the organismal well being; and the cells going astray must, therefore, be eliminated with caution. This is why multicellularity has evolved multiple paths for programmed cell death [1,2].

Tumors arise when such unruly, deviant cells evade programmed cell death [3,4]. It is generally accepted that such cells have gained alterations in essential genes that control cell death, cell differentiation or cell proliferation. These alterations endow the cells with a set of six special advantages over the normal cells: (i) self-sufficiency in growth signals, (ii) insensitivity to growth-inhibitory signals, (iii) evading apoptosis, (iv) unlimited replicative potential, (v) sustained angiogenesis, and (vi) tissue invasion and metastasis [5] over a long, multistep process culminating in cancer [6,7]. How the process of tumorigenesis begins is still unclear, and is a question at the center of intense debates. One of the limitations of the current research on cancer biology is its heavy dependence on a detectable phenotype—a stage well past initiation. This has led to many theories and hypotheses which do not explain all features of carcinogenesis, or, in many cases, contradict each other. For an example, according to the somatic mutation theory (SMT), there is a set of mutations that, coupled with clonal selection, impairs the cellular physiology towards proliferative advantage [8–11]. However, it has also been proposed that cancers cause mutations rather than mutations causing cancer; and the inception of cancer is attributed to alterations in gene expression due to epigenetic mechanisms [12]. As opposed to somatic mutations, it is argued that cancer is rather a disease of disrupted tissue organization [13]. In addition, changes in immune system [12], signaling between tissues [14] and hormonal status [15] have also been implicated in tumorigenesis.

On the other hand, morphological abnormalities in chromosomes were observed in tumor samples as early as late 19th century, which inspired Theodor Boveri to propose that a ‘definite abnormal chromosome complex’ would always result in tumors [16]. Ever since, the theory of chromosomal abnormality has been a strong contender to the SMT as a cause for tumorigenesis (see [17] for a discussion). The majority of the current thinkers in the field of tumorigenesis and carcinogenesis appear to favor either one or the other theory [18]. Here, we make an attempt to discuss both these theories with an emphasis on aneuploidy, apoptosis, chromosomal cohesion, and to extract a plausible reconciliatory explanation to the cause of cancer.

2. Genetic instability in cancer

The concept of individuality of chromosomes in a given cell was given by Boveri in late nineteenth century, at a time when all chromosomes in a cell were considered to possess same qualities. Later in 1914, in his proposition that cancer is a genetic disease of somatic cells, Boveri envisioned that abnormal chromosomal numbers would lead to abnormal cellular phenotypes culminating in tumorigenesis [16]. Normal eukaryotic somatic cells should contain a diploid genome comprised of multiple chromosomes. During successive normal cell divisions, this set-up is normally preserved. Over several decades after Boveri, tumor cells have invariably been found to contain many genetic abnormalities. These abnormalities include aberrant number of chromosomes and chromosomal fragmentations, indicating instability in the genetic integrity of these cells. Even though the earliest observations of genetic instability were the visible changes in chromosome number and architecture, over the decades thereafter the term ‘genetic instability’ (GIN) has evolved to include genomic alterations at the nucleotide level as well [19]. Causes of GIN have primarily been attributed to defects in replication, transcription, recombination, and DNA-damage repair [20].

The nucleotide-level changes include base-substitution mutations, or deletions or insertions of a few nucleotides; and these cannot be detected through classical cytogenetic analyses. These genetic changes normally form the basis of the oncogenic mutation (OM) mechanism for cancer causation, and will be discussed later in the text. When the mismatch repair pathway is compromised, a staggering level of short DNA repeats are found all over the genome in cancers like the hereditary colorectal cancer, which is known as micro-satellite instability (MIN) [21]. At a higher level of the chromatin, epigenetic dysregulation is being reported for more and more genes in cancer cells. These include promoter DNA methylation and hypoacetylation and methylation of histones on corresponding genes [22]. It is also proposed that epigenetic dysregulation may have a causal role in cancer inception [23]. The next level of GIN involves structural changes to the chromosomes known as chromosomal instability (CIN), which includes alteration in ploidy and generation of chromosomal translocations [24]. An alteration in ploidy can be a linear multiplication of the entire set of chromosomes (polyploidy), or a loss or gain of single chromosomes or fragments thereof (aneuploidy). Aneuploidy is so prevalent in cancer that any cell from a cancer epithelium can represent the whole range of structural and numerical chromosome anomaly usually found in cancers [25]. Most human cancers differ in the over-all number of chromosomes their cells contain, which often ranges from 60 to 90 [26]. Moreover, individual cells within a certain tumor may also