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Review

Chromosomal instability: A common feature and a therapeutic target of cancer

Kozo Tanaka [a,*], Toru Hirota [b,*]

[a] Department of Molecular Oncology, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8575, Japan
[b] Division of Experimental Pathology, Cancer Institute, Japanese Foundation for Cancer Research, Ariake 3-8-31, Koto-ku, Tokyo 135-8550, Japan

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ABSTRACT

Most cancer cells are aneuploid, containing abnormal numbers of chromosomes, mainly caused by elevated levels of chromosome missegregation, known as chromosomal instability (CIN). These well-recognized, but poorly understood, features of cancers have recently been studied extensively, unraveling causal relationships between CIN and cancer. Here we review recent findings regarding how CIN and aneuploidy occur, how they affect cellular functions, how cells respond to them, and their relevance to diseases, especially cancer. Aneuploid cells are under various kinds of stresses that result in reduced cellular fitness. Nevertheless, genetic heterogeneity derived from CIN allows the selection of cells better adapted to their environment, which supposedly facilitates generation and progression of cancer. We also discuss how we can exploit the properties of cancer cells exhibiting CIN for effective cancer therapy.

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* Corresponding authors.
E-mail addresses: kozo.tanaka.d2@tohoku.ac.jp (K. Tanaka), thirota@jfcr.or.jp (T. Hirota).

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1. Introduction

Genomic instability is one of the cancer hallmarks [1]. Genomic instability comprises different levels of genetic changes ranging from the nucleotide to the chromosome level, and the resultant genetic diversity expedites oncogenesis, together with epigenetic changes. Aneuploidy and chromosomal instability (CIN) are distinct, but closely related, concepts that describe the chromosome-level genetic changes. Aneuploidy is the state that denotes the presence of an abnormal number of chromosomes in cells, which is found in the majority (70–90%) of cancer cells [2]. It is defined as a chromosome content that is not a multiple of complete sets of chromosomes. Human somatic cells in their normal (euploid) state possess 23 pairs of chromosomes (diploid), and a chromosome content of more than two sets is collectively called polyploidy, which is seen physiologically in cells such as hepatocytes and megakaryocytes. Typically, aneuploidy means the gain or loss of entire chromosomes (whole chromosome aneuploidy), while structural (or segmental) aneuploidy denotes amplification or loss of parts of chromosomes. In contrast, CIN is the condition in which chromosome missegregation occurs at a high rate e.g. every 1–5 mitoses, in contrast to less than once in 100 mitoses in normal cells [3]. CIN usually underlies aneuploidy found in cancer cells. CIN is also divided into whole chromosomal instability (w-CIN) and structural chromosomal instability (s-CIN), depending on whether chromosome gains/losses or chromosome breaks/rearrangements occur at high rates. Prevalence of aneuploidy and CIN in cancer cells implies a strong relationship between mitosis and oncogenesis. In this review, we discuss the causes and consequences of aneuploidy and CIN in relation to disease, especially cancer, and propose the strategies to target CIN for cancer intervention.

2. Causes of aneuploidy

As seen in most cancer cells, aneuploidy is an inevitable consequence of CIN, the etiologies of which will be discussed later. However, it is important to point out that there are also instances where aneuploidy is formed via different routes. Congenital aneuploidy is caused by chromosome segregation errors during gametogenesis and result in the abnormal karyotype being present throughout the body. The frequency of aneuploidy increases with maternal age, and the reason for this is thought to be related to weakened chromosome cohesion and resultant disintegration of bivalents as oocytes age [4–6]. Aneuploidy is a major cause of miscarriage and congenital disorders. Among autosomal chromosome disorders, only trisomies of Chr. 13, 18, 21 are viable, and only trisomy 21 (Down syndrome) individuals survive to adulthood. Another example of generation of aneuploidy without CIN is DNA damage and breakage, which cause chromosomal deletions, duplications and translocations, resulting in partial aneuploidy. Cells exposed to ionizing radiation causing various DNA damage show increased rates of structural chromosomal aberrations, such as dicentric chromosomes and chromosomal translocation, in proportion to radiation dose. Therefore, these structural chromosomal aberrations are used as indices to evaluate the irradiated dose [7]. A recent report suggests that whole chromosome aneuploidy can also be caused by DNA damage through microtubule stabilization [8].

3. Effects of aneuploidy

3.1. Reduced cellular fitness

Aneuploidy is basically detrimental to cells. As mentioned earlier, all autosomal monosomies, and most autosomal trisomies, in humans are lethal. Aneuploidy in a variety of other organisms causes developmental defects and lethality [9]. Aneuploid yeast and mammalian cells show reduced proliferation [10]. It has been shown that aneuploidy causes changes in gene dosage corresponding to the changes in gene copy number [11–13], and the resulting altered gene expression is responsible for the reduced cellular fitness of aneuploid cells [14].

As a result of altered expression of hundreds of genes from the aneuploid chromosomes, imbalances in critical proteins may affect various cellular functions and signaling pathways, showing gene-specific phenotypes [15]. Such proteins work either on their own, or as stoichiometric components of complexes. In addition, imbalanced gene expression from the aneuploid chromosomes challenges the maintenance of protein homeostasis, causing proteotoxic stress, irrespective of the chromosomes affected [15]. First, increased expression of proteins titrates away chaperones required for proper protein folding. Aneuploid yeast strains are prone to form protein aggregates [14], indicating impaired folding. Moreover, reduced folding activity of the Hsp90 chaperone was seen in aneuploid yeast and human cells [14,16]. Accordingly, murine and human aneuploid cells were sensitive to chemical inhibition of Hsp90 [16,17]. In human cells, Hsp90 expression was decreased due to compromised expression of HSP1, an upstream regulator of heat shock-induced transcription [16]. Resulting misfolded proteins, and excessive components of complexes, are subjected to degradation, putting an extra burden on proteolysis systems. A screening of aneuploidy-tolerant mutations in yeast identified Ubp6, a deubiquitylating enzyme working on the proteasome, the loss of which accelerated substrate degradation [18]. Deletion of Ubp6 improved the growth rates as well as protein imbalances, suggesting that proteotoxic stress plays a crucial role in the reduced cellular fitness of aneuploid cells. Aneuploid cells also have altered metabolism and increased energy needs [11,13], which may be related to increased energy consumption needed to deal with proteotoxic stress.

3.2. CIN

Haploid-derived yeast strains containing one extra chromosome exhibited high rates of chromosome loss in many cases [19]. This finding suggests that the relationship between CIN and aneuploidy is not simply a cause-and-effect relationship, but that they can affect each other (Fig. 1). It was also reported that individuals with trisomies 13, 18, and 21 show aneuploidy in their lymphocytes with twice the incidence of