Review

Physiological significance of polyploidization in mammalian cells

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Programmed polyploidization occurs in all mammalian species during development and aging in selected tissues, but the biological properties of polyploid cells remain obscure. Spontaneous polyploidization arises during stress and has been observed in a variety of pathological conditions, such as cancer and degenerative diseases. A major challenge in the field is to test the predicted functions of polyploidization *in vivo*. However, recent genetic mouse models with diminished polyploidization phenotypes represent novel, powerful tools to unravel the biological function of polyploidization. Contrary to a longstanding hypothesis, polyploidization appears to not be required for differentiation and has no obvious impact on proliferation. Instead, polyploidization leads to increased cell size and genetic diversity, which could promote better adaptation to chronic injury or stress. We discuss here the consequences of reducing polyploidization in mice and review which stress responses and molecular signals trigger polyploidization during development and disease.

Biological function of polyploidization

Polyploidization, the addition of one or multiple complete sets of chromosomes, is one of the most dramatic changes known to occur in the genome. Surprisingly, this fascinating phenomenon is well tolerated and common in nature, especially in plants, flies, and fungi [1]. In mammals, polyploidy occurs in specific tissues, such as the placenta, bone marrow, heart, and liver [2]. Given that cellular stress promotes polyploidization, and many diseased organs contain polyploid cells, it is also assumed that polyploidization represents a pathological lesion that influences cellular function such as proliferation or metabolism. However, to define the physiological role of polyploidization it will be crucial to determine the consequences of reducing polyploidization *in vivo*. Recently, multiple mouse studies have provided surprising new insights into the physiological function of polyploidization and refuted some of the main postulated function of polyploidization. We discuss here the different postulated functions for polyploidization which have been based on when and where polyploidization occurs and the circumstances that trigger polyploidization.

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Polyploidization increases cell size

Does polyploidization of a cell really have physiological consequences, or does it merely create a similar cell of a larger size? Previous studies demonstrated that doubling in ploidy is accompanied by an approximately twofold increase in cell volume in human and mouse liver cells [3]. However, when cell volume increases twofold, surface area only increases 1.4-fold, resulting in a subsequent change in spatial relationships between different components within the cell. Hence, interactions between subcellular structures, such as transport between nucleus and cytoplasm, might be less efficient. In addition, the different scales within a polyploid nucleus could have effects on spindle geometry, and might result in genomic instability [4]. Interestingly, a genome-wide screen in yeast to identify ploidy-specific lethality genes revealed that, of the genes required for growth of polyploid cells, but not diploid cells, the majority affect genomic stability [5]. These findings suggest that one important consequence of polyploidization could be reduced genomic stability, possibly due to altered spatial relationships within the nucleus after polyploidization.

Polyploidization creates genetic diversity

Recent elegant work by Duncan *et al*. showed that polyploid liver cells can not only increase their DNA content but can also reduce their DNA content by a process called ploidy reversal [6]. Because polyploid hepatocytes contain increased numbers of centrosomes they can form either bipolar spindles or multipolar spindles during mitotic division. Bipolar spindles are established through centrosomal clustering, whereas centrosomes in multipolar spindles are oriented on more than two distinct poles. During mitosis, the multipolar spindles can generate progeny with reduced ploidy: for example one octoploid cell can generate four diploid cells. Importantly, during this reductive ploidization process, frequent chromosome mis-segregation leads to structural rearrangements of chromosomes and the formation of aneuploid hepatocytes (Figure 1). Although the mechanisms for inducing ploidy reversal are unknown, it appears to be a frequent event because the majority of hepatocytes in human (30–90%) and mice (60%) are aneuploid [7].

Is there any advantage for a normal mammalian cell to develop aneuploidy, or is it simply a sequel of the polyploidization process? Recent studies suggest a model in which random aneuploidy can promote adaptation to hepatic injury by increasing genetic diversity [8]. In this

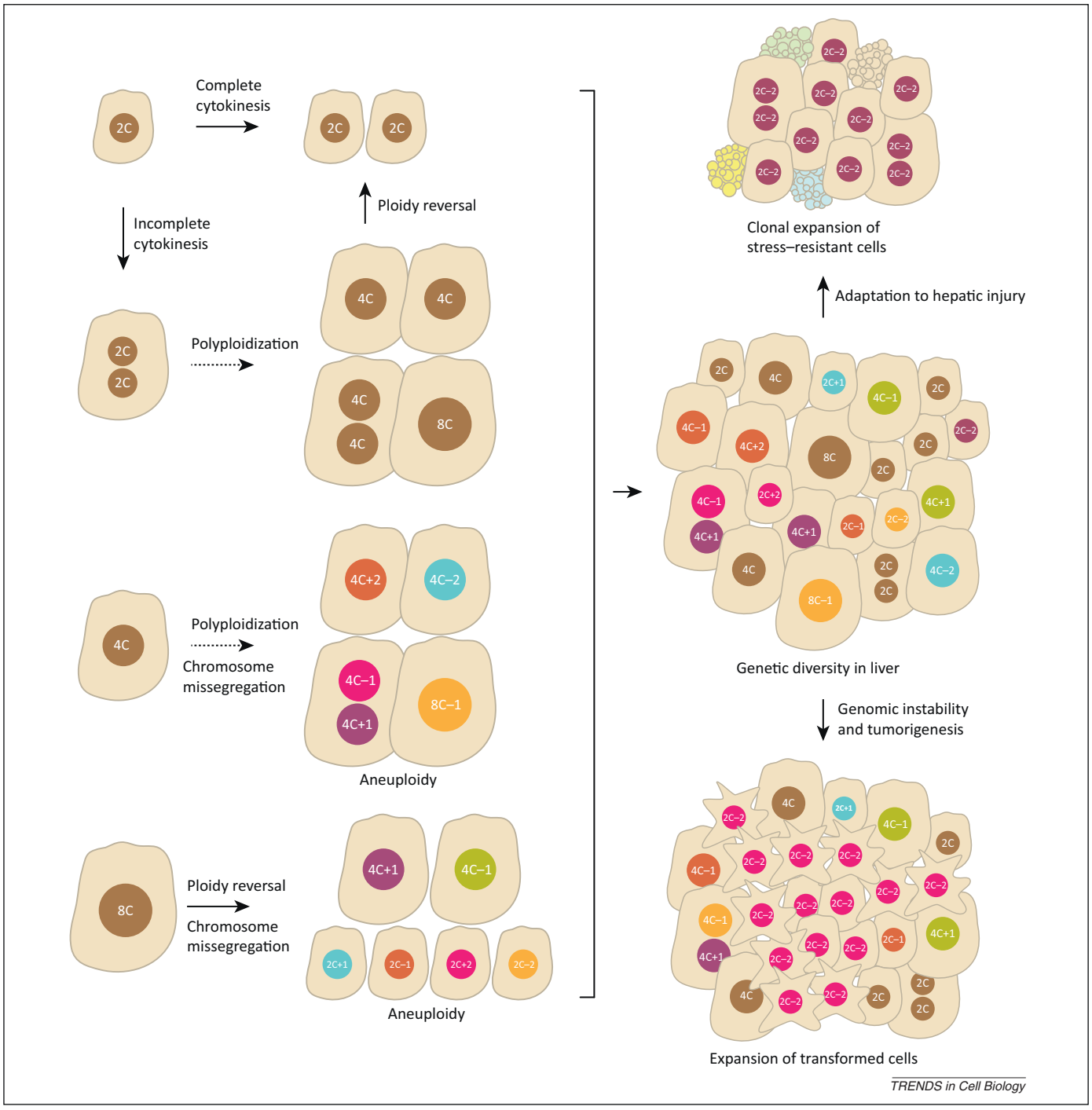

Figure 1. Genetic diversity in hepatocytes through polyploidization. Gradual polyploidization occurs in the rodent liver during postnatal development. During this process a proportion of diploid (2C) hepatocytes undergo incomplete cytokinesis and generate binucleated tetraploid (4C) hepatocytes (2×2C). Binucleated cells progressing through the next cell cycle with normal cytokinesis form two mononucleated tetraploid cells. This continued process leads to formation of mono- or binucleated tetraploid and octoploid (8C) hepatocytes and so on (the broken arrow indicates several ways leading to polyploidization). Interestingly, polyploid cells can also reduce ploidy through multipolar spindle formation, a process known as ploidy reversal. During this ploidy reversal process chromosome segregation errors are common, resulting in the formation of aneuploid daughter cells [gain (+) or loss (−) of one or more individual chromosomes]. Genetic diversity in the liver could be beneficial as well as detrimental. The liver responds to injury or stress by expanding its injury-resistant aneuploid cells. By contrast, genetic diversity can also lead to genomic instability and tumorigenesis.

model, toxic injury leads to the selection of hepatocytes with a specific aneuploid karyotype, rendering them differentially resistant to chronic liver injury. A similar mechanism might also be valid for the adaptation of tumor cells, where loss or gain of chromosomes provides them with a growth advantage (Figure 1).

Polyploidization as a stress response

Polyploidization appears in some cells as a normal developmental process, whereas in others it occurs as a result of stress. This appears to be especially relevant for hepatocytes given their role in detoxification. There is an extensive correlation between the generation of polyploid cells