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Review

Aneuploidy, polyploidy and ploidy reversal in the liver

Andrew W. Duncan*

Department of Pathology, McGowan Institute for Regenerative Medicine, University of Pittsburgh, 450 Technology Drive, Suite 300, Pittsburgh, PA 15219, United States

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ABSTRACT

Polyploidy has been described in the liver for over 100 years. The frequency of polyploid hepatocytes varies by age and species, but up to 90% of mouse hepatocytes and approximately 50% of human hepatocytes are polyploid. In addition to alterations in the entire complement of chromosomes, variations in chromosome copy number have been recently described. Aneuploidy in the liver is pervasive, affecting 60% of hepatocytes in mice and 30–90% of hepatocytes in humans. Polyploidy and aneuploidy in the liver are closely linked, and the ploidy conveyor model describes this relationship. Diploid hepatocytes undergo failed cytokinesis to generate polyploid cells. Proliferating polyploid hepatocytes, which form multipolar spindles during cell division, generate reduced ploidy progeny (*e.g.*, diploid hepatocytes from tetraploids or octaploids) and/or aneuploid daughters. New evidence suggests that random hepatic aneuploidy can promote adaptation to liver injury. For instance, in response to chronic liver damage, subsets of aneuploid hepatocytes that are differentially resistant to the injury remain healthy, regenerate the liver and restore function. Future work is required to elucidate the mechanisms regulating dynamic chromosome changes in the liver and to understand how these processes impact normal and abnormal liver function.

Contents

1. Introduction

The liver is the largest solid organ in the body, representing 2% of total body weight in humans and 5% in mice. A number of excellent reviews describe liver organization, function and pathology [1,2]. Briefly, the liver is responsible for a myriad of functions, including synthesis of serum proteins, bile production/secretion, metabolism of carbohydrates, lipids and amino acids and detoxification of xenobiotic compounds. These roles are performed primarily by hepatocytes that comprise 70–80% of the liver mass. The liver is

Abbreviations: 2n, diploid cell; 4n, tetraploid cell; 8n, octaploid cell; Ch, chromosome; FACS, fluorescence activated cell sorting; FISH, fluorescence *in situ* hybridization; Fah, fumarylacetoacetate hydrolase; Hgd, homegentisic acid dioxygenase; NTBC, 2-(2-nitro-4-trifluoro- methylbenzoyl)-1,3-cyclo-hexanedione.

* Tel.: +1 412 624 5302; fax: +1 412 624 5363.
E-mail address: duncana@pitt.edu

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unique among other organs in its regenerative capacity. Hepatocyte turnover occurs slowly in adults with average hepatic lifespan ranging from 200 to 300 days [3]. It has been estimated that fewer than 0.1% of hepatocytes are cycling at any given time [2]. Although hepatocytes are mostly quiescent in non-injury situations, these cells harbor tremendous regenerative potential in response to liver injury. For example, rats survived and regenerated their livers in response to seven sequential 50% partial hepatectomies [4]. Similarly, mature mouse and human hepatocytes transplanted into mice undergoing liver failure proliferated 50–100-fold to restore the entire liver mass [5,6]. Moreover, serial transplantation revealed even greater proliferative capacity with 10^{20}-fold hepatocyte expansion. Mature hepatocytes are the primary drivers of liver regeneration in the adult, but hepatic stem/progenitor cells can also contribute to the regenerative response, especially when mature hepatocytes are inhibited [7–9]. Processes such as cell fusion [10–12] and transdifferentiation [13,14] have also been shown to promote liver regeneration.

In addition to the diverse functions required for homeostasis and regeneration, the liver is also characterized by variations in nuclear content. The most extensively described type of nuclear alteration in the liver is polyploidy, an increase in the number of chromosome sets per cell [15]. Although polyploid hepatocytes have been well described [16,17], the function of these cells is not well understood. A second and more recently characterized type of hepatic nuclear alteration is aneuploidy. Aneuploidy refers to the gain or loss of individual chromosomes. While aneuploidy is frequently associated with cancer, this does not seem to be the case in the liver. This article will focus on hepatic polyploidy and aneuploidy and explore how these processes cooperate to regulate liver function.

2. Polyploidy in the liver

Polyploidy in the liver has been described in the literature for well over 100 years [18]. Initially, analysis of liver sections revealed a great deal of heterogeneity among hepatocytes. Cell and nuclear size varied between hepatocytes, as well as the number of nuclei per cell. We now know that hepatocyte ploidy depends on the DNA content of each nucleus (*e.g.*, diploid, tetraploid, octaploid, *etc.*) plus the number of nuclei per cell [19]. The vast majority of hepatocytes are either mononucleate or binucleate, but rare trinucleate and tetranucleate hepatocytes are occasionally seen. Hepatic polyploidization is an age-dependent process. Most hepatocytes are diploid in young individuals, and in humans approximately half of adult hepatocytes are polyploid [20]. The degree of polyploidy is even more striking in rodents. Up to 90% of hepatocytes are polyploid in adult C57Bl mice [21].

2.1. Mechanisms for hepatic polyploidization

Polyploid cells are born in a tissue-type specific manner [22]. For instance, cell fusion occurs between myoblasts to generate myofibrils [23] and macrophages to produce osteoclasts [24]; endoreplication involves DNA replication without nuclear division and occurs in megakaryocytes [25]; and cytokinesis failure can generate tetraploid cardiac cells [26] and cancer cells [27]. In the liver, the predominant mechanism leading to polyploidy is failed cytokinesis. Elegant studies in the rat by Desdouets and colleagues clearly elucidated the process (Fig. 1). Prior to weaning, rat hepatocytes are nearly exclusively diploid. Changes in insulin signaling occur at weaning in an AKT-dependent manner that induce cytokinesis failure [28]. First, a subset of diploid hepatocytes undergoes failed cytokinesis to generate tetraploid daughter cells, each with two diploid nuclei [19,29]. Secondly, binucleate tetraploid hepatocytes go through DNA replication with successful cytokinesis, generating pairs of mononucleate tetraploid hepatocytes (with a single tetraploid nucleus per cell). Next, a subset of mononucleate tetraploid hepatocytes undergoes cytokinesis failure during mitosis, leading to the formation of binucleate octaploid daughters. Finally, the process continues, generating mononucleate octaploids, binucleate hexadecaploids and so on. In mice and humans, polyploidization is believed to also occur primarily by failed cytokinesis. However, the kinetics of polyploidization differs somewhat between mice and rats. Whereas polyploidization begins at weaning in rats, nearly half of mouse hepatocytes are already polyploid at this time [21].

In addition to the insulin pathway, other factors have been shown to promote polyploidy. For instance, partial hepatectomy [30], oxidative stress [31], iron overload [32] and p53 deficiency [33] lead to increased liver polyploidization. Pathological conditions, such as viral hepatitis, are also associated with enrichment for polyploid hepatocytes [34]. It remains to be determined how all these divergent signals integrate to control hepatic ploidy at the global level.

Although cytokinesis failure is the major pathway leading to hepatic polyploidy, cell fusion has also been shown to occur in the liver. Homotypic cell fusion between hepatocytes is controversial. One report indicates that hepatocyte–hepatocyte fusion occurs readily during development [12], whereas another report concludes that hepatocyte–hepatocyte fusion in adults does not occur

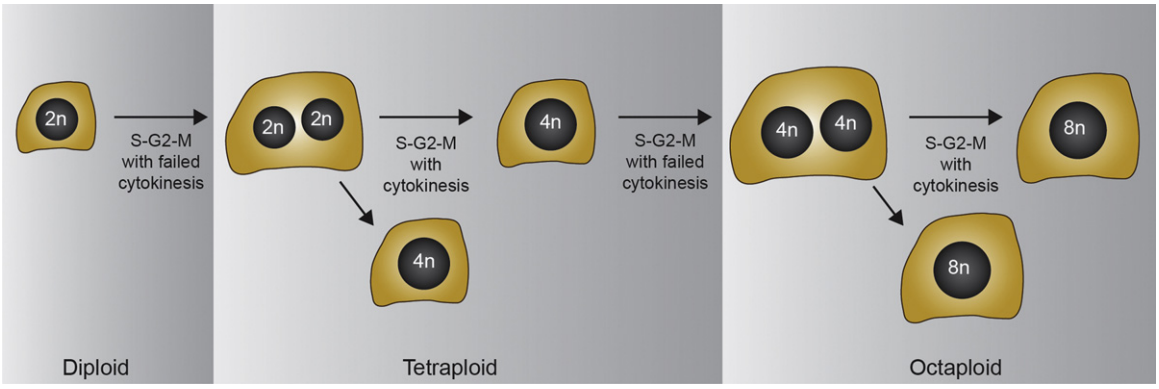

Fig. 1. Polyploidization by failed cytokinesis. Diploid hepatocytes undergo a complete cell cycle with failed cytokinesis to form a binucleate tetraploid hepatocyte (where nuclei are 2n). The binucleate tetraploid completes a successful cell cycle plus mitosis, generating two mononucleate tetraploids (where each nucleus is 4n). A subsequent cell cycle plus mitosis with failed cytokinesis produces a binucleate octaploid (where each nucleus is 4n). The cycle continues, producing mononucleate octaploids, hexadecaploids, *etc.*