Polyploidy: Mechanisms and Cancer Promotion in Hematopoietic and Other Cells
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Abstract

Polyploidy, the state of having greater than a diploid content of DNA (e.g., tetraploid, octaploid, etc.) has been recognized in a large variety of both, plant and animal cells. Human and murine megakaryocytes, hepatocytes, arterial smooth muscle cells and cardiac myocytes, all develop a certain degree of polyploidy during their normal lifespan. In addition, polyploid cells may be found in some tissues under conditions of stress, including uterine smooth muscle during pregnancy, aortic vascular smooth muscle cells during aging and hypertension, beta-cells in diabetic human or mouse thyroid cells in hyperthyroidism and cells in seminal vesicles with aging. Polyploid cells are also found in malignant tissues in which they are believed to contribute to the development of cells with intermediate DNA content values (e.g., 3n, 4.5n, etc.) (reviewed in refs. 1,2). With the use of micro-array, researchers have demonstrated that genetically identical yeast strains (Saccharomyces cerevisiae) with differences only in ploidy status (from haploid to tetraploid) display a substantial difference in gene expression, including of the G1 cyclins.3 This finding has suggested that DNA content per se might affect cellular functions.

Overview: Characteristics of Polyploidy and Its Induction Under Different Conditions

Currently, the relationships between polyploidy and aneuploidy has not been studied extensively considering the prominent role of genetic instability in tumorigenesis.4 An understanding of the biochemical, gene expression and signaling pathways that drive normal and abnormal polyploidization could lead to useful insights with respect to novel anticancer therapeutic approaches. The occurrence of polyploidy in normal and transformed cells poses a number of questions. Is polyploidy a protective mechanism upon stress, as suggested,2,5,6 or rather a maladaptive response? What mechanisms or signaling pathways are employed by normal developing polyploid cells (e.g., megakaryocytes) to safeguard them from becoming aneuploid?

In megakaryocytes, polyploidization up to 128N can be attained, if the cells undergo repeated endomitotic cell cycles, characterized by a well coordinated entry of cells into a normal early mitotic phase, which includes prophase, metaphase and early anaphase. However, these cells skip late anaphase and cytokinesis (this truncated mitosis is referred to as polyploidy via endomitosis, reviewed in ref. 2). In contrast, polyploidy may result from another type of truncated mitosis, referred to as polyploidy via abortive mitosis to describe the generally uncoordinated events that are driven by spindle checkpoint defects or by chemical treatments. These events are often associated with pathological

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conditions (reviewed in refs. 1, 2, 4 and see Illustration 1). It has been shown, in both tissue culture and in transgenic mice, that polyploidy via endomitosis in megakaryocytes is tightly regulated by a series of signaling pathways and gene expressions, including signaling through thrombopoietin (TPO), binding to its receptors c-Mpl and its associated with elevated cyclin D3 expression and reentry into S-phase.7-9 There is also evidence that these cells possess a gene expression profile that is different from their diploid counterparts, including low expression of the tumor suppressor gene p53 in conjunction with high expression of the cell cycle inhibitor p21 to allow a short-lived progression through G1 phase.11,12 Numerous studies have shown that normal diploid cells of other lineages can be induced to undergo polyploidization via endomitosis as a consequence of stress (e.g., hypertension and senescence) (reviewed in ref. 2). In addition, polyploid hepatocytes have been shown to increase in number dramatically upon oxidative stress or after partial hepatectomy.13,14 Endothelial cells and fibroblasts have been shown in tissue biopsies and in cell culture to become polyploid upon aging and during tissue repair.8,16 Hypertension can induce vascular smooth muscle cells and cardiac myocytes to become polyploid.17,18 In these cases, polyploidy is believed to be a protective mechanism, which acts to prevent cellular proliferation in the vasculature or to increase DNA content in order to compensate for mutations introduced by genotoxic agents.19 The other hand, tetraploidy (cells with a double diploid DNA content) may reflect tissue damage as in Barret's esophagus,20 in which there is dysplasia of the

Figure 1. Pathways to polyploidy. Left panel) Polyploidy via Endomitosis—a shortened mitosis without anaphase-B and cytokinesis, followed by reentry into G1 phase of cell-cycle. This well-controlled truncated mitosis is a part of megakaryocytes development.2,4 Right panel) Polyploidy via Abortive Mitosis—an abrupt termination of mitosis at metaphase, anaphase A, B or cytokinesis, followed by reentry into the cell-cycle with a tetraploid DNA content. These cells can have a single or multiple nuclei, depending on the timing of the defective events. This phenomenon is often associated with pathological conditions, including cancer (reviewed in refs. 2, 4).