Current Genetics (2019) 65:1081–1088
https://doi.org/10.1007/s00294-019-00967-x

REVIEW

Histone stress: an unexplored source of chromosomal instability in cancer?

Douglas Maya Miles[1] · Chantal Desdouets[2] · Vincent Géli[1]

Received: 22 February 2019 / Revised: 27 February 2019 / Accepted: 3 April 2019 / Published online: 11 April 2019

Abstract

Ploidy is stably maintained in most human somatic cells by a sequential and tight coordination of cell cycle events. Undesired whole genome doublings or duplications are frequent in tumours and have been quite recently described as macroevolutionary events associated with poor prognosis. In vitro and in vivo studies suggest that polyploidy can favour genome instability, facilitate the formation and progression of tumours, and modify their sensitivity to chemotherapeutic agents. Stress is strongly related to changes in ploidy and whole genome doublings. In this review, we summarize different mechanisms that promote polyploidization, describe a new type of stress able to trigger WGDs in *S. cerevisiae*, histone stress, and provide some examples and theoretical scenarios that support that cancer cells might suffer from this type of stress. We finally highlight some results showing that the kinase Swe1 (Wee1 in humans) has a role in sensing histone levels before cells enter mitosis, thereby avoiding their undesired consequences on chromosome segregation and ploidy control.

Keywords Histones · Whole genome duplication · Polyploidy · Swe1 · Genome instability · Cancer

Introduction

Polyploidy, a state in which cells possess more than two sets of homologous chromosomes, occurs frequently in nature (Otto 2007; Van de Peer et al. 2017). The additional set (or sets) of chromosomes may originate from the same individual (autopolyploid) or from the hybridization of two different species (allopolyploid). Polyploidy is most common among plants, particularly angiosperms (Ramsey and Schemske 1998). These polyploid species commonly arise from unreduced gametes by nondisjunction of chromosomes in the germline. Polyploidy is very likely to modify plant morphology, phenology, physiology and/or ecology, and thus generates individuals that can flourish in novel habitats and fluctuating environments, or outcompete progenitor species (Leitch and Leitch 2008). Polyploidy is less tolerated in animals than in plants. However, there are numerous cases of polyploid fish, amphibians, insects and reptiles (Otto and Whitton 2000). In mammals, polyploidy occurs in specific tissues such as placenta, heart, mammary gland and liver. In fact, different studies have demonstrated a major role, in specific tissues, of "diploid–polyploid conversion" during the physiological processes (e.g. embryogenesis, terminal differentiation), but also during pathological conditions (e.g. mechanical, genotoxic or metabolic stress) (Gentric et al. 2015; Gentric and Desdouets 2014; Pandit et al. 2013). Alarmingly, proliferating polyploid cells have been demonstrated also to be genetically unstable and can facilitate tumour development in specific tissues (Davoli and de Lange 2011; Fujiwara et al. 2005). Accumulating evidence points to a significant contribution of polyploid intermediates in shaping the composition of cancer genomes: the majority of solid tumours exhibit polyploid or near polyploid karyotypes (Jamal-Hanjani et al. 2017; Zack et al. 2013). In a recent report, whole genome doublings (WGDs) were detected in the tumours of nearly 30% of 9692 prospectively sequenced advanced cancer patients and predicted for increased morbidity across many different cancer types (Bielski et al. 2018).

Communicated by M. Kupiec.

✉ Vincent Géli
vincent.geli@inserm.fr

[1] Marseille Cancer Research Centre (CRCM), U1068 Inserm, UMR7258, CNRS, Aix-Marseille Université, Institut Paoli-Calmettes, Equipe labellisée Ligue, Marseille 13273, France

[2] Centre de Recherche des Cordeliers, UMR 1162, Inserm, Université Paris Descartes, 75006 Paris, France

Mechanisms of polyploidization

How does a diploid cell become polyploid? In a physiological or pathological context, there are a number of mechanisms that promote the genesis of polyploid cells (Fig. 1).

Cell fusion is the only process leading to polyploidy that does not require a previous cell cycle defect. By this mechanism, membranes merge and cytoplasm mixes leading to the genesis of mostly multinuclear cells. Many species (e.g. yeast, nematodes, mammals) and cell types (e.g. gametes, epithelia and myoblasts) carry out physiological cell–cell fusion to maintain tissue homoeostasis (Larsson et al. 2008). Pathological viral infection has also an important role in polyploid cell formation by cell fusion (Duelli and Lazebnik 2007). For instance, human papilloma virus (HPV) infection, a risk factor for the development of cervical cancer, has been shown to induce cell fusion and tetraploidy (Gao and Zheng 2011).

Endoreplication occurs through *Endocycle*, in which periods of S and G phases alternate with no mitosis, or through *Endomitosis*, which displays features of mitosis but lacks cytokinesis (Ovrebo and Edgar 2018). Endoreplication occurs in the life cycle of protozoa, plants, flies and mammals and often produces terminally differentiated cells. This process has been extensively studied in *Drosophila melanogaster*, where cells in most larval tissues, as well as in many adult tissues, switch to endoreplication cycles. Notably, in mammals, during the implantation of blastocysts, trophoblast giant cells (TGC) perform endoreplication cycles and accumulate DNA up to 1000 sets of chromosomes. Numerous studies have also shown a link between persistent DNA damage response (e.g. DNA repair defect, telomere dysfunction, oncogene expression) and endoreplication cycles (Davoli and de Lange 2011).

Cytokinesis failure process has been described during tumorigenesis and leads to the genesis of binucleated polyploid cells. These cells can be generated following dysfunction of any of a large number of different proteins controlling the cytokinesis process (D'Avino et al. 2015). In addition, bulk chromatin or even a single lagging chromosome trapped in the cleavage furrow can induce cytokinesis failure and tetraploidization (Lacroix and Maddox 2012; Shi and King 2005). Remarkably, studies have also demonstrated that the cytokinesis failure process is also a programmed step in normal development (e.g. liver, heart, placenta tissues) producing differentiated binucleated polyploid progenies (Gentric et al. 2015; Gentric and Desdouets 2014).

Determining the specific function of polyploid cells is a key challenge in the field. Interestingly, in different mammal tissues, polyploidy is related to modifications of the genome, epigenome, transcriptome and metabolome (Schoenfelder and Fox 2015). Different advantages have been associated with polyploidy status as resistance to apoptosis, modification of metabolism, tissue repair and blood brain barrier (Ovrebo and Edgar 2018; Miettinen et al. 2014; Orr-Weaver 2015). Alarmingly, polyploidization in specific tissue is a

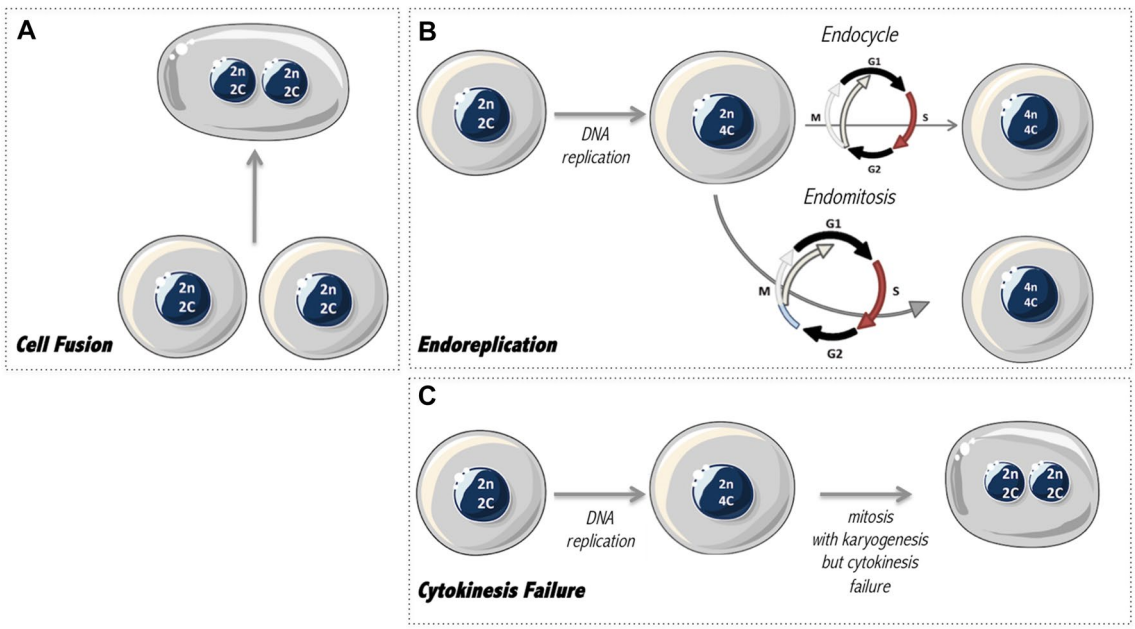

Fig. 1 Mechanisms leading to the genesis of tetraploid cells. Tetraploid cells can be generated by cell fusion (**a**), or by abortive cell cycles after DNA replication (**b** endoreplication, **c** cytokinesis failure). Although cell fusion and cytokinesis failure produce binuclear progeny, endoreplication (endocycle and endomitosis) results in a mononuclear cell. *c* chromatid number; *n* chromosome number

clear disadvantage, as there is a clear association between polyploidy, aneuploidy providing and tumorigenesis (Davoli and de Lange 2011; Ganem et al. 2007).

Histone stress can trigger whole genome doublings in *S. cerevisiae*

Each time a cell divides, several millions of histones, small basic proteins that conform to nucleosomes, are synthesized and incorporated as the replication machinery copies DNA. Chromatin replication requires the synthesis and incorporation of four different histones, H2A, H2B, H3 (H3.1 and H3.2 in higher eukaryotes) and H4, which are commonly known as canonical histones, and the incorporation of the linker histone H1. Canonical histones can be regulated at transcriptional, post-transcriptional, translational and post-translational levels. The importance of each pathway on histone metabolism largely depends on the organism, but all of them tend to have several redundant pathways to control their amounts and produce them exclusively during the replicative S-phase, and more specifically when replication is actively taking place (Cook et al. 2011; Eriksson et al. 2012; Groth et al. 2005; Marzluff et al. 2008; Maya et al. 2013; Prado and Maya 2017). In addition to canonical histones, all eukaryotes have several histone variants that can replace specific canonical histones in chromatin. These variants play critical roles in the cell such as transcription, chromosome segregation, DNA repair and recombination, chromatin remodelling, ADP-ribosylation, germline-specific and DNA packaging, pluripotency and environmental responses (Skene and Henikoff 2013; Talbert et al. 2012; Talbert and Henikoff 2014). Mutations in some of them have been associated with the development of certain diseases such as cancer (Henikoff and Smith 2015; Quénet 2018; Wang et al. 2018). Understanding where and how histone variants are incorporated and how histone modifications are maintained through replication is, therefore, an important biological question. Recent studies are starting to shed some light on the field (Clément et al. 2018; Reverón-Gómez et al. 2018), but further research is required to solve this complex histone puzzle. One interesting question regarding histone variants is how do cells regulate the specific incorporation of one or another variant to a specific region. Several theoretical scenarios are possible including: (1) histone variants are opportunistic and occupy chromatin when other histone variants are absent or in lower levels that disfavour their incorporation; (2) they display spatiotemporal features that ensure that their incorporation takes place at specific loci or during specific time windows and (3) they have specific modifiable residues that change their affinity for chromatin and/or for the protein complexes that mediate their entry or exit to chromatin. Research done so far supports all three of them. For certain variants, several types of regulation coexist (Melters et al. 2015; Mendiratta et al. 2019; Talbert and Henikoff 2017).

Stress is strongly related to WGDs in plants and has been proposed as an adaptive response that provides plasticity to mitigate its effects (Scholes and Paige 2015). Injury and cellular stress can also promote WGDs in higher eukaryotes, and there are several examples of tissues that can use endocycles and/or cell–cell fusions to compensate for losses of tissue mass (Ovrebo and Edgar 2018). Yeast cells exposed to certain type of stresses, such as ethanol or KCl, for long periods of time can also trigger WGDs and or provide selective growth advantages to cells with a higher DNA content (Harari et al. 2018a, b).

We have recently uncovered a new type of stress, histone stress, defined as cells in which canonical histones are not properly regulated during the cell cycle, which triggers WGDs and can also provide a growth advantage to cells with a higher DNA content (Maya Miles et al. 2018). Cells in which canonical histones H2A and H2B are persistently expressed throughout the cell cycle experience clear delays in nuclear division that can trigger aberrant endomitosis in which daughter cells retain both nuclei (Fig. 2). The fact that the frequency of WGDs depends on the relative levels of H2A.Z and H2A suggests a competition model in which both histones can compete for the same substrate(s), similar to the one previously proposed for histone H3 and the centromeric isoform CENP-A (Au et al. 2008; Castillo et al. 2007). The authors show in this work that cells in which the two key pathways involved in canonical histone degradation are absent suffer profound changes in chromatin structure that include a chromatin more resistant to MNase degradation that loses the characteristic ladder of nucleosomes obtained with partial digestions and a significant decrease of histone H2A.Z incorporation to several regions including pericentromeric chromatin. High levels of H2A.Z incorporation at pericentromeres have also been linked to spontaneous WGDs in *S. cerevisiae* (Chambers et al. 2012), suggesting that the relative levels of histone H2AZ that are incorporated to these regions are essential to maintain ploidy control. The fact that the overproduction of histones H3 and H4 can also trigger WGDs in cells in which the kinase activity of Rad53 (Maya Miles et al. 2018), required for the degradation of canonical histones, is absent suggests that the H2A/H2A.Z competition model is not the only way in which excessive canonical histones trigger WGDs. Accordingly, defects in the incorporation of several other histone variants with key roles in chromosome segregation, such as H3.3 and CENP-A, have also been shown to trigger genome instability through aneuploidy or polyploidy (Au et al. 2008; Castillo et al. 2007; Collins et al. 2007; Tomonaga et al. 2003; Jang et al. 2015). The fact that their patterns of expression and/or incorporation are also uncoupled from DNA replication

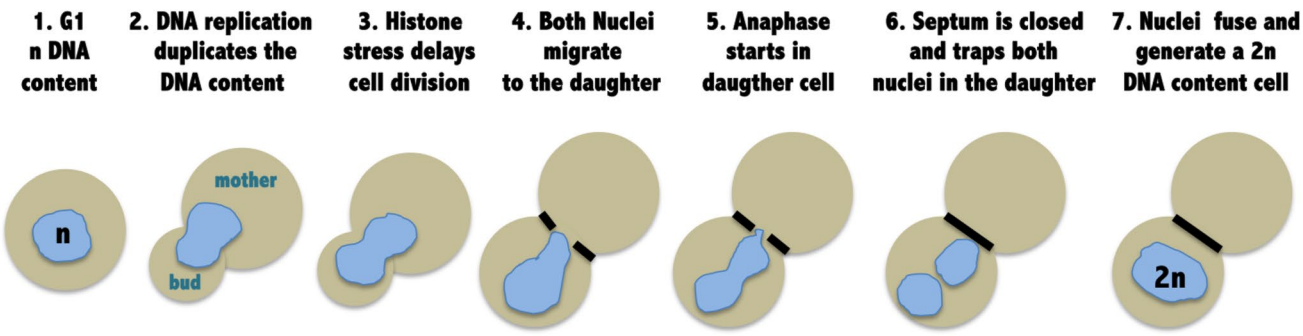

Fig. 2 High levels of histone promoted undesired WGDs. Live microscopy reveals that 20% of yeast cells expressing abnormal levels of histones remain blocked in metaphase for a couple of hours and display an undivided nucleus. In a small proportion of these cells, the whole nucleus migrates to the daughter before anaphase, and mitosis starts in daughter cells once the septin ring has already closed trapping both nuclei in the daughter and leaving an empty mother. The fusion of the two nuclei generates a diploid daughter cell that is selected over the haploids due to its growth advantage. This diploid cell does not show any major chromosome reorganization and is able to form triploids when crossed with a strain from the opposite mating type

(Mendiratta et al. 2019) suggests that maintaining an appropriate balance between canonical and non-canonical histones is essential to preserve genome integrity and avoid undesired WGDs.

Histone stress: an unexplored source of chromosomal instability in cancer?

Histone expression in humans can be regulated at transcriptional, post-transcriptional and post-translational levels and recent work highlights that their location could also be important to boost the efficiency of histone mRNA biosynthesis (Mendiratta et al. 2019; Duronio and Marzluff 2017). Most histone genes are clustered in chromosome 6 (6p22), which contains 55 histone genes. There are in addition two smaller clusters on human chromosome 1, *HIST2* and *HIST3* (1q21 and 42), which contain ten and three genes (Marzluff et al. 2002). Their expression throughout the cell cycle is controlled at multiple levels by many different factors that can modulate the expression of specific clusters or have a general role in all of them (Gokhman et al. 2013; Rattray and Müller 2012). Human replicative histones lack introns, have relatively short UTRs, and produce transcripts with a conserved 3′ stem loop that is not polyadenylated and that plays a key role in their cell cycle regulation (Marzluff et al. 2008; Mei et al. 2017). This structure can be recognized by SLBP, a protein critical for the regulation of histone expression during the cell cycle that is also cell cycle regulated and is usually only present when replication actively takes place. Canonical histone mRNAs are rapidly degraded at the end of the S-phase or when DNA replication is inhibited. Degradation requires the stem–loop sequence and SLBP. The initial step in histone mRNA degradation is the addition of uridines to the 3′ end of the histone mRNA. The Lsm1-7 complex is required for histone mRNA degradation and is thought to bind to the oligo(U) tail and form a complex on the 3′ end of histone mRNA containing SLBP and several other factors. Both the 5′ pathway and the 3′ pathway are involved in histone mRNA degradation, and individual molecules of histone mRNA can be simultaneously degraded 5′ to 3′ and 3′ to 5′ (Mullen and Marzluff 2008). H3 and H4 levels can also be regulated at a post-translational level. This mechanism, mediated by the human histone chaperone nuclear autoantigenic sperm protein (NASP) is able to prevent their degradation via chaperone-mediated autophagy and maintain a cytosolic soluble pool of H3–H4 dimers protected from degradation (Cook et al. 2011).

Discrete chromosome segregation defects and WGDs are two phenomena frequently observed in cancer (Zack et al. 2013). Several reports support an important role for both in tumorigenesis (Davoli and de Lange 2011; Dewhurst et al. 2014; Santaguida and Amon 2015), adaptation (Yant and Bomblies 2015) and resistance to chemotherapeutic agents (Sharma et al. 2013). One of the most obvious consequences of both is that the gain of additional copies of chromosomes alters the number of gene copies of several hundreds of genes, something that has been proven to impact their expression and most likely hinders the ability of cells to maintain appropriate levels of the proteins encoded or regulated by them (Dürrbaum and Storchová 2016; Jackson and Chen 2010; Wertheim et al. 2013). It is tempting to consider that these changes in copy number have an impact on the efficient regulation of canonical histone synthesis during the cell cycle and that cells in which this regulation is broken might be more subject to trigger genome instability through new events promoted by histone stress. Validation of this hypothesis requires mainly two things. The first one would be to demonstrate that histone levels are not efficiently cell

cycle regulated in tumours prone to genome instability and these tend to experience undesired WGDs and/or become aneuploid. The second is to demonstrate that histone excess can trigger these phenomena in higher eukaryotes, and more specifically in humans. Depletion of SLBP in drosophila results in a defect in the synthesis of canonical histones during DNA replication and also in the accumulation of abnormal polyadenylated histones mRNAs that can be translated and escape their usual cell cycle regulation restricted to DNA replication (Sullivan et al. 2001; Lanzotti et al. 2002). SLBP mutants in drosophila display several features of genome instability, including loss of heterozygosity (LOH) and tetraploidy (Salzler et al. 2009). Treatment with arsenic, a carcinogenic compound that can promote both aneuploidy and polyploidy, was recently shown to cause a depletion of SLBP in bronchial epithelial cells, which induces aberrant polyadenylation of canonical histone H3.1 mRNA that accumulates beyond the S-phase (Brocato et al. 2014). Brocato et al. (2015) further evaluated the effects of polyadenylated histone H3.1 mRNA and SLBP depletion on carcinogenesis and found that both of them are able to enhance the anchorage-independent cell growth of these cells in soft agar plates. Arsenic-induced cellular transformation has been recently coupled with genome-wide changes in chromatin structure (Riedmann et al. 2015), something that we have also observed when canonical histones are not degraded (Maya Miles et al. 2018). This result, however, has to be assessed carefully since this compound can also affect the activity of histone-modifying enzymes (Chervona et al. 2012). Histone H3.1 mRNA accumulation is not exclusive for arsenic and can also be observed in cells treated with nickel, another carcinogenic metal compound that promotes genome instability and can change the chromatin landscape (Jordan et al. 2017). Overexpression of histone H2A has been linked to the transformation of normal liver to the preneoplastic and neoplastic stages of hepatocellular carcinoma (Khare et al. 2011) in which WGDs are frequent (Gentric and Desdouets 2014). A number of microarray studies examining the expression of polyadenylated mRNAs have identified changes in the levels of histone transcripts during differentiation and tumorigenesis (Kari et al. 2013). Collectively, all these results point out the need to revisit how efficient is the regulation of histone synthesis in cancers with a predisposition to WGDs, aneuploidy and genome instability and even to reconsider the effects of anticancer drugs that can target histone levels such as arsenic. It is interesting to point out that chromosome 6p22 amplification, which contains 55 out of the 68 genes that encode canonical histones, is frequently observed in many different tumours and that it correlates with cancer aggressiveness and poor prognosis (Santos et al. 2007).

A histone-sensing checkpoint?

Several studies have demonstrated that cells are able to modulate cell cycle progression when histones become limiting to ensure the faithful replication of chromatin and avoid genome instability (Groth et al. 2007; Murillo-Pineda et al. 2014). The fact that histone excess is also linked to genome instability and chromosome segregation defects (Au et al. 2008; Castillo et al. 2007; Gunjan and Verreault 2003; Takayama et al. 2010) raises the question of whether cells could also have a mechanism(s) that would allow them to sense or respond to high levels of them.

We have recently observed that cells unable to promote canonical histone degradation stabilize the kinase Swe1 (Wee1 in mammals and *S. pombe*). Swe1^{WEE1} that is conserved in yeast to humans is expressed during replication and degraded before mitosis (Howell and Lew 2012; Botchkarev and Haber 2018). Swe1^{WEE1} phosphorylates Tyr_{19} of Cdc28^{CDK1} (Tyr_{15} in humans)—the only cyclin-dependent kinase present in *S. cerevisiae*—thereby inhibiting its activity and delaying the metaphase to anaphase transition (Lew 2000). Swe1^{WEE1} can also be stabilized upon DNA damage (Palou et al. 2017). In cells exposed to a persistent transcription of canonical histones H2A and H2B (that also have a slower transition from G2/M to the next G1), Cdc28^{CDK1} phosphorylation is maintained for a longer period of time (Maya Miles et al. 2018). This kinase able to modulate cell cycle progression in response to actin cytoskeleton perturbations (Lew 2000) can physically interact and modify histone H2B in both human and yeast and facilitate the repression of histone transcription at the end of the S-phase (Mahajan et al. 2012). The fact that Swe1 is able to regulate at the same time histone levels and cell cycle progression through the phosphorylation of histone H2B and Cdc28, respectively—added to the fact that it seems to be stabilized when canonical histones accumulate—favours a key role for Swe1 in histone homoeostasis that cells might have acquired to prevent the undesired consequences of high levels of canonical histones on chromosome segregation. Interestingly, histone deprivation has been previously shown to block mitosis in drosophila embryos through a transcriptional down-regulation of the Cdc25 phosphatase string, which triggers CDK1 dephosphorylation (Gunesdogan et al. 2014). Regulation of Cdc28 activity therefore appears to be a mechanism by which cells can respond to both, high and low levels of histones, ensuring a proper histone supply during replication but its absence before mitosis.

Acknowledgements We thank Sebastian Chavez, Manuel Mendoza and Marie-Noelle Simon for discussions. Work in V.G. laboratory was supported by "Ligue contre le Cancer" (Equipe Labéllisée 2018).

References

Au WC, Crisp MJ, DeLuca SZ, Rando OJ, Basrai MA (2008) Altered dosage and mislocalization of histone H3 and Cse4p lead to chromosome loss in Saccharomyces cerevisiae. Genetics 179:263–275

Bielski CM, Zehir A, Penson AV, Donoghue MTA, Chatila W, Armenia J, Chang MT, Schram AM, Jonsson P, Bandlamudi C, Razavi P, Iyer G, Robson ME, Stadler ZK, Schultz N, Baselga J, Solit DB, Hyman DM, Berger MF, Taylor BS (2018) Genome doubling shapes the evolution and prognosis of advanced cancers. Nat Genet 50(8):1189–1195

Botchkarev VV, Haber JE (2018) Functions and regulation of the Polo-like kinase Cdc5 in the absence and presence of DNA damage. Curr Genet 64:87

Brocato J, Fang L, Chervona Y, Chen D, Kiok K, Sun H, Tseng HC, Xu D, Shamy M, Jin C, Costa M (2014) Arsenic induces polyadenylation of canonical histone mRNA by down-regulating stem-loop-binding protein gene expression. J Biol Chem 289(46):31751–31764

Brocato J, Chen D, Liu J, Fang L, Jin C, Costa M (2015) A potential new mechanism of arsenic carcinogenesis: depletion of stem-loop binding protein and increase in polyadenylated canonical histone H3.1 mRNA. Biol Trace Elem Res 166:72–81

Castillo AG, Mellone BG, Partridge JF, Richardson W, Hamilton GL, Allshire RC, Pidoux AL (2007) Plasticity of fission yeast CENP-A chromatin driven by relative levels of histone H3 and H4. PLoS Genet 3:e121

Chambers AL, Ormerod G, Durley SC, Sing TL, Brown GW, Kent NA, Downs JA (2012) The INO80 chromatin remodeling complex prevents polyploidy and maintains normal chromatin structure at centromeres. Genes Dev 26(23):2590–2603

Chervona Y, Arita A, Costa M (2012) Carcinogenic metals and the epigenome: understanding the effect of nickel, arsenic, and chromium. Metallomics 4(7):619–627

Clément C, Orsi GA, Gatto A, Boyarchuk E, Forest A, Hajj B, Miné-Hattab J, Garnier M, Gurard-Levin ZA, Quivy JP, Almouzni G (2018) High-resolution visualization of H3 variants during replication reveals their controlled recycling. Nat Commun 9(1):3181

Collins SR, Miller KM, Maas NL, Roguev A, Fillingham J, Chu CS, Schuldiner M, Gebbia M, Recht J, Shales M, Ding H, Xu H, Han J, Ingvarsdottir K, Cheng B, Andrews B, Boone C, Berger SL, Hieter P, Zhang Z, Brown GW, Ingles CJ, Emili A, Allis CD, Toczyski DP, Weissman JS, Greenblatt JF, Krogan NJ (2007) Functional dissection of protein complexes involved in yeast chromosome biology using a genetic interaction map. Nature 446(7137):806–810

Cook AJ, Gurard-Levin ZA, Vassias L, Almouzni G (2011) A specific function for the histone chaperone NASP to fine-tune a reservoir of soluble H3-H4 in the histone supply chain. Mol Cell 44:918–927

D'Avino PP, Giansanti MG, Petronczki M (2015) Cytokinesis in animal cells. Cold Spring Harb Perspect Biol 7:a015834

Davoli T, de Lange T (2011) The causes and consequences of polyploidy in normal development and cancer. Annu Rev Cell Dev Biol 27:585–610

Dewhurst SM, McGranahan N, Burrell RA, Rowan AJ, Gronroos E, Endesfelder D, Joshi T, Mouradov D, Gibbs P, Ward RL, Hawkins NJ, Szallasi Z, Sieber OM, Swanton C et al (2014) Tolerance of whole-genome doubling propagates chromosomal instability and accelerates cancer genome evolution. Cancer Discov 4:175–185

Duelli D, Lazebnik Y (2007) Cell-to-cell fusion as a link between viruses and cancer. Nat Rev Cancer 7:968–976

Duronio RJ, Marzluff WF (2017) Coordinating cell cycle-regulated histone gene expression through assembly and function of the histone locus body. RNA Biol 14(6):726–738

Dürrbaum M, Storchová Z (2016) Effects of aneuploidy on gene expression: implications for cancer. FEBS J 283(5):791–802

Eriksson PR, Ganguli D, Nagarajavel V, Clark DJ (2012) Regulation of histone gene expression in budding yeast. Genetics 191(1):7–20

Fujiwara T, Bandi M, Nitta M, Ivanova EV, Bronson RT, Pellman D (2005) Cytokinesis failure generating tetraploids promotes tumorigenesis in p53-null cells. Nature 437:1043–1047

Ganem NJ, Storchova Z, Pellman D (2007) Tetraploidy, aneuploidy and cancer. Curr Opin Genet Dev 17:157–162

Gao P, Zheng J (2011) Oncogenic virus-mediated cell fusion: new insights into initiation and progression of oncogenic viruses-related cancers. Cancer Lett 303:1–8

Gentric G, Desdouets C (2014) Polyploidization in liver tissue. Am J Pathol 184:322–331

Gentric G, Celton-Morizur S, Desdouets C (2015) Polyploidy and liver proliferation. Clin Res Hepatol Gastroenterol 36:29–34

Gokhman D, Livyatan I, Sailaja BS, Melcer S (2013) Meshorer E (2013) Multilayered chromatin analysis reveals E2f, Smad and Zfx as transcriptional regulators of histones. Nat Struct Mol Biol. 20(1):119–126

Groth A, Ray-Gallet D, Quivy JP, Lukas J, Bartek J, Almouzni G (2005) Human Asf1 regulates the flow of S phase histones during replicational stress. Mol Cell 17:301–311

Groth A, Rocha W, Verreault A, Almouzni G (2007) Chromatin challenges during DNA replication and repair. Cell 128(4):721–733

Gunesdogan U, Jackle H, Herzig A (2014) Histone supply regulates S phase timing and cell cycle progression. Elife 3:e02443

Gunjan A, Verreault A (2003) A Rad53 kinase-dependent surveillance mechanism that regulates histone protein levels in *S. cerevisiae*. Cell 115:537–549

Harari Y, Ram Y, Rappoport N, Hadany L, Kupiec M (2018a) Spontaneous changes in ploidy are common in yeast. Curr Biol 28(6):825–835

Harari Y, Ram Y, Kupiec M (2018b) Frequent ploidy changes in growing yeast cultures. Curr Genet 64(5):1001–1004

Henikoff S, Smith MM (2015) Histone variants and epigenetics. Cold Spring Harbor Perspect Biol 7(1):a019364

Howell AS, Lew DJ (2012) Morphogenesis and the cell cycle. Genetics 190:51–77

Jackson S, Chen ZJ (2010) Genomic and expression plasticity of polyploidy. Curr Opin Plant Biol 13(2):153–159

Jamal-Hanjani M, Wilson GA, McGranahan N, Birkbak NJ, Watkins TBK, Veeriah S et al (2017) Tracking the evolution of non-small-cell lung cancer. N Engl J Med 376:2109–2121

Jang CW, Shibata Y, Starmer J, Yee D, Magnuson T (2015) Histone H3.3 maintains genome integrity during mammalian development. Genes Dev 29(13):1377–1392

Jordan A, Zhang X, Li J, Laulicht-Glick F, Sun H, Costa M (2017) Nickel and cadmium-induced SLBP depletion: a potential pathway to metal mediated cellular transformation. PLoS One 12(3):e0173624

Kari V, Karpiuk O, Tieg B, Kriegs M, Dikomey E, Krebber H, Begus-Nahrmann Y, Johnsen SA (2013) A subset of histone H2B genes produces polyadenylated mRNAs under a variety of cellular conditions. PLoS One 8(5):e63745. https://doi.org/10.1371/journal.pone.0063745

Khare SP, Sharma A, Deodhar KK, Gupta S (2011) Overexpression of histone variant H2A.1 and cellular transformation are related in *N*-nitrosodiethylamine-induced sequential hepatocarcinogenesis. Exp Biol Med 236:30–35

Lacroix B, Maddox AS (2012) Cytokinesis, ploidy and aneuploidy. J Pathol 226:338–351

Lanzotti DJ, Kaygun H, Yang X, Duronio RJ, Marzluff WF (2002) Developmental control of histone mRNA and dSLBP synthesis during *Drosophila embryogenesis* and the role of dSLBP

in histone mRNA 3′ end processing in vivo. Mol Cell Biol 22(7):2267–2282
Larsson LI, Bjerregaard B, Talts JF (2008) Cell fusions in mammals. Histochem Cell Biol 129:551–561
Leitch AR, Leitch IJ (2008) Genomic plasticity and the diversity of polyploid plants. Science 320:481–483
Lew DJ (2000) Cell-cycle checkpoints that ensure coordination between nuclear and cytoplasmic events in Saccharomyces cerevisiae. Curr Opin Genet Dev 10:47–53
Mahajan K, Fang B, Koomen JM, Mahajan NP (2012) H2B Tyr37 phosphorylation suppresses expression of replication-dependent core histone genes. Nat Struct Mol Biol 19:930–937
Marzluff WF, Gongidi P, Woods KR, Jin J, Maltais LJ (2002) The human and mouse replication-dependent histone genes. Genomics 80(5):487–498
Marzluff WF, Wagner EJ, Duronio RJ (2008) Metabolism and regulation of canonical histone mRNAs: life without a poly(A) tail. Nat Rev Genet 9:843–854
Maya Miles D, Peñate Salas X, Sanmartín Olmo T, Jourquin F, de la Cruz Muñoz Centeno M, Mendoza M, Simon MN, Chávez S, Géli V (2018) High levels of histones promote whole-genome-duplications and trigger a Swe1WEE1 dependent phosphorylation of Cdc28CDK1. Elife 7:e35337
Maya D, Morillo-Huesca M, Delgado L, Chavez S, Munoz-Centeno MC (2013) A histone cycle. In: Stuart D (ed) The mechanisms of DNA replication. InTech, Rijeka
Mei Q, Huang J, Chen W, Tang J, Xu C, Yu Q, Cheng Y, Ma L, Yu X, Li S (2017) Regulation of DNA replication-coupled histone gene expression. Oncotarget 8(55):95005–95022
Melters DP, Nye J, Zhao H, Dalal Y (2015) Chromatin dynamics in vivo: a game of musical chairs. Genes 6(3):751–776
Mendiratta S, Gatto A, Almouzni G (2019) Histone supply: multitiered regulation ensures chromatin dynamics throughout the cell cycle. J Cell Biol 218(1):39–54
Miettinen TP, Pessa HK, Caldez MJ, Fuhrer T, Diril MK, Sauer U, Kaldis P, Björklund M (2014) Identification of transcriptional and metabolic programs related to mammalian cell size. Curr Biol CB 24(6):598–608
Mullen TE, Marzluff WF (2008) Degradation of histone mRNA requires oligouridylation followed by decapping and simultaneous degradation of the mRNA both 5′ to 3′ and 3′ to 5′. Genes Dev 22(1):50–65
Murillo-Pineda M, Cabello-Lobato MJ, Clemente-Ruiz M, Monje-Casas F, Prado F (2014) Defective histone supply causes condensin-dependent chromatin alterations, SAC activation and chromosome decatenation impairment. Nucleic Acids Res 42:12469–12482
Orr-Weaver TL (2015) When bigger is better: the role of polyploidy in organogenesis. Trends Genet 31:307–315
Otto SP (2007) The evolutionary consequences of polyploidy. Cell 131:452–462
Otto SP, Whitton J (2000) Polyploid incidence and evolution. Annu Rev Genet 34:401–437
Ovrebo JI, Edgar BA (2018) Polyploidy in tissue homeostasis and regeneration. Development 145(14):dev156034
Palou R, Palou G, Quintana DG (2017) A role for the spindle assembly checkpoint in the DNA damage response. Curr Genet 63:275
Pandit SK, Westendorp B, de Bruin A (2013) Physiological significance of polyploidization in mammalian cells. Trends Cell Biol 23:556–566
Prado F, Maya D (2017) Regulation of replication fork advance and stability by nucleosome assembly. Genes 8(2):49
Quénet D (2018) Histone variants and disease. Int Rev Cell Mol Biol 335:1–39
Ramsey J, Schemske DW (1998) Pathways, mechanisms and rates of polyploid formation in flowering plants. Annu Rev Ecol Syst 29:467–501
Rattray AM, Müller B (2012) The control of histone gene expression. Biochem Soc Trans 40(4):880–885. https://doi.org/10.1042/BST20120065
Reverón-Gómez N, González-Aguilera C, Stewart-Morgan KR, Petryk N, Flury V, Graziano S, Johansen JV, Jakobsen JS, Alabert C, Groth A (2018) Accurate recycling of parental histones reproduces the histone modification landscape during DNA replication. Mol Cell 72(2):239.e5–249.e5
Riedmann C, Ma Y, Melikishvili M, Godfrey SG, Zhang Z, Chen KC, Rouchka EC, Fondufe-Mittendorf YN (2015) Inorganic Arsenic-induced cellular transformation is coupled with genome wide changes in chromatin structure, transcriptome and splicing patterns. BMC Genom 16(1):212
Salzler HR, Davidson JM, Montgomery ND, Duronio RJ (2009) Loss of the histone pre-mRNA processing factor stem-loop binding protein in *Drosophila* causes genomic instability and impaired cellular proliferation. PLoS One 4:e8168
Santaguida S, Amon A (2015) Short- and long-term effects of chromosome mis-segregation and aneuploidy. Nat Rev Mol Cell Biol 16:473–485
Santos GC, Zielenska M, Prasad M, Squire JA (2007) Chromosome 6p amplification and cancer progression. J Clin Pathol 60:1–7
Schoenfelder KP, Fox DT (2015) The expanding implications of polyploidy. J Cell Biol 209:485–491
Scholes DR, Paige KN (2015) Plasticity in ploidy: a generalized response to stress. Trends Plant Sci 20(3):165–175
Sharma S, Zeng JY, Zhuang CM, Zhou YQ, Yao HP, Hu X, Zhang R, Wang MH (2013) Small-molecule inhibitor BMS-777607 induces breast cancer cell polyploidy with increased resistance to cytotoxic chemotherapy agents. Mol Cancer Ther 12(5):725–736
Shi Q, King RW (2005) Chromosome nondisjunction yields tetraploid rather than aneuploid cells in human cell lines. Nature 437:1038–1042
Skene PJ, Henikoff S (2013) Histone variants in pluripotency and disease. Development 140(12):2513–2524
Sullivan E, Santiago C, Parker ED, Dominski Z, Yang X, Lanzotti DJ, Ingledue TC, Marzluff WF, Duronio RJ (2001) *Drosophila* stem loop binding protein coordinates accumulation of mature histone mRNA with cell cycle progression. Genes Dev 15(2):173–187
Takayama Y, Mamnun YM, Trickey M, Dhut S, Masuda F, Yamano H, Toda T, Saitoh S (2010) Hsk1- and SCF(Pof3)-dependent proteolysis of S. pombe Ams2 ensures histone homeostasis and centromere function. Dev Cell 18:385–396
Talbert PB, Henikoff S (2014) Environmental responses mediated by histone variants. Trends Cell Biol 24(11):642–650
Talbert PB, Henikoff S (2017) Histone variants on the move: substrates for chromatin dynamics. Nat Rev Mol Cell Biol 18(2):115–126
Talbert PB, Ahmad K, Almouzni G, Ausió J, Berger F, Bhalla PL, Bonner WM, Cande WZ, Chadwick BP, Chan SW, Cross GA, Cui L, Dimitrov SI, Doenecke D, Eirin-López JM, Gorovsky MA, Hake SB, Hamkalo BA, Holec S, Jacobsen SE, Kamieniarz K, Khochbin S, Ladurner AG, Landsman D, Latham JA, Loppin B, Malik HS, Marzluff WF, Pehrson JR, Postberg J, Schneider R, Singh MB, Smith MM, Thompson E, Torres-Padilla ME, Tremethick DJ, Turner BM, Waterborg JH, Wollmann H, Yelagandula R, Zhu B, Henikoff S (2012) A unified phylogeny-based nomenclature for histone variants. Epigenetics Chromatin 21(5):7
Tomonaga T, Matsushita K, Yamaguchi S, Oohashi T, Shimada H, Ochiai T, Yoda K, Nomura F (2003) Overexpression and mistargeting of centromere protein-A in human primary colorectal cancer. Cancer Res. 63(13):3511–3516
Van de Peer Y, Mizrachi E, Marchal K (2017) The evolutionary significance of polyploidy. Nat Rev Genet 18:411–424

Wang T, Chuffart F, Bourova-Flin E, Wang J, Mi J, Rousseaux S, Khochbin S (2018) Histone variants: critical determinants in tumour heterogeneity. Front Med. https://doi.org/10.1007/s11684-018-0667-3

Wertheim B, Beukeboom LW, van de Zande L (2013) Polyploidy in animals: effects of gene expression on sex determination, evolution and ecology. Cytogenet Genome Res 140:256–269

Yant L, Bomblies K (2015) Genome management and mismanagement—cell-level opportunities and challenges of whole-genome duplication. Genes Dev 29(23):2405–2419

Zack TL, Schumacher SE, Carter SL, Cherniack AD, Saksena G, Tabak B, Lawrence MS, Zhsng CZ, Wala J, Mermel CH, Sougnez C, Gabriel SB, Hernandez B, Shen H, Laird PW, Getz G, Meyerson M, Beroukhim R (2013) Pan-cancer patterns of somatic copy number alteration. Nat Genet 45:1134–1140