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

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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 macro-evolutionary events associated to 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.

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 et al., 1998). These polyploid species commonly arise from unreduced gametes by nondisjunction of chromosomes in the germ line. Polyploidy is very likely to modify plant morphology, phenology, physiology and/or ecology, and thus generate individuals that can flourish in novel habitats and fluctuating environments, or outcompete progenitor species (Leitch et al., 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 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., 2008). 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 9,692 prospectively sequenced advanced cancer patients and predicted for increased morbidity across many different cancer types (Bielski et al., 2018).

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 (Figure 1).

Cell fusion is the only process leading to polyploidy that does not require a previous cell cycle defect. By this mechanism, membrane merge and cytoplasm mix 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 homeostasis (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 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 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 mammals 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 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 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 et al., 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 to the development of certain diseases like cancer (Henikoff and Smith, 2015; Quenet, 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 (Clement 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; Mendirata et al., 2018; Talbert and Henikoff, 2016).

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, 2014). 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 (Øvrebø and Edgar, 2018). Yeast cells exposed to certain type of stresses, like 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; Harari et al., 2018b).

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, that triggers WGDs and can also provide a growth advantage to cells with a higher DNA content (Maya 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 (figure 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 one previously proposed for histone H3 and the centromeric isoform CENP-A (Au et al 2008; Castillo et al., 2007). 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 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, like 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 (Mendirata et al., 2018) 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, posttranscriptional and posttranslational levels and recent work highlights that their location could also be important to boost the efficiency of histone mRNA biosynthesis (Mendirrata et al., 2018; 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 10 and 3 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 is actively taking place. Canonical histone mRNAs are rapidly degraded at the end of 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 posttranslational 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 (Dürbaum and Storchova, 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 that tend to experience undesired WGDs and/or become aneuploid. The second, demonstrating 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 histone 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 (Salzer 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 that induces aberrant polyadenylation of canonical histone H3.1 mRNA that accumulates beyond S-phase (Brocato et al., 2014). Brocato et al. 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 (Brocato et al., 2015). 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 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 of 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 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) rises 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*) and promote the phosphorylation and inhibition of Cdc28, the only Cyclin-Dependent Kinase present in *S. cerevisiae*. This inhibitory mark which is able to delay the G2/M transition is maintained for a longer period of time 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) (Maya 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 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 homeostasis 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.

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Figures and Figure Legends

Figure 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.

Figure 2. High levels of histone levels 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.

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