Asymmetric Segregation of Aged Spindle Pole Bodies During Cell Division: Mechanisms and Relevance Beyond Budding Yeast?

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Asymmetric cell division generates cell diversity and contributes to cellular aging and rejuvenation. Here, we review the molecular mechanisms enabling budding yeast to recognize spindle pole bodies (SPB, centrosome equivalent) based on their age, and guide their non-random mitotic segregation: SPB inheritance requires the distinction of old from new SPBs and is regulated by the SPB-inheritance network (SPIN) and the mitotic exit network (MEN). The SPIN marks the pre-existing SPB as old and the MEN recognizes these marks translating them into spindle orientation. We next revisit other molecules and structures that partition depending on their age rather than their abundance at mitosis as, for example, DNA, centrosomes, mitochondria, and histones in yeast and other systems. The recurrence of this differential behavior suggests a functional significance for numerous cell types, which we then discuss. We conclude that non-random segregation may facilitate asymmetric cell fate determination and thereby indirectly aging and rejuvenation. Also see the video abstract here: https://youtu.be/1sQ4rAomnWY.

1. Introduction

Both uni- and multicellular organisms display a broad diversity in cellular features and fates. For multicellular organisms, this diversity is generated through cell-cell communication (non-cell autonomous events) and through specialized cells dividing asymmetrically into daughters with distinct potentials (cell autonomous events). During these divisions, cell-fate determinants comprising differentiation and aging factors partition asymmetrically between the two daughters. These determinants include transcription factors, messenger RNAs, extra chromosomal DNA circles and protein-aggregates and have been extensively studied and reviewed.[1–5] Here, we focus on ubiquitous molecules and structures partitioning asymmetrically not according to mass but to their age (Figure 1). For example, while cells segregate chromosomes symmetrically between daughter cells during mitosis, some co-segregate their oldest DNA strands specifically to one of the two distinct daughter cells, whereas the chromatids made of younger DNA partition to the other daughter.[6–10] Age-dependent segregation is also observed for other structures like histones,[11,12] mitochondria,[13] and centrosomes.[14–19] However, it is not evident how pre-existing material is different from recently synthesized one and how cells differentiate between them is largely unclear except for recent advances in the case of yeast spindle pole bodies.

Also, little is known about the biological relevance underlying the process of age-dependent inheritance. It is speculated that it contributes to cellular self-renewal, differentiation, and aging. Aging is broadly defined as a time-dependent functional decline that increases the likelihood of cellular mortality.[20] In contrast to the age of molecules, we refer here to this process as physiological aging. Interestingly, it is quite unclear how molecular and physiological aging are related to each other and how time affects the stability or function of individual molecular entities thereby potentially globally affecting cellular fitness. Thus, we review here the nature of the molecules and structures that are partitioned as a function of their age during mitosis, the mechanisms guiding this asymmetry, and their possible physiological roles during differentiation and aging.

2. The Intriguing Case of Yeast SPBs Reveals How They Differentiate With Age

In most cells, each pole of the mitotic spindle is structured by microtubule-organisation centres (MTOCs) that are semi-conservatively duplicated.[21,22] For example, MTOCs of metazoans, called centrosomes, form a mother centrosome containing their oldest centriole and a daughter centrosome made of younger centrioles. MTOCs provide a striking instance of age-dependent segregation. Different stem cells in the fruit fly and the mouse have been shown to segregate their centrosomes...
Figure 1. Difference between asymmetric and age-dependent cell division. A cell producing two different daughter cells by (a) asymmetrically dividing cell fate determinants, like ageing factors, to only one of the two progenies and (b) partitioning otherwise ubiquitous molecules and structures, like DNA, according to their age.

Stereotypically between the renewing stem cell and the differentiating daughter cell, budding yeast cells also segregate their MTOCs, called spindle pole bodies (SPBs), non-randomly. Some parts of the SPB duplicate conservatively such that each mitotic cell contains a pre-existing SPB inherited from the previous mitosis and a newly assembled SPB. During mitosis, the older SPB partitions into the bud and the new one remains in the mother cell. The mechanisms of SPB inheritance provided some surprises. Original studies established that one of the two SPBs, the old one, nucleates more and longer astral microtubules than the other. These longer microtubules interact with the bud cortex and orient the corresponding SPB toward the future daughter cell. A recurring hypothesis was that SPB maturation caused the old SPB to nucleate more microtubules because the young SPB is too immature to provide a binding platform for dynein or microtubules. However, detailed analyses of SPBs composition and activity indicate that they assemble rapidly early in the cell cycle. Very shortly after mitotic entry and SPB separation, the SPB outer-plaque, from which the astral microtubules emanate, is indistinguishable between pre-existing and new SPBs. Furthermore, both SPBs show a similar ability to form long astral microtubules: irrespective of which SPB faces the bud, this SPB always nucleates longer astral microtubules than the other. How the cortex stimulates microtubule nucleation on the SPB is unclear. However, it likely involves the phosphorylation of an evolutionarily conserved residue, Y362, of γ-tubulin. Thus, the microtubule organization capacity of SPBs is not intrinsically determined by their age and maturation but rather by regulatory cues provided by the cell cortex.

This process of microtubule formation does not explain how cells reliably orient the old SPB toward the bud. Inactivation of the spindle-positioning protein Kar9 is one perturbation that efficiently randomizes SPB segregation. During metaphase, Kar9 localizes to the tip of the astral microtubules emanating from the old SPB. There, it recruits the type V myosin Myo2 promoting microtubule movement along actin cables toward the bud. This process drives the segregation of the old SPB into the bud. Remarkably, dissociation of Myo2 from Kar9 randomizes SPB orientation. Yet, in these cells Kar9 remains associated with the old SPB unlike microtubules, which accumulate on the bud-proximal SPB irrespective of its age. Thus, the SPB controls Kar9 localization in an age-dependent manner explaining why the old SPB orients toward the bud and, consequently, forms longer microtubules. These data support the model that SPBs direct their own inheritance by controlling Kar9 distribution.

How does this work? Restriction of Kar9 to the pre-existing SPB in metaphase depends on the mitotic exit network (MEN), a kinase cascade that also drives mitotic exit in telophase and is related to the Hippo pathway in metazoans. The establishment of Kar9 asymmetry involves the MEN kinases Cdc15 and Dbf2/20 and their regulatory GTPase Tem1, but not the downstream phosphatase Cdc14, which acts specifically in mitotic exit. Dbf2/20 phosphorylate Kar9 promoting its accumulation to only the aster of the old SPB. Interestingly, MEN also promotes the age-dependent selection of SPBs during sporulation. Thus, SPB inheritance requires that the cell distinguishes old from new SPBs, a process that we term SPB specification, and is regulated by the MEN.

2.1. SPB Specification is Mother’s Business: SPB Inheritance Network (SPIN) Guides Age-Dependent Segregation of SPBs at Mitosis

An additional signaling network, the SPB Inheritance Network (SPIN), controls SPB specification (Figure 2). Its most upstream player, the Swe1 kinase (Wee1 in other eukaryotes), phosphorylates the SPB outer-plaque protein Nud1 (centrinol in mammals) on the pre-existing SPB during the G1-phase of the cell cycle. Subsequent inactivation of Swe1 protects the newly assembling SPB from being marked. Thus, the relative timing of Swe1 inactivation and SPB assembly ensures that only the pre-existing SPB carries the phosphorylation mark. The specification of the pre-existing SPB does not depend on Swe1 thereafter, but on downstream SPIN components, the acetyltransferase Nua4 and the kinase Kin3. These enzymes may recognize the marks deposited by Swe1 and further modify Nud1 as well as other SPB components, such as the receptor of the γ-tubulin complex on the outer-plaque of the SPB, Spc72. Importantly, preventing SPB...
modification either by inactivating SPIN or by mutating its target sites on the SPB randomizes SPB inheritance, indicating that SPIN is essential for specifying SPB identity.

The mark deposited by SPIN on SPBs likely acts by instructing MEN function. Indeed, Nud1 is a key scaffold for MEN activation at SPBs. Furthermore, SPIN-dependent modification of the SPB enhances the localization of the MEN-regulator Bfa1-Bub2 to the old SPB. Bfa1 and Bub2 function as a bipartite GTPase activating protein (GAP) for Tem1 and therefore inhibit MEN. Thus, one option is that the recruitment of Bub2-Bfa1 to the old SPB restricts MEN signaling to the new SPB, displacing Kar9 from its aster. Indeed, equilibrating Bub2-Bfa1 levels between SPBs forces Swe1 to modify both SPBs and randomizes their inheritance. Furthermore, perturbing SPIN function showed no detectable effect on SPB maturation.\(^{24}\) Thus, the orientation of the old SPB to the bud is not a direct consequence of its maturation state, but the result of dedicated regulatory pathways, SPIN and MEN. The SPIN acts in marking the pre-existing SPB as old and the MEN in recognizing these marks and translating them into Kar9 localization.

### 3. Writing and Reading on SPBs Follow the Pattern of the Histone Code

As illustrated in **Figure 3**, the control of SPB inheritance in yeast is comparable to a coding/decoding process to “write,” “store,” and “pass on” information. The following steps characterize it: i) encoding of information as marks; ii) maintenance and possibly transport of these marks; and iii) decoding by the recipient, which interpret the information. Therefore, encoding has several advantages. First, encoding itself is an information extraction process that transposes selected features and events of the analogue world into digital marks. Second, these marks represent these features and events but are not these features or events themselves and persist independently of them.

**Figure 2.** The genetic network comprising the acetyltransferase NuA4 and the kinases Swe1 and Kin3 called the SPB inheritance network (SPIN). In G1, 1) Swe1 earmarks newly assembles SPBs as they enter their second division cycle and become young pre-existing SPBs. This key event relies on its timing: 2) Swe1 down-regulation prior to Nud1 incorporation into the new SPB ensures that Swe1 earmarks only pre-existing SPBs. 3) This earmark controls the Bfa1-Bub2 recruitment, which directs Kar9 towards the pre-existing SPB and hence its movement towards the bud. 4) The maintenance of SPB’s identity thereafter relies on NuA4 and Kin3 function. Thus, the SPIN distinguishes SPBs to reflect their history.
Therefore, their subsequent interpretation depends on the decoding entity and not anymore on the encoding one. Thus, they can be translated into effects that do not necessarily follow the original event by direct causality. Theoretically, a direct causal modality for the orientation of SPBs toward the bud could, for example, be if this process would directly depend on an intrinsic ability of the old SPB to produce microtubules. In the experimentally demonstrated case, the introduction of an encoding step interrupts this first order causality and generates a second order one: The system now has gained some “freedom” to choose how it interprets the encoded information. For example, if Tem1’s GAP were to bind preferentially the unlabeled form of Nud1, then the new SPB is predicted to orient toward the bud instead of the old. Further regulatory potential to the system is provided by the decision of whether or not to interpret the code. Interestingly, around 5% of wild type cells actually orient SPBs the other way around and this proportion declines to as low as 2% in response to stress.\cite{36} Thus, SPB inheritance is indeed a regulated process and the analogy to coding is conceptually useful.

The code analogy is extensively used to describe chromatin regulation. Here, the protein coat packing the genome is subjected to numerous post-translational modifications (PTMs) that regulate access to DNA. These modifications affect chromatin directly by structurally affecting its compaction or indirectly by forming marks. These marks subsequently recruit binding factors called readers, which modulate chromatin states. One key distinction is that in the first case the effects directly cause the modification event itself. For example, H4 acetylation on K16 controls by itself nucleosome-nucleosome interaction.\cite{37} In contrast, marks of the second category have no direct effect on their own and depend on downstream effectors/readers. These effects can be delayed until “readers” are expressed and depend on the nature of these readers. Thus, these marks frequently serve to encode and epigenetically memorize events up until memory is “recalled” and interpreted. Accordingly, numerous histone-PTMs synergistically or antagonistically regulate the recruitment of chromatin-associated proteins to indirectly control a dynamic switch between transcriptionally active or inactive chromatin states. Together, they form what is termed the “histone code.”\cite{38} Remarkably, the modification of SPBs by the SPIN resembles this code: 1 – it provides a memory to recall which of the two SPBs was already present in the G1 phase, 2 – the translation of this information into mitotic effects requires readers, here the Bfa1-Bub2 complex, and 3 – the modifications involved, phosphorylation and acetylation, are the same as for the histone code. Given the observation that the methyltransferase Hsl7 localizes to the SPB early in the cell cycle, it will be interesting to test whether protein methylation is involved as well. In summary, the SPIN encodes age onto SPBs to guide their age-dependent segregation at mitosis.

4. Centrosomes Segregate Age-Dependently in a Wide Range of Animal Cells

As mentioned, animal centrosomes also show patterns of non-random segregation.\cite{40} For instance, mouse neural stem cells (NSCs, or radial glia cells) retain the mother centrosome in their renewing stem daughter cell, in a Ninein-dependent manner.\cite{15} Likewise, in Drosophila male germline stem cells (mGSCs) the mother centrosome is the most active MTOC, anchors itself to the cell cortex in a microtubule-dependent manner and is retained in the renewing stem cell at mitosis.\cite{14} Thus, these stem cells segregate the older MTOC to the renewing stem daughter cell.

In contrast, the female GSCs of Drosophila stereotypically retain the daughter rather than the mother centrosome.\cite{16} Drosophila neuroblasts follow the same pattern. They enter interphase with disengaged centrioles of which the daughter...
centriole carries Centrobin (CNB). Upon phosphorylation by the Polo-like kinase, CNB recruits pericentriolar material (PCM) including CNN and γ-tubulin to organize microtubules. These microtubules anchor the daughter centriole to the apical-cortex of the neuroblast while the mother centriole remains mobile, orients toward the opposite end of the cell and segregates into the differentiating ganglion cell at mitosis. Interestingly, upon serum starvation, CNB localizes also with mother centrioles suggesting that the pattern of inheritance is flexible and can be adjusted to environmental changes. How the localization of CNB is specifically controlled and more generally how animal cells differentiate their centrosomes is still largely unclear. However, since mother and daughter centrosomes behave differently in distinct cell types, centrosome specification may not be a mere question of centriole maturation.

Remarkably, the SPIN components are conserved in metazoans. Their orthologues Wee1 (Swe1), Nek2 (Kin3), Tip60 (NuA4) are observed at centrosomes, whose functional relevance for the cell.

5.1. Cell Poles

In some cases, such as bacterial cell poles, the mechanism of segregation is structural. For example, the division of *E. coli* generates a new pole opposite to the pre-existing pole. Cells inheriting the pre-existing pole tend to slow down growth rate and show an increasing risk of death. Thus, the older pole might deteriorate with time and influence cellular fitness. Nevertheless, the age-difference of the poles could also facilitate the asymmetric accumulation of aging factors (e.g. DNA damage) in only one cell, which then leads to the observed reduction in fitness in only one daughter cell.

Interestingly, in Mycobacteria new growth occurs almost exclusively in those cells inheriting the older pole, generating a large heterogeneity of growth rates among the cells in the population. As most antibiotics target growing bacteria, this heterogeneity is thought to diversify the cells’ susceptibility to antibiotics and thus contribute to the persistence of this pathogen to antibiotic treatments, a strategy known as hedging. Thus, the poles’ age can significantly influence the division potential of bacteria. However, it is likely that the underlying mechanisms evolved differently between species, depending on the biological strategy of the organism. Nevertheless, labelling of the pre-existing material might identify the pre-existing bacterial pole.
5.3. Mitochondria

The deterioration of a structure with age can also drive its segregation as observed for mitochondria. Since mitochondria cannot form de novo, it is crucial that both daughter cells inherit mitochondria at mitosis. In some cells, the young or functional mitochondria partition to the stem-like daughter cell, whereas the differentiating daughter inherits the rest. This process is observed in human mammary stem-like cells and budding yeast, respectively. Interestingly, non-stem-like human mammary epithelial cells segregate mitochondria irrespective of age.

In some yeast strains, the function-dependent segregation of mitochondria contributes to the functional decline of the mother cell and is influenced by retrograde actin cable flow. The mitochondrial F-box protein (Mfb1) and the DSL1 tethering protein MMR1. At the moment, it is not clearly distinguished whether mitochondria are selected based on their function in the mother cell and then selectively segregated into the bud, whether their segregation is random and the bud-located mitochondria are rejuvenated or whether it is a combination of both possibilities. Indeed, such a rejuvenation of mitochondria may be, for example, a result of increased antioxidant activity in the daughter cell or bud-specific recycling of aged mitochondria.

In this context, it is interesting to mention that in some genetic backgrounds, such as BY, the respiratory function of mitochondria is not relevant for the aging process. Upon limited or absent glucose, the replicative life span of yeast cells is increased. At the same time, these cells shift to the mitochondrial respiratory metabolism. But, this shift is not causal for the extended division potential as rho yeast cells, which lack the mitochondrial genome and cannot respire, are long-lived during calorie restriction (CR).

While we start understanding how yeast cells sort their mitochondria, little is known about mammalian cells. It is tempting to speculate that mechanisms that control the segregation of dysfunctional mitochondria in budding yeast are conserved in other eukaryotes.

5.4. DNA Strands

There are several instances of asymmetrically dividing cell types segregating their chromosomes in a non-random fashion in both cultured cells and stem cell compartments in...
The biased segregation of DNA was proposed to protect stem cells from errors in the new DNA strands occurring during DNA duplication and is known as "immortal strand" hypothesis. Indeed, several stem-like cell types keep the chromatids with older templates during asymmetric cell division. Nevertheless, other types of stem cells appear to not segregate DNA strands in this orderly fashion. One explanation suggests that if the examined cells were not undergoing asymmetric self-renewal, non-random segregation might not be expected. Indeed, many stem cells are capable of undergoing symmetric and asymmetric divisions. Nevertheless, the immortal strand hypothesis generated a considerable debate because, for example, replication errors are not the only source of mutations in stem cells. The alternative silent sister hypothesis suggests that age-dependent DNA segregation helps to specify the daughters cell fate: two sister chromatids in metaphase chromosomes may carry distinct epigenetic marks at certain stem cell genes. Those epigenetic differences may direct non-random segregation of sister chromatids during mitosis and for some genes the differential epigenetic regulation of sister copies could control their differential expression following mitosis. In any case, as for now no molecular mechanism for the selective retention of immortal template strands in stem cells has been identified. Thus, it will be exciting to further understand the mechanisms of this process and how it relates to the fate of stem cells.

5.5. Histones

One case is reminiscent of MTOCs segregation. The Drosophila mGSCs segregate pre-existing histone 3 (H3) to the self-renewing mGSC, while newly synthesized H3 partitions to the differentiating daughter, also called gonialblast. Male flies that mis-segregate H3 show mGSC loss, germline tumors and hub enlargement phenotypes, indicating that H3 distribution may contribute to cell fate determination in this tissue by carrying epigenetic marks involved in stem cell maintenance. Furthermore, the distribution pattern of histone H2B resembles the H3-pattern after the first mGSC division. Similar to SPBs, the biased partition of H3 depends on the phosphorylation of pre-existing protein by the haspin kinase. However, it is unclear how haspin distinguishes old and new nucleosomes, and how H3 phosphorylation drives the orientation of the corresponding chromatids on the spindle. Additionally, it is not yet known how the majority of pre-existing H3 stays on or redistributes to the same chromatid upon replication. Interestingly, Wee1 and Tip60 post-translationally modify histones H2B and H3 respectively. Thus, it is tempting to speculate that Wee1 and Tip60 might influence nucleosome segregation during mGSC division. If these proteins also control centrosome specification, SPIN might affect nucleosome segregation through the orientation of the centrosome and chromatid on the spindle. Indeed, the orientation of pre-existing H3 toward the renewing stem cell suggests that the corresponding chromatids specifically attach to the mother centrosome. Therefore, age-dependent segregation of the centrosomes might affect cell fate determination through age-dependent segregation of histones.

6. Perspective: Is the Age of the Cell Influenced by the Age of Its Proteins?

In summary, the stepwise labeling of a given cellular component before the duplicative synthesis of a younger copy, as described for yeast SPBs, is a potent mechanism for distinguishing old from new copies and allows their age-dependent differentiation and partition.

An interesting question is whether the molecules’ age is linked to physiological aging in a direct or indirect manner. In the case E. coli, the aging of the cell pole may directly contribute to the functional decline of cellular fitness with time while this does not seem to be a universal feature of prokaryotes. For DNA, replication mistakes are predicted to accumulate in the new DNA while the pre-existing strand carries the original sequence. Indeed, in those cells that segregate their DNA according to its age, the old and “error-free” chromosome is inherited by the long-lived stem cell, indicating also that old DNA does not directly cause physiological aging of the cell receiving it. Furthermore, the alternative silent sister hypothesis proposes that age-dependent DNA segregation helps to specify the daughters cell fate via differential modification of chosen genes to differentially regulate their expression in the next mitosis. Thus, it might be the marks on the DNA that influence asymmetric cell division rather than the age of the DNA. The cases of age-dependent MTOC segregation are not consistent with molecular aging being reproducibly linked to physiological aging. The differentiating sister indeed receives the older MTOC during the division of Drosophila female GSC and neuroblast. Nevertheless, in budding yeast, neocortex radial glia progenitor cells and Drosophila mGSCs the pre-existing MTOC is segregated to the stem-like cell suggesting that the old MTOC is not becoming dysfunctional with age and does not directly induce aging. It might rather show a different signaling activity, possibly promoting the differential segregation of other factors, as discussed above. The case is similar for the age-dependent segregation of histones in mGSCs. LARPs are age-dependently retained in the mother yeast cell and some were shown to contribute to its declining division potential. Nevertheless, it is challenging to distinguish whether their asymmetric distribution or their age-difference is causal for aging. If we assume that aged mitochondria are less functional, only in this case a direct relationship between the age of the organelle and that of the cell seems so far relatively evident. In summary, the potential impact of aged structures on cellular aging is likely and mostly indirect.

7. Conclusions and Outlook

Taken together, the considerations raised in this review suggest that the age of molecules is not a direct cause of physiological aging. The duplication of DNA, histones, MTOCs, and cell poles creates a difference in age of the co-existing copies as by-product of this process and it seems that some asymmetrically dividing cells conveniently take advantage of this difference to subsequently amplify other asymmetries between daughter cells. The mechanisms by which yeast cells identify old and new SPBs and implement their distinctive segregation indicate that rather than
being the direct consequence of the actual age of the organelle, the fate of the SPBs is established by a dedicated sorting machinery that identifies and labels the old SPB. We suggest that the formation of such marks over time likely promotes the asymmetric distribution of differentiation and aging factors during cell division to ensure that one daughter cell renews itself and remains young while the other differentiates and undergoes aging. However, this remains a sheer hypothesis that will need testing. In budding yeast, the progressive accumulation of aging factors in the mother cells causes its functional decline, while the daughter cell is born rejuvenated, enabling it to live a full lifespan. Whether the non-random partition of SPBs contributes to the asymmetric segregation of aging factors is an attractive idea that will be interesting to test, now that we can surgically interfere with this process. Importantly, if it were to be the case, similar processes would then be predicted to contribute to the aging process of stem cells. Thus, in most cases, aging seems to be more than just the deterioration of aging molecules and cellular components, but a highly controlled process that we are just starting to better understand. Budding yeast stands here again as a powerful system for dissecting the molecular mechanisms involved and testing our models and assumptions.

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Conflict of Interest
The authors declare no conflict of interest.

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