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**Killing two birds with one stone:
how budding yeast Mps1 controls chromosome segregation and spindle
assembly checkpoint through phosphorylation of a single kinetochore protein**

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Keywords: mitosis; chromosome biorientation; spindle assembly checkpoint;

kinetochore; Mps1; Aurora B

Abstract

1
2 During mitosis, the identical sister chromatids of each chromosome must attach
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4 through their kinetochores to microtubules emanating from opposite spindle poles.
5

6
7 This process, referred to as chromosome biorientation, is essential for equal
8
9 partitioning of the genetic information to the two daughter cells. Defects in
10
11 chromosome biorientation can give rise to aneuploidy, a hallmark of cancer and
12
13 genetic diseases. A conserved surveillance mechanism called spindle assembly
14
15 checkpoint (SAC) prevents the onset of anaphase until biorientation is attained. Key
16
17 to chromosome biorientation is an error correction mechanism that, by disengaging
18
19 faulty kinetochore-microtubule connections, allows kinetochores to establish proper
20
21 bipolar attachments. Error correction relies on the Aurora B and Mps1 kinases that
22
23 also promote SAC signalling, raising the possibility that they are part of a single
24
25 sensory device responding to improper attachments and concomitantly controlling
26
27 both their disengagement and a temporary mitotic arrest.
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34 In budding yeast Aurora B and Mps1 promote error correction independently from
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36 one another, but while the substrates of Aurora B in this process are at least partially
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38 known, the mechanism underlying the involvement of Mps1 in the error correction
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40 pathway is unknown. Through the characterization of a novel *mps1* mutant and an
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42 unbiased genetic screen for extragenic suppressors, we recently gained evidence
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44 that a common mechanism based on Mps1-dependent phosphorylation of the
45
46 Knl1/Spc105 kinetochore scaffold and subsequent recruitment of the Bub1 kinase is
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48 critical for the function of Mps1 in chromosome biorientation as well as for SAC
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50 activation (Benzi et al., EMBO Rep. 2020 Apr 19:e50257. doi:
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56 10.15252/embr.202050257).
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Introduction

Chromosome segregation is a vulnerable, error-prone process that must be tightly regulated in time and space. Several requirements must be fulfilled in order for daughter cells to get an equal chromosome complement. First, chromosomes must be faithfully duplicated into identical sister chromatids through DNA replication. Second, sister chromatids must be glued together by sister chromatid cohesion, which allows cells to distinguish genetically identical from distinct chromosomes. Third, sister chromatids need to attach via their kinetochores to microtubules emanating from opposite spindle poles, a process referred to as chromosome biorientation (reviewed in Bloom and Yeh, 2010). If this fails, a surveillance mechanism called Spindle Assembly Checkpoint (SAC) temporarily halts cell cycle progression in metaphase to allow error correction. Conversely, when all chromosomes are bipolarly attached, SAC is satisfied and anaphase can shortly ensue.

SAC detects the lack of attachment between spindle microtubules and kinetochores (reviewed in Maresca and Salmon, 2010), which are large protein assemblies residing at the centromere of each chromosome (reviewed in Musacchio and Desai 2017). Unattached kinetochores generate an alert signal that ultimately leads to the formation of a Mitotic Checkpoint Complex (MCC), made by Bub3, Mad2, BubR1 (Mad3 in yeast) and Cdc20, that binds to and inhibits the E3 ubiquitin ligase Anaphase Promoting Complex bound to its activator Cdc20 (APC^{Cdc20}). In turn, stabilisation of APC^{Cdc20} targets, such as securin and cyclin B, prevents sister chromatid separation and mitotic exit, thereby imposing a reversible metaphase arrest that provides the time for correction of improper kinetochore-microtubule connections (reviewed in Musacchio, 2015 ; Sacristan and Kops, 2015).

1 The dual-specificity mitotic kinase Mps1 (Monopolar spinde 1) is a key player in SAC
2 signaling. Mps1 was first identified in budding yeast (Winey et al. 1991) due to its
3
4 involvement in the duplication of spindle pole bodies (SPBs), the functional
5
6 equivalents of centrosomes in animal cells.
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9 While the involvement of Mps1 in centrosome duplication in eukaryotic cells other
10
11 than yeast is controversial (Stucke et al. 2002; Fisk et al. 2003; Kwiatkowski et al.
12
13 2010), Mps1 is almost universally implicated in SAC activation (reviewed in Pachis
14
15 and Kops, 2018). Mps1 works at the apex of SAC signaling through phosphorylation
16
17 of the kinetochore protein Knl1/Spc105 on its N terminal MELT repeats, which in turn
18
19 is essential for the kinetochore recruitment of the Bub1-Bub3 complex (London et al.
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21 2012; Shepperd et al. 2012; Yamagishi et al. 2012; Primorac et al. 2013). Mps1 also
22
23 phosphorylates Bub1 and Mad1, allowing their interaction and kinetochore
24
25 recruitment of Mad2 that acts as a catalyzer for MCC assembly (Faesen et al., 2017;
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27 Ji et al., 2018; London and Biggins, 2014; Mora-Santos et al., 2016; Moyle et al.,
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29 2014).
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39 **Coupling chromosome biorientation with the Spindle Assembly Checkpoint**

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41 During the SAC induced-metaphase arrest, cells rectify the tensionless kinetochore-
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43 microtubule attachments with the aim of establishing chromosome biorientation. An
44
45 error correction mechanism involves the continuous detachment of improper
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47 attachments to provide kinetochores with further opportunities to capture
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49 microtubules (reviewed in Lampson and Grishchuk, 2017). When tension across
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51 kinetochores is finally established, bipolar attachments are stabilized and
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53 chromosomes congress to the cell's equator, due to the equilibrium between pulling
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55 and cohesive forces (by microtubules and sister chromatid cohesion, respectively).
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1 A key player in the error correction pathway is the Chromosomal Passenger Complex
2 (CPC). The CPC is composed of the Aurora B kinase, the inner centromere protein
3 INCENP, Survivin and Borealin (Ipl1, Sli15, Bir1 and Nbl1, respectively, in budding
4 yeast) (reviewed in Carmena et al., 2012). Aurora B detaches improper kinetochore-
5 microtubule connections by progressively phosphorylating Ndc80/Hec1, the subunit
6 of the NDC80 complex that directly interacts with microtubules (Cheeseman et al.
7 2006; DeLuca et al. 2006; Ciferri et al. 2008; Alushin et al. 2010; Tooley et al. 2011;
8 Zaytsev et al. 2014, 2015). Moreover, Aurora B/Ipl1 phosphorylates the DAM1
9 complex in budding yeast and its functional homolog SKA complex in mammalian
10 cells (Chan et al., 2012; Cheeseman et al., 2002; Kalantzaki et al., 2015; Lampert et
11 al., 2010; Tien et al., 2010), which couples chromosome movement to microtubule
12 depolymerization (Abad et al., 2014; Asbury et al., 2006; Grishchuk et al., 2008;
13 Lampert et al., 2010; Schmidt et al., 2012; Tien et al., 2010; Welburn et al., 2009;
14 Westermann et al., 2006).

15 Besides correcting improper kinetochore-microtubule connections, Aurora B is also
16 part of SAC signaling (reviewed in Krenn and Musacchio, 2015). On one side, it
17 generates unattached kinetochores that are sensed by SAC (Pinsky et al. 2006). On
18 the other, it facilitates the rapid recruitment of Mps1 to kinetochores (Santaguida et
19 al., 2011; Saurin et al., 2011) and phosphorylates the RVSF motif in KNL1 (Liu et al.
20 2010). The latter hampers the binding of the PP1 phosphatase, which is required for
21 SAC silencing (Liu et al., 2010; Pinsky et al., 2006; Rosenberg et al., 2011;
22 Vanoosthuyse and Hardwick, 2009). Thus, Aurora B contributes to chromosome
23 biorientation by both promoting error correction and sustaining SAC signaling.
24 Similarly, The Mps1 kinase has been involved in the correction of faulty kinetochore-
25 microtubule attachments, in addition to triggering SAC activity (Jones et al., 2005;
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Maure et al., 2007; Santaguida et al., 2010; Hewitt et al., 2010; Maciejowski et al.,
2010). However, its role in the error correction pathway is far from being understood.
While in mammalian cells Mps1 seems to work in concert with Aurora B (Vigneron et
al. 2004; Jelluma et al. 2008; Saurin et al. 2011; Santaguida et al. 2011), in yeast the
two kinases appear to play independent roles (Maure et al. 2007; Storchová et al.
2011). In addition, while in mammalian cells the SKA complex has been proposed to
be a relevant Mps1 substrate in the error correction pathway (Maciejowski et al.,
2017), in the budding yeast *S. cerevisiae* the critical targets of Mps1 in this process
remain to be identified. Indeed, although *S.c.Mps1* phosphorylates Dam1 and Ndc80
on several residues, none of these phosphorylations is required for chromosome
biorientation (Shimogawa et al. 2006; Kemmler et al. 2009; Kalantzaki et al. 2015).
The identification of the critical targets of *S.c.Mps1* in chromosome biorientation is
not an easy task, and is complicated by the essential function of *S.c.Mps1* in SPB
duplication and spindle assembly (Weiss and Winey 1996). Indeed, the initial
discovery that Mps1 is involved in the error correction pathway was based on a
complex experimental set-up (Maure et al. 2007).

41 **A novel genetic tool to dissect the function of Mps1 in chromosome** 42 43 **biorientation**

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46 We have recently characterized a novel temperature-sensitive mutant, named *mps1-*
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48 *3*, that bears a single substitution of serine 635 to phenylalanine. The *mps1-3* mutant
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50 is lethal at temperatures above 32°C, and at temperatures ranging from 32°C to 34°C
51
52 is severely defective in chromosome biorientation but proficient in SPB duplication
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54 and spindle elongation (Benzi et al. 2020), unlike the majority of *mps1* mutants
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56 (Weiss and Winey 1996; Schutz and Winey 1998; Castillo et al. 2002; Araki et al.
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2010). Contextually, *mps1-3* cells are also SAC-deficient, which allows them to progress through the cell cycle in the face of chromosome misalignment, thus accumulating massive aneuploidy. We could attribute lack of chromosome biorientation in *mps1-3* cells to faulty correction of improper attachments, rather than to a failure to establish kinetochore-microtubule connections, in agreement with earlier conclusions on Mps1 inhibition through an analogue-sensitive mutant (Jones et al. 2005; Maure et al. 2007). Consistent with defects in the error correction pathway, in *mps1-3* cells sister chromatids co-segregate preferentially toward the bud (Benzi et al. 2020), where the old SPB usually migrates during anaphase (Pereira et al. 2001). This phenotype had been previously described for *ipl1* (Aurora B) mutants and is likely due to a delay in the gain of microtubule-nucleating activity of the new versus the old SPB, thereby biasing kinetochore attachment to the old, mature SPB (Tanaka et al. 2002).

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To our surprise, the *mps1-3* mutation, which hits the kinase domain of the protein (aa 440-720), increases the *in vitro* kinase activity of Mps1 relative to the wild type protein. However, the Mps1-3 does not localize at kinetochores at restrictive temperatures. Although Mps1 can sustain SAC signaling away from kinetochores under non-physiological conditions (Maciejowski et al., 2017; Fraschini et al., 2001; Yuan et al., 2017), its kinetochore recruitment clearly contributes to proficient chromosome biorientation and SAC signaling in normal cells (Jelluma et al. 2010; Saurin et al. 2011; Heinrich et al. 2012; Nijenhuis et al. 2013; Zhu et al. 2013; Aravamudhan et al. 2016). Thus, the SAC and chromosome segregation defects of *mps1-3* mutant cells likely stem from the lack of phosphorylation of critical Mps1 substrates at kinetochores. Consistently, phosphorylation of known Mps1 substrates at kinetochores, such as Spc105/Knl1, Bub1, and Mad1 (Shepperd et al. 2012;

1 Yamagishi et al. 2012; Primorac et al. 2013; London and Biggins 2014; Moyle et al.
2 2014; Mora-Santos et al. 2016; Faesen et al. 2017; Qian et al. 2017; Ji et al. 2018) is
3
4 markedly compromised in *mps1-3* mutant cells. Additionally, artificial anchoring of
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6 Mps1 to the kinetochore protein Mtw1 partially restores proper chromosome
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8 segregation in *mps1-3* cells (Benzi et al. 2020).
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11 The domain responsible for Mps1 kinetochore localization lies at the N-terminus of
12
13 the protein, far from the catalytic domain (Ji et al.; Liu et al. 2003; Stucke et al. 2004;
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15 Kemmler et al. 2009; Araki et al. 2010; Hached et al. 2011; Nijenhuis et al. 2013;
16
17 Hiruma et al. 2015; Maciejowski et al. 2017). Thus, it is unlikely that the *mps1-3*
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19 mutation interferes directly with Mps1 binding to its kinetochore receptor(s).
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23 Nonetheless, Mps1 has been proposed to accelerate its own kinetochore turnover
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25 through autophosphorylation (Sliedrecht et al. 2010; Kwiatkowski et al. 2010; Hewitt
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27 et al. 2010; Santaguida et al. 2010; Jelluma et al. 2010; Wang et al. 2014; Dou et al.
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29 2015; Koch et al. 2019; Hayward et al. 2019). Furthermore, activation of the Mps1
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31 kinase leads to extensive conformational changes in the protein (Combes et al.
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33 2018), which in turn could mask its kinetochore-binding regions. Thus, the increased
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35 kinase activity of Mps1-3 could reduce its retention time at kinetochores, thereby
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37 impairing SAC signaling and chromosome biorientation. We attempted to test directly
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39 this hypothesis by introducing into the *mps1-3* allele the analog-sensitive *mps1-as1*
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41 mutation, which inhibits the kinase in the presence of the ATP analog inhibitor 1-NM-
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43 PP1 (Jones et al. 2005). However, the double mutant turned out to be lethal even in
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45 the absence of the analog (our unpublished data), making this approach
46
47 inconclusive. The characterization of the internal suppressors that we identified (see
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49 below) might provide us with alternative tools to test the contribution of the
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51 hyperactivity of the Mps1-3 kinase in its own kinetochore turnover.
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2 **The Spc105/Knl1 kinetochore scaffold as a critical target of Mps1 in**
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4 **chromosome biorientation beyond SAC signaling**
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7 Out of the two processes that are affected by the *mps1-3* mutation, i.e. SAC signaling
8 and chromosome biorientation, only the latter is essential for cell viability and
9 accounts for the lethality of *mps1-3* cells at high temperatures. This makes the *mps1-*
10 *3* mutant a valuable genetic tool to underpin the molecular bases underlying the
11 involvement of Mps1 in the error correction pathway. We therefore exploited the
12 potential of budding yeast as a powerful genetic tool to identify spontaneous
13 suppressors that enable *mps1-3* cells to divide at 34°C. This unbiased genetic screen
14 was instrumental to our current model envisioning a common Mps1 substrate
15 (Spc105/Knl1, i.e. the stone) in the control of both chromosome biorientation and
16 SAC (i.e. the two birds).
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31 Through our genetic screen we isolated several intragenic suppressors that carried
32 second site mutations within the *mps1-3* allele. These were all missense mutations in
33 the catalytic kinase domain. Their future characterization might reveal important
34 insights into the control of Mps1 activity and kinetochore recruitment. We also
35 isolated extragenic suppressors that bore, instead, a suppressing mutation in genes
36 other than *MPS1*. Strikingly, all of them rescued both chromosome segregation and
37 SAC defects of *mps1-3* cells, suggesting that a common mechanism underlies the
38 role of Mps1 in these processes. Among these suppressors, we found mutations in
39 *SPC105*, which codes for the kinetochore protein Spc105/Knl1, and *GLC7*, which
40 codes for the catalytic subunit of the protein phosphatase PP1. Importantly, the
41 *spc105* suppressing mutations hit the motif (RVSF) for Spc105 binding to PP1, while
42 the *GLC7* suppressors carried a missense mutation of Phe256, which resides in the
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1 hydrophobic groove involved in PP1 interaction with partners carrying the RV/IXF
2 consensus motif (Wu and Tatchell 2001). As mentioned above, Mps1-dependent
3 phosphorylation of Spc105/Knl1 at its MELT repeats recruits the Bub3-Bub1 complex
4 and is critical for SAC signaling (London et al. 2012; Shepperd et al. 2012; Yamagishi
5 et al. 2012; Primorac et al. 2013). Upon chromosome biorientation, Spc105/Knl1
6 phosphorylation is reversed by the phosphatase PP1, which binds the RVSF motif
7 and silences the SAC (Pinsky et al. 2009; Vanoosthuysse and Hardwick 2009; Liu et
8 al. 2010; Rosenberg et al. 2011; Meadows et al. 2011; London et al. 2012; Moura et
9 al. 2017). Importantly, the *spc105* and *GLC7* suppressors that we isolated did not
10 restore Mps1 kinetochore localization, strongly suggesting that PP1 opposes Mps1
11 activity at kinetochores for both proper chromosome biorientation and SAC signaling.
12 The antagonism between Mps1 and PP1 has been well characterized for SAC, while
13 its involvement in the error correction pathway had not been established. Altogether,
14 our data have two important implications: first, the same Mps1-dependent sensory
15 device may be used for both correction of improper kinetochore-microtubule
16 attachments and SAC signaling, in line with previous proposals (Musacchio 2011;
17 Caldas et al. 2013); second, PP1 is expected to stabilize kinetochore-microtubule
18 attachments in yeast, as it does in human cells (Liu et al. 2010).

19 On the basis of our results, we wondered if Spc105 phosphorylation and subsequent
20 Bub1 recruitment could be the main function of Mps1 in the error correction pathway,
21 as it is in SAC activation. Consistent with this idea, Bub1 is no longer recruited to
22 kinetochores in *mps1-3* mutant cells, while it regains kinetochore binding in the
23 suppressors. Furthermore, artificial tethering of Bub1 to Spc105 is sufficient to
24 restore balanced chromosome segregation and partial SAC signaling in *mps1-3* cells
25 (Benzi et al. 2020). Thus, our data strongly imply that Mps1 promotes the error

1 correction pathway and SAC activity via a common mechanism that relies on
2 Spc105/Knl1 phosphorylation (Fig. 1). Along this line, phosphorylation of other Mps1
3
4 kinetochore targets, such as Dam1 and Ndc80, turned out to be dispensable for
5
6 equal chromosome segregation (Shimogawa et al. 2006; Kemmler et al. 2009;
7
8 Kalantzaki et al. 2015).
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11 The main conclusion of our paper is consistent with several published observations: a
12
13 *spc105-6A* yeast mutant with unphosphorylatable MELT repeats is defective in Bub1
14
15 kinetochore recruitment and displays chromosome missegregation (London et al.
16
17 2012); phospho-mimicking mutations in the MELT repeats of Spc7 (the fission yeast
18
19 homologue of Spc105/Knl1) partially suppress the chromosome biorientation defects
20
21 of fission yeast *mps1Δ* cells, though in fission yeast Mps1 only modestly contributes
22
23 to chromosome biorientation (Yamagishi et al. 2012). Finally, Knl1 depletion in
24
25 human cells impairs Aurora B activity and chromosome alignment on the metaphase
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27 plate (Caldas et al. 2013).
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36 **Is Bub1 kinetochore recruitment the only function of Mps1 in chromosome** 37 **biorientation?** 38 39

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41 Bub1 has been extensively involved in chromosome biorientation through
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43 phosphorylation of T120 of histone H2A (S121 in yeast), which in turn recruits
44
45 shugoshin proteins (Sgo1 in budding yeast) to pericentromeres (Fernius and
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47 Hardwick 2005; Kawashima et al. 2010; Yamagishi et al. 2010; Liu et al. 2015).
48
49 Shugoshins, in turn, promote recruitment of the CPC and biorientation of sister
50
51 chromatids (Indjeian et al. 2005; Kawashima et al. 2007; Huang et al. 2007; Kiburz et
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53 al. 2008; Tsukahara et al. 2010; Yamagishi et al. 2010; Verzijlbergen et al. 2014; Liu
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55 et al. 2015). Consistent with Bub1 being required for Sgo1 accumulation at
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1 pericentromeres, localization of Sgo1 at kinetochores is compromised in *mps1-3*
2 mutant cells. However, the synthetic lethality between the *mps1-3* mutation and
3
4 SGO1 deletion suggests that Mps1 could have at least one additional function in
5 chromosome biorientation, besides recruiting Bub1 to kinetochores. Indeed, Bub1
6
7 and Sgo1 are not essential proteins, in contrast to Mps1. Furthermore, artificial
8
9 tethering of Bub1 to Spc105 cannot fully rescue the chromosome biorientation
10
11 defects and temperature-sensitivity of *mps1-3* cells (Benzi et al. 2020), suggesting
12
13 that other Mps1 substrates and/or other factors binding to Spc105 might intervene.
14
15 One intriguing hypothesis, which would be supported by our genetic data, is that
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17 Mps1 could keep PP1 inhibited at kinetochores. PP1, in turn, stabilizes bipolar
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19 attachments (Liu et al. 2010).
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26 Another interesting candidate that might play a function complementary to Bub1 in
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28 chromosome biorientation, downstream of Mps1, is the microtubule rescue factor
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30 Stu1, which is a member of the CLASP family (Al-Bassam and Chang 2011). At
31
32 kinetochores, Stu1 stabilizes microtubules, and, consistently, it gets sequestered at
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34 unattached kinetochores to facilitate their own capturing (Funk et al. 2014). Stu1
35
36 sequestration at unattached kinetochores requires Mps1 and Spc105
37
38 phosphorylation of its MELT repeats, but not Bub1 (Kolenda et al. 2018), suggesting
39
40 that Stu1 and Bub1 might cooperate at Spc105 to achieve successful bipolar
41
42 attachment. Stu1 recruits Stu2, a microtubule-associated protein of the XMAP215
43
44 family, to polymerize kinetochore-microtubules (Vasileva et al. 2017). Remarkably,
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46 Stu2 has been recently proposed to mediate an error correction pathway
47
48 independent of Aurora B/Ipl1 in budding yeast (Miller et al. 2016, 2019). Whether and
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50 how Mps1 modulates Stu1 and/or Stu2 function at kinetochores to achieve
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1 chromosome biorientation is an important question that deserves future
2 investigations.

3
4 Another important question that remains open is whether an interplay between
5 S.c.Mps1 and the CPC in the error correction pathway can be completely ruled out.
6

7 As already mentioned, in budding yeast Mps1 and Ipl1 were proposed to operate
8 independently from one another (Maure et al. 2007; Storchová et al. 2011). Our data
9 are consistent with this view. First, phosphorylation of the known kinetochore
10 substrate of Ipl1/Aurora B Dam1 is not affected in *mps1-3* cells (Benzi et al. 2020).
11

12 Similarly, Mps1 inhibition does not perturb phosphorylation of Aurora B substrates in
13 human cells (Hewitt et al. 2010; Maciejowski et al. 2010; Santaguida et al. 2010).
14

15 Second, the temperature-sensitivity of *mps1-3* cells cannot be suppressed by either
16 the *NDC80-13D* phospho-mimicking mutant allele where all Mps1-dependent
17 phosphorylation sites of Ndc80 have been replaced by aspartate (Kemmler et al.
18 2009), or the *DAM1-S221F* allele (also known as *DAM1-765*, (Shimogawa et al.
19 2006), which was previously found to suppress the temperature-sensitivity of *ipl1-321*
20 mutant cells (Shimogawa et al. 2010; our unpublished data). Third, mutations in the
21 CPC subunit Sli15 that activate Ipl1/Aurora B and rescue the sickness of *bir1Δ*,
22 *bub1Δ* and *sgo1Δ* cells (Campbell and Desai 2013) do not suppress the lethality and
23 chromosome segregation defects of *mps1-3* cells at high temperature (Benzi et al.
24 2020). Thus, we favour the hypothesis that Mps1 sets in motion an error correction
25 mechanism that does not involve Aurora B/Ipl1. However, it remains possible that,
26 while differing in their respective upstream targets, the Mps1- and Ipl1-dependent
27 error correction pathways ultimately converge on shared downstream effectors to
28 destabilise flawed attachments. Future work will certainly shed light on this exciting
29 possibility.
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