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Dynein prevents erroneous kinetochore-microtubule attachments in mitosis

Marin Barisic[1,2,*] and Helder Maiato[1,2,3,*]

[1]Chromosome Instability & Dynamics Laboratory; Instituto de Biologia Molecular e Celular; Universidade do Porto; Porto, Portugal; [2]Instituto de Investigação e Inovação em Saúde – i3S; Universidade do Porto; Portugal; [3]Cell Division Unit; Department of Experimental Biology; Faculdade de Medicina; Universidade do Porto; Porto, Portugal

Equal distribution of the genetic material during cell division relies on efficient congression of chromosomes to the metaphase plate. Prior to their alignment, the Dynein motor recruited to kinetochores transports a fraction of laterally-attached chromosomes along microtubules toward the spindle poles. By doing that, Dynein not only contributes to chromosome movements, but also prevents premature stabilization of end-on kinetochore-microtubule attachments. This is achieved by 2 parallel mechanisms: 1) Dynein-mediated poleward movement of chromosomes counteracts opposite polar-ejection forces (PEFs) on chromosome arms by the microtubule plus-end-directed motors chromokinesins. Otherwise, they could stabilize erroneous syntelic kinetochore-microtubule attachments and lead to the random ejection of chromosomes away from the spindle poles; and 2) By transporting chromosomes to the spindle poles, Dynein brings the former to the zone of highest Aurora A kinase activity, further destabilizing kinetochore-microtubule attachments. Thus, Dynein plays an important role in keeping chromosome segregation error-free by preventing premature stabilization of kinetochore-microtubule attachments near the spindle poles.

Keywords: Aurora A, Dynein, error correction, kinetochore, spindle pole

*Correspondence to: Marin Barisic; Email: marin.barisic@ibmc.up.pt; Helder Maiato; Email: maiato@ibmc.up.pt

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Introduction

In order to maintain genome integrity chromosomes must be accurately distributed during mitosis. This is achieved after chromosome bi-orientation, in which sister kinetochores become attached to microtubules from opposite poles of the mitotic spindle and chromosomes align at the metaphase plate prior to sister chromatid separation in anaphase. Chromosome movement toward the spindle equator is initiated immediately after nuclear envelope breakdown (NEB) in prometaphase and is known as chromosome congression.[1,2] Chromosome movements during congression are driven by 2 main mechanisms: microtubule polymerization/depolymerization-based motion[3] and motor-dependent transport along microtubules.[4-6] The latter is mainly achieved through the coordinated activities of cytoplasmic Dynein, CENP-E and chromokinesins.[5]

Cytoplasmic Dynein (from here on referred as Dynein) is a large protein complex (1.6 MDa) consisting of several subunits: 2 heavy chains containing ATPase motor domains, 2 intermediate chains, 2 light intermediate chains and 3 different types of light chains.[7] Dynein interacts with many different proteins that regulate its activity and localization, enabling Dynein to perform its various cellular tasks.[8] Dynactin, another large multi-protein complex (1 MDa) is involved in most Dynein functions, both by targeting it to specific locations and by increasing its processivity.[9] Lis1, NudE and NudEL are important for Dynein function at kinetochores, nuclear and spindle positioning, as well as organelle and mRNA transport.[8] Bicaudal D also plays a role in Dynein-mediated organelle transport and, together with NudE and NudEL, targets Dynein to the nuclear envelope where it contributes to the separation of spindle poles in early mitosis.[10] The Rod, ZW10 and Zwilch (RZZ) complex and Spindly target

Dynein specifically to kinetochores, coupling its function to kinetochore-microtubule attachments and the spindle assembly checkpoint.[11] Thus, a number of different binding partners, together with a diverse distribution of specific subunits[12] and their phospho-regulation,[13] allow a single motor protein - Dynein - to be involved in numerous independent cellular functions, including chromosome congression.[14-16]

Another kinetochore-localized motor protein involved in chromosome movements is the kinesin-7 CENP-E. Although it localizes at the kinetochore fibrous corona,[17,18] just like Dynein,[19] CENP-E works in opposite direction, having the ability to move chromosomes toward the plus-ends of microtubules. By doing this, CENP-E directly supports the alignment of chromosomes to the metaphase plate.[20-23]

In an elegant, laser microsurgery-based study, it was shown that polar ejection forces (PEFs) on chromosome arms (also known as "polar winds") actively contribute to chromosome movement away from the pole.[24] Additional studies revealed that these forces are mainly generated by the microtubule plus-end-directed motor proteins chromokinesins.[25-32]

During the coordinated action of all these motor activities that mediate chromosome congression it is crucial to prevent and/or correct potential erroneous kinetochore-microtubule attachments. Syntelic attachments occur when both sister kinetochores become attached by microtubules originated from a single pole, while merotelic attachments arise when a single kinetochore becomes attached to both spindle poles. The best-studied error correction system is based on the action of the centromere-localized kinase Aurora B, which destabilizes kinetochore-microtubule attachments through phosphorylation of microtubule depolymerases (such as the kinesin-13 proteins MCAK and Kif2B)[33-35] and Ndc80, a protein required for the stabilization of end-on kinetochore-microtubule attachments.[36-38] Once chromosomes become bi-oriented and tension is applied between sister kinetochores, Ndc80 moves away from Aurora B, resulting in kinetochore-microtubule attachment stabilization.[39,40]

Here we elaborate on recent studies that demonstrated a role of Dynein,[5] chromokinesins[5,41] and Aurora A kinase[5,41,42] in the prevention and correction of erroneous kinetochore-microtubule attachments during chromosome congression.

Congression of Peripheral Chromosomes Depends on Motor Proteins

Chromosomes can congress to the metaphase plate either using polymerization/depolymerization of kinetochore microtubules or motor protein-mediated transport along microtubules. However, it remained unclear why some chromosomes prefer one pathway over the other. Chromosomes that depend on motor proteins first move to the spindle pole and only after initiate alignment to the spindle equator. This initial poleward movement depends on the microtubule minus-end-directed motor Dynein at unattached kinetochores,[14-16,43,44] whereas the subsequent motion toward the equator depends on the microtubule plus-end-directed motor proteins CENP-E at kinetochores[20] and chromokinesins on chromosome arms.[25,27,28] We sought to investigate whether the dependence on motor proteins for chromosome congression correlates with chromosome positioning at NEB. To address this, we generated a stable U2OS cell line expressing GFP-CENP-A and mCherry-α-tubulin, which allowed us to track kinetochore positions relative to the mitotic spindle using high-resolution live-cell imaging. Then we inhibited CENP-E, which resulted in Dynein-mediated accumulation of few chromosomes (~15%) near spindle poles. By backtracking these polar chromosomes to their original positions at NEB, we found that they initially occupied a peripheral region outside the interpolar spindle ellipsoid, and were always significantly closer to one of the poles.[5] In contrast, chromosomes that were already positioned in the interpolar region at NEB were easily accessible by microtubules from both spindle poles and became bi-oriented soon after NEB. Importantly, these chromosomes completed alignment in the absence of all 3 motor activities.[5] Thus, we concluded thatonly peripheral chromosomes that cannot bi-orient soon after NEB require motor proteins to congress.

Dynein Prevents Premature Kinetochore-Microtubule Attachments by Counteracting Polar Ejection Forces

Dynein-dependent poleward transport of peripheral chromosomes plays an important role in preventing premature and potentially erroneous stabilization of end-on kinetochore-microtubule attachments.[5] Dynein achieves this by counteracting PEFs generated mainly by the microtubule plus-end directed motor proteins chromokinesins.[25-32] Co-depletion of CENP-E and Dynein in live U2OS cells stably expressing H2B-GFP and mCherry-α-tubulin to simultaneously visualize chromosomes and microtubules, respectively, led to the ejection of polar chromosomes from spindle poles and stabilization of their kinetochore-microtubule attachments.[5] This was opposite from the behavior of chromosomes that remained locked at the poles and lacked stable end-on kinetochore-microtubule attachments in CENP-E inhibited cells, in which Dynein function was left intact.[5,45,46] Importantly, chromosome ejection and attachment stabilization in the absence of Dynein were both repressed after simultaneous depletion of the 2 human chromokinesins (Kid and Kif4A),[5] in line with a recently reported role of PEFs in the stabilization of syntelic attachments in *Drosophila* S2 cells.[47]

To dissect the functions of motor proteins at distinct chromosomal loci, as well as their respective contribution to chromosome movements, we used laser microsurgery to physically separate the chromosome arms from the kinetochore-containing chromosome body.[5] To specifically investigate polar chromosomes we inhibited CENP-E prior to laser microsurgery, which locked a group of chromosomes at the spindle poles. After laser microsurgery, acentric (i.e. without kinetochore) chromosomal fragments moved in random directions (not only toward the spindle equator, but also toward the cell

cortex) in a chromokinesin-dependent manner, while kinetochore-containing fragments remained stationary at the poles.[5] Thus, kinetochore-mediated forces are dominant over PEFs acting on the arms of polar chromosomes.

Previous electron microscopy studies have shown that polar chromosomes in CENP-E inhibited cells lacked stable end-on kinetochore-microtubule attachments.[45,46] As so, we reasoned that Dynein must accumulate on these unattached kinetochores and prevent chromokinesins to move chromosomes away from the spindle poles after CENP-E inhibition. To directly test this, we used high-resolution live-cell imaging of HeLa cells stably expressing GFP-labeled Dynein Heavy Chain (DHC).[48] While DHC-GFP was stripped off the kinetochores during chromosome congression in control cells, polar kinetochores from CENP-E-inhibited cells were highly enriched of DHC-GFP (**Fig. 1** and **Video S1**). Overall, these data leads to the conclusion that Dynein-mediated poleward force is dominant over chromokinesin-generated PEFs, thereby preventing premature and erroneous stabilization of kinetochore-microtubule attachments and random ejection of chromosomes from spindle poles.

Dynein Prevents Premature Kinetochore-Microtubule Attachments by Bringing Peripheral Chromosomes Closer to Aurora A Kinase at the Spindle Poles

To further examine the stability of kinetochore-microtubule attachments of polar chromosomes in CENP-E-inhibited cells lacking Dynein activity, we performed immunofluorescence analysis with antibodies against Mad1.[5] Mad1 is a spindle assembly checkpoint protein that is removed from kinetochores upon end-on attachment to microtubules, and therefore can be used as an attachment sensor. Contrary to CENP-E-inhibited cells in which Dynein activity remains present, kinetochores from chromosomes that were ejected from spindle poles in the absence of Dynein and CENP-E inhibition showed reduced Mad1 levels, confirming the premature stabilization of kinetochore-microtubule attachments. As expected, a similar effect was observed in CENP-E-inhibited cells after co-inhibition of Aurora B kinase, which we used as a positive control. Surprisingly, Mad1 levels were also reduced on polar chromosomes after inhibition of Aurora A kinase, indicating a role of Aurora A in the spatial regulation of kinetochore-microtubule attachments near the spindle poles. Indeed, Aurora A had been previously implicated in the stabilization of kinetochore-microtubule attachments,[49,50] which might be explained by the fact that Aurora A shares 70% identity of its catalytical domain with Aurora B[51] and that both kinases recognize almost identical consensus target motifs.[52] Thus, Aurora A and Aurora B might have overlapping functions in the correction of kinetochore-microtubule attachments that are spatially regulated by their different localization (Aurora A being placed at the centrosomes and Aurora B at the centromeres), which is defined by their different binding partners.[51] Additionally, Aurora A might play other important roles in chromosome congression by regulating proteins directly involved in this process.[53,54]

Two recent studies further confirmed our observation about the role of Aurora A in error correction near the poles in mitosis and also in meiosis I. Ye and colleagues[41] demonstrated the existence of an Aurora A activity gradient centered on the spindle poles in *Drosophila* S2 cells using a Fluorescence Resonance Energy Transfer sensor bound to microtubules that was

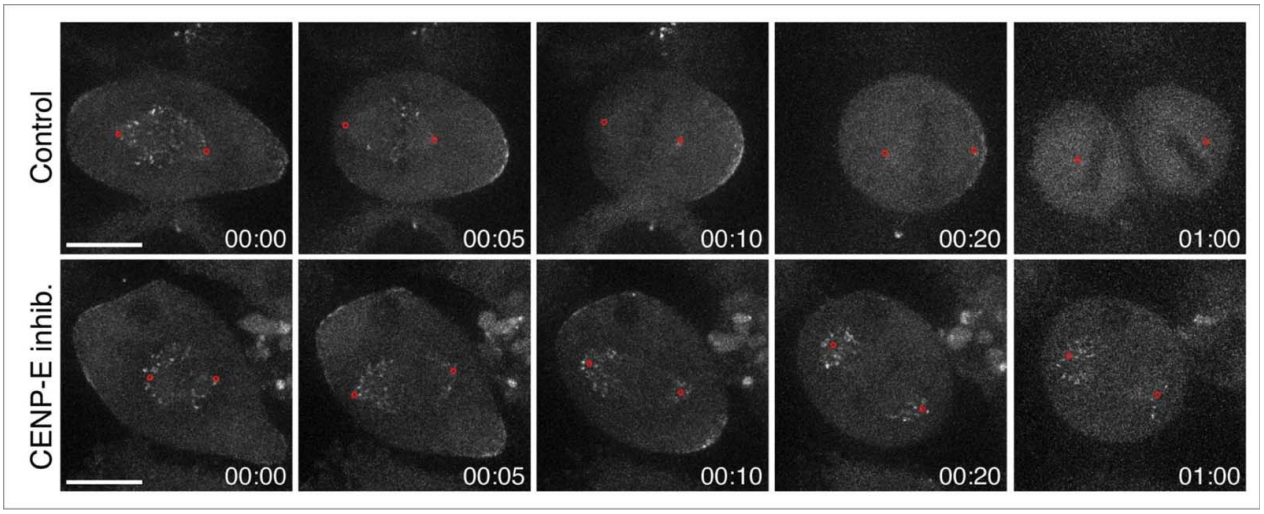

Figure 1. Dynein "locks" peripheral chromosomes at the spindle poles after CENP-E inhibition. High-resolution live-cell imaging (eleven 1μm-separated z-planes; 10 sec time interval) of HeLa cells stably expressing DHC-GFP (kind gift from Iain Cheeseman, Whitehead Institute, MIT, USA). Images were taken with an iXonEMC electron-multiplying CCD camera (Andor Technology), using a 100x 1.4 NA Plan-Apochromatic DIC objective on an inverted microscope (TE2000U; Nikon) equipped with a CSU-X1 spinning-disc confocal head (Yokogawa Corporation of America). Note that DHC-GFP is highly expressed at unattached kinetochores from polar chromosomes after CENP-E inhibition with 20 nM GSK92329 (MedChemexpress). Red circles indicate the position of the spindle poles. Scale bar: 10 μm. Time: hrs:mins

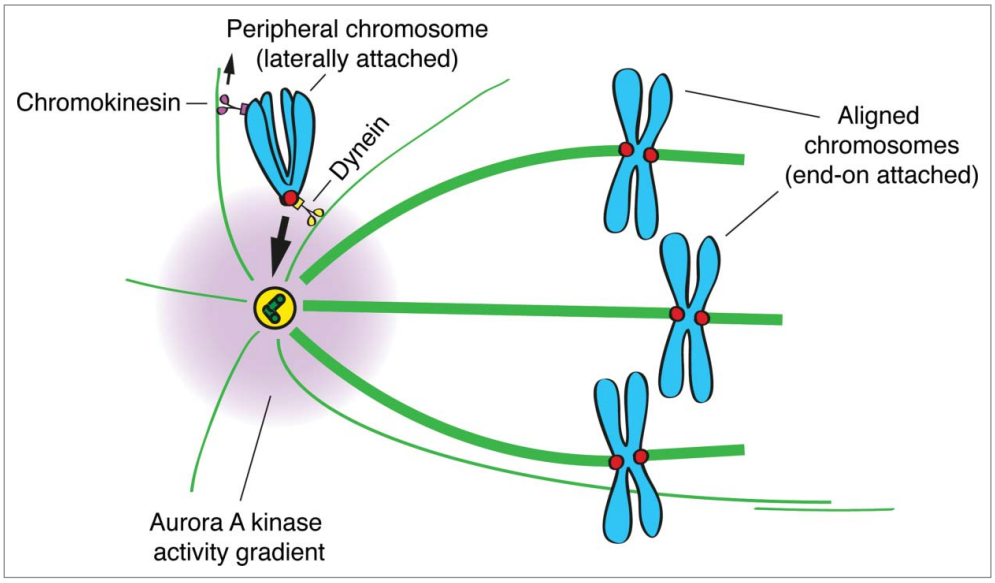

Figure 2. Dynein prevents premature stabilization of erroneous kinetochore-microtubule attachments by counteracting PEFs and by bringing chromosomes closer to Aurora A activity at the spindle poles. Illustrative model depicting the dominant role of Dynein in bringing peripheral chromosomes toward the center of an Aurora A activity gradient at the spindle poles, against chromokinesin-mediated PEFs.

sensitive to Aurora A phosphorylation. They also showed that Aurora A reduces the stability of kinetochore-microtubule attachments and that it counteracts the attachment stabilization effect of chromokinesin-generated PEFs. Finally, they confirmed the role of Aurora A in error correction also in human and PtK1 cells and defined Ser-55 of Ndc80 as an Aurora A-specific phosphorylation site at kinetochores, shedding light on the molecular mechanism of Aurora A-based error correction. Chmatal and colleagues[42] investigated the role of Aurora A in error correction using oocytes from mice generated by crossing a strain containing Robertsonian chromosomes (chromosomes created by fusion of 2 telocentric chromosomes at the centromeres) with a standard laboratory strain, containing all telocentric chromosomes. This resulted in oocytes containing trivalents, which were placed off the center of the spindle equator, toward one of the spindle poles. Kinetochore-microtubule attachments on chromosomes closer to the pole were always less stable than the attachments on chromosomes near the spindle equator, unless Aurora A kinase was inhibited, demonstrating its role in attachment destabilization near the spindle poles. Moreover, they used live-cell imaging to show that Mad1-GFP signal accumulated on kinetochores near the spindle pole, both in trivalents and syntelically-attached bivalents that became efficiently corrected as they approached the spindle pole. Altogether, these studies in 4 different systems[5,41,42] demonstrate that, in addition to a centromeric-based error correction mechanism mainly driven by Aurora B, an Aurora A-regulated error correction mechanism exists in the vicinity of the spindle poles to prevent the premature stabilization of end-on kinetochore microtubule attachments. This is likely to be important for subsequent CENP-E-mediated congression of polar chromosomes along pre-existing spindle microtubules.[20]

Fighting the "polar winds" to see the Aurora (A): an integrated model for how Dynein prevents incorrect kinetochore-microtubule attachments at the spindle poles

Here we propose an integrated mechanism for how Dynein prevents the premature stabilization of (erroneous) kinetochore-microtubule attachments near the spindle poles (**Fig. 2**). This is achieved by moving peripheral chromosomes toward one of the spindle poles before congression to the spindle equator. By transporting peripheral chromosomes to the vicinity of the spindle poles, Dynein counteracts the stabilizing effect of chromokinesin-mediated PEFs, while bringing these chromosomes to the zone of highest Aurora A activity, which further prevents stabilization of end-on kinetochore-microtubule attachments.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Supplemental Material

Supplemental data for this article can be accessed on the publisher's website.

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