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Leave no sister behind

Michael A. Hadders[1] and Susanne M.A. Lens[1,*]
[1]Oncode Institute, Center for Molecular Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
*Correspondence: s.m.a.lens@umcutrecht.nl
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Recent work published in *Cell Reports* and *Developmental Cell* from Sen et al., Orr et al., and Papini et al., demonstrates that midzone-based Aurora B resolves chromosome segregation errors during anaphase.

Chromosomal instability (CIN), defined as an elevated rate of chromosome mis-segregation events during mitosis, is a prominent feature of cancer cells. A frequently observed type of mis-segregation is a so-called lagging chromosome: a sister chromatid that lags behind the two main masses of sister chromatids segregating toward opposite spindle poles during anaphase (Thompson and Compton, 2008). Lagging chromosomes are at risk of getting damaged by the cytokinesis machinery or of forming a micronucleus (MN) in one of the daughter cells (Janssen et al., 2011, Zhang et al., 2015). The DNA in an MN is more prone to damage during the next cell cycle, which may result in further structural rearrangements, such as chromotrypsis (Zhang et al., 2015).

High-fidelity chromosome segregation requires that chromosomes bi-orient on the mitotic spindle. This means that a kinetochore (KT; the microtubule receptor on chromosomes) of one chromatid is connected to microtubules (MTs) originating from one spindle pole, while its sister is attached to MTs derived from the opposite spindle pole. Bi-orientation is promoted by ''error correction,'' the process wherein erroneous KT-MT interactions, such as syntelic (both sister chromatids attached by MTs originating from the same spindle pole) and merotelic (the KT of one of the sister chromatids is attached by MTs from opposite poles) attachments, are destabilized and replaced by ''correct,'' bi-oriented attachments that generate inter-sister KT tension. Aurora B kinase plays an essential role in this process. Aurora B phosphorylates KT proteins that interact with spindle MTs. This lowers the MT binding affinity of the KT, thereby creating a dynamic KT-MT interface that supports error correction (Godek et al., 2015). The prevailing idea is that erroneous KT-MT attachments are corrected before anaphase onset, when Aurora B is localized at centromeres and KTs. However, Orr et al. (2021) and Sen et al. (2021) now build a strong case for ongoing error correction during anaphase by spindle-midzone-localized Aurora B, which reduces the risk of MN formation.

Using high-resolution live-cell imaging of histone H2B-GFP in human cancer (U2OS) and non-cancer (hTERT-RPE1) cells, Orr et al. found that lagging chromosomes are frequently observed in early anaphase, but that less than 10% of these laggards ultimately form an MN. Sen et al. reached a similar conclusion about the transient nature of the majority of lagging chromosomes. They instead imaged the endogenously tagged KT protein HEC1/NDC80 in hTERT-RPE1 cells using lattice light-sheet microscopy. This allowed them to track individual kinetochores through mitosis with very high temporal resolution. Their data inspired the development of a novel metric named laziness, which describes a lagging chromosome on the basis of the distance of its kinetochore to the center of the cluster of kinetochores to which it belongs. Tracing of lazy kinetochore trajectories back in time allowed the authors to study in (pro)metaphase the KT features that correlate with laziness in anaphase.

It turns out that lazy kinetochores often displayed reduced inter-sister KT-KT distances in metaphase and that the vast majority were rapidly resolved in early anaphase. Interestingly, lazy KTs that persisted during anaphase frequently exhibited dampened metaphase oscillatory dynamics and more often had a stretched appearance in anaphase. Sen et al. attribute these altered metaphase features of lazy kinetochores to their merotelic attachment status, suggesting that a transient lazy KT is attached to a larger number of MTs from the correct pole than from the incorrect pole (unbalanced), while a persistent lazy KT is bound by a more equal number of MTs from the correct and incorrect spindle poles (balanced).

From both studies, it appears that merotelically attached kinetochores escape (pro)metaphase error correction more often than originally anticipated. Thus, a correcting mechanism that serves as a back-up in anaphase to resolve the consequent lagging chromosomes appears warranted. The prominent role of Aurora B in error correction prior to anaphase made this kinase a prime suspect to mediate anaphase error correction. When cells transit into anaphase, Aurora B relocates from centromeres and KTs to the spindle midzone, where it generates a phosphorylation gradient (Fuller et al., 2008). Inhibition of Aurora B kinase activity at anaphase onset increased the frequency of lazy KTs, lagging chromosomes, and MN formation. Importantly, knock-down or inhibition of MKLP2/KIF20A, which disrupts midzone localization of Aurora B, also increased the frequency of lagging chromosomes that formed MNs, indicating that it is the midzone-based Aurora B activity gradient that helps to resolve lagging chromosomes during anaphase (Orr et al., 2021; Sen et al., 2021).

How then does Aurora B mediate anaphase error correction? Interestingly, this is where the two studies reach different conclusions. Sen et al. observed that Aurora B inhibition increased the number of persistently stretched kinetochores. The lack of KT recoiling suggested that the merotelic KT-MT

attachments causing KT distortion are no longer resolved. The authors further showed that Aurora B phosphorylates the kinetochore protein KNL1 on lagging chromosomes in the midzone, at a site known to contribute to MT binding (Welburn et al., 2010). This led them to propose that midzone-based Aurora B facilitates destabilization of merotelic KT-MT attachments in a way akin to its role in error correction during (pro)metaphase. However, exactly how midzone-based Aurora B facilitates detachment of merotelic KT-MT interactions remains unclear, because HEC1/NDC80, the main MT binding protein in KTs, remains dephosphorylated on lagging chromosomes (Papini et al., 2021).

Orr et al. instead suggest that midzone-based Aurora B stabilizes KT-MT attachments, which they propose is necessary to transduce the spindle forces required for anaphase error correction (Cimini et al., 2004). In line with this suggestion, reducing spindle elongation by Eg5 inhibition increased the number of cells with laggards and MNs (Orr et al., 2021). A KT-MT stabilizing role for Aurora B during anaphase is further supported by work from Papini et al., (2021). Although this study did not directly address anaphase error correction, it provides evidence that Aurora B can indirectly support KT-MT attachment stability through phosphorylation of the kinetochore protein DSN1, which prevents kinetochore disassembly during anaphase.

Although at first glance it might seem contradictory that Aurora B can both stabilize and destabilize KT-MT attachments, these roles need not be mutually exclusive. If Aurora B substrates involved in sustaining KT stability require lower Aurora B activity for phosphorylation than substrates involved in KT-MT destabilization, chromosomes lagging in early anaphase, and close to center of the gradient, would have stable KTs, whereas the incorrect attachment site (the site closest to the midzone center) of the merotelic KT would become destabilized. This would result in movement of the kinetochore out of the Aurora B phosphorylation gradient. Subsequent lower levels of Aurora B activity would still be sufficient to sustain KT stability, thereby supporting spindle forces that facilitate segregation into the correct daughter cell. Further investigations, including high-resolution live-cell monitoring of KT-MT attachments on lagging chromosomes, should provide clues as to how this intriguing anaphase error-correction process precisely operates in human cells.

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