

# Better check late than never: The chromosome segregation checkpoint

(comment on DOI 10.1002/bies.201400140)

Vera L. Oliveira and Floris Foijer\*

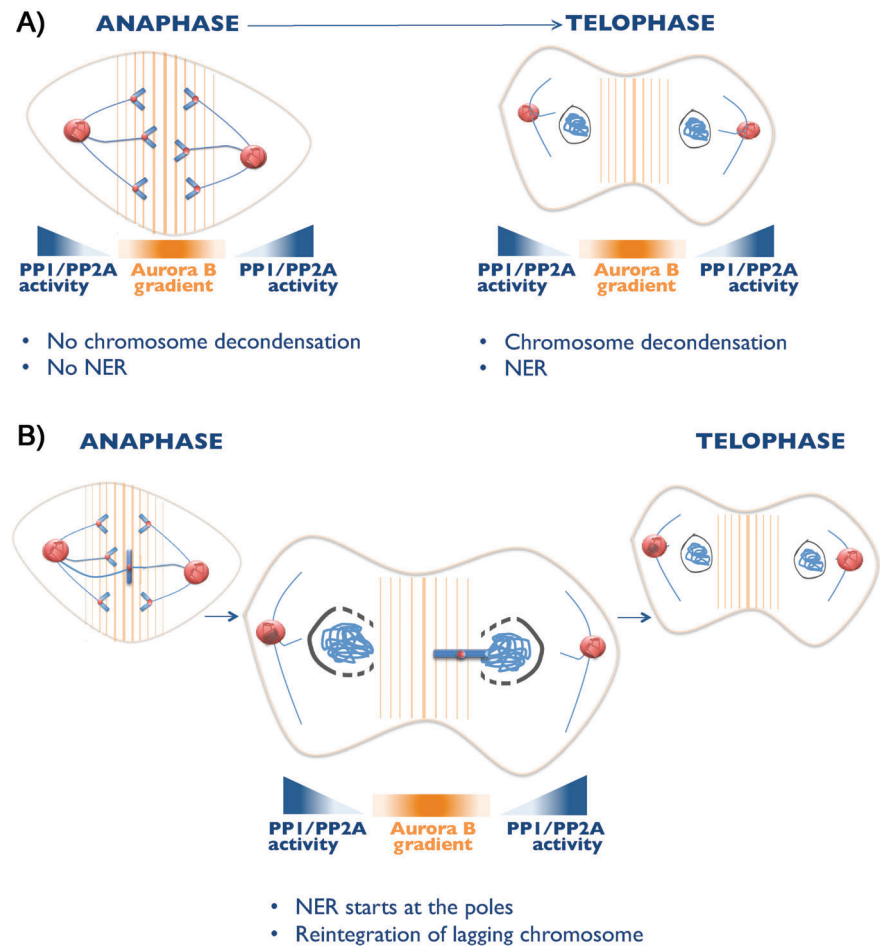
Aneuploidy is the result of errors in chromosome segregation and is manifested in two out of three cancers. The spindle assembly checkpoint (SAC) has evolved to prevent aneuploidy by inhibiting onset of anaphase until all chromosomes are properly aligned and attached. When the SAC is satisfied and cells progress from anaphase to telophase, the sister chromatids are separated and decondensed, and the nuclear envelope is reformed (NER). While the SAC detects many types of erroneous attachments that can lead to chromosome missegregation, including monopolar or syntelic attachments (attachment to one pole only), it does not detect merotelic attachments, (one sister chromatid attached to both poles), as the latter type of attachments produce similar tension across sister chromatids as correct (amphitelic) attachments.

When merotelic attachments are not resolved prior to anaphase, chromatids will lag behind during anaphase, compromising their segregation to the correct spindle pole. Lagging chromosomes often result in micronuclei, a major mechanism of chromosomal instability in cancer cells [1]. However, various lines of evidence indicate that incomplete chromosome separation can delay transition to telophase, suggesting a surveillance mechanism beyond the SAC, operating late in anaphase. For example, recent work from Helder Maiato and co-workers identified a

potential molecular mechanism for such a “chromosome separation checkpoint” (CSC) [2], a hypothesis they further elaborate in this issue of BioEssays [3].

The CSC is proposed to delay the anaphase-telophase transition through a midzone phosphorylation gradient produced by Aurora B kinase that is

counteracted by protein phosphatases 1 and 2A (PP1 and PP2A) (Fig. 1A). As the spindle elongates, the separating sister chromatids are pulled away from the midzone-localized Aurora B kinase and directed towards the counteracting phosphatase activity, triggering chromosome decondensation and NER (Fig. 1A). The Aurora B gradient thus



**Figure 1.** Schematic overview of the CSC proposed by Afonso et al. **A:** Telophase onset is determined by a midzone phosphorylation gradient produced by Aurora B and counteracting phosphatase activity. **B:** The Aurora B phosphorylation gradient delays NER at the midzone, allowing for reintegration of lagging chromosomes into the main nucleus before transition to telophase.

DOI 10.1002/bies.201400212

European Research Institute for the Biology of Ageing, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

\*Corresponding author:  
Floris Foijer  
E-mail: f.foijer@umcg.nl

acts as a sensor for chromosome separation during anaphase: when segregation is compromised, the segregating chromatids remain near Aurora B activity longer, thus locally delaying NER and consequently the onset of telophase. The CSC thus allows for correcting a lagging chromosome, by delaying NER until the lagging chromosome has reintegrated into the main nucleus (Fig. 1B) [3].

The classic definition of a checkpoint states that it should be extrinsic to the process being monitored. As Aurora B kinase activity is required for spindle elongation, and therefore part of the process it monitors, technically the CSC is not a checkpoint. However, this is also true for the SAC, in which key sensors (e.g. Mad2) also participate in the response by actively repressing the downstream E3-ligase, the APC/c. As Aurora B has multiple roles in mitosis, including the execution of the CSC, its

inhibition provokes a pleiotropic response, complicating the measurement of the consequences of a defective CSC. Therefore, to better understand the molecular mechanism behind the CSC, the identification of the direct substrates of Aurora B and PP1/PP2A will be crucial. One potential downstream target of the CSC is Condensin I, an established Aurora B substrate with a known role in chromosome decondensation, whose chromatin-recruitment is indeed required for the spatial regulation of the anaphase-telophase transition [2].

Mutations in the CSC pathway could explain the large number of micronuclei and resulting aneuploidy observed in human cancer [1]. Therefore, a better molecular understanding of the CSC could also reveal new therapeutic intervention strategies that target aneuploid cells specifically, for instance through CSC inhibitors that

aggravate the aneuploidy and consequently kill the cancer cells. While Aurora B inhibitors are showing promising results in clinical trials [4], targeted CSC inhibitors would potentially trigger fewer side effects, and might therefore have great therapeutic potential.

## References

1. **Holland AJ, Cleveland DW.** 2009. Boveri revisited: chromosomal instability, aneuploidy and tumorigenesis. *Nat Rev Mol Cell Biol* **10**: 478–87.
2. **Afonso O, Matos I, Pereira AJ, Aguiar P,** et al. 2014. Feedback control of chromosome separation by a midzone Aurora B gradient. *Science* **345**: 332–6.
3. **Maiato H, Afonso O, Matos I.** 2015. A chromosome separation checkpoint. *BioEssays* **37**: 257–66.
4. **Lens SM, Voest EE, Medema RH.** 2010. Shared and separate functions of polo-like kinases and aurora kinases in cancer. *Nat Rev Cancer* **10**: 825–41.