

## **Aurora B kinase Controls The Separation of Centromeric and Telomeric Heterochromatin**

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# Aurora B kinase Controls The Separation of Centromeric and Telomeric Heterochromatin

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## ABSTRACT

The segregation of chromosomes is coordinated at multiple levels to prevent chromosome loss, a phenotype frequently observed in cancers. We recently described an essential role for telomeres in the physical separation of chromosomes and identified Aurora B kinase as a double agent involved in the separation of centromeric and telomeric heterochromatin.

## ARTICLE HISTORY

Received 13 April 2015

Revised 14 April 2015

Accepted 14 April 2015

## KEYWORDS

Aurora B kinase; aneuploidy; chromosome bi-orientation; chromosome instability; fission yeast; HP1/Swi6; mitosis; telomere

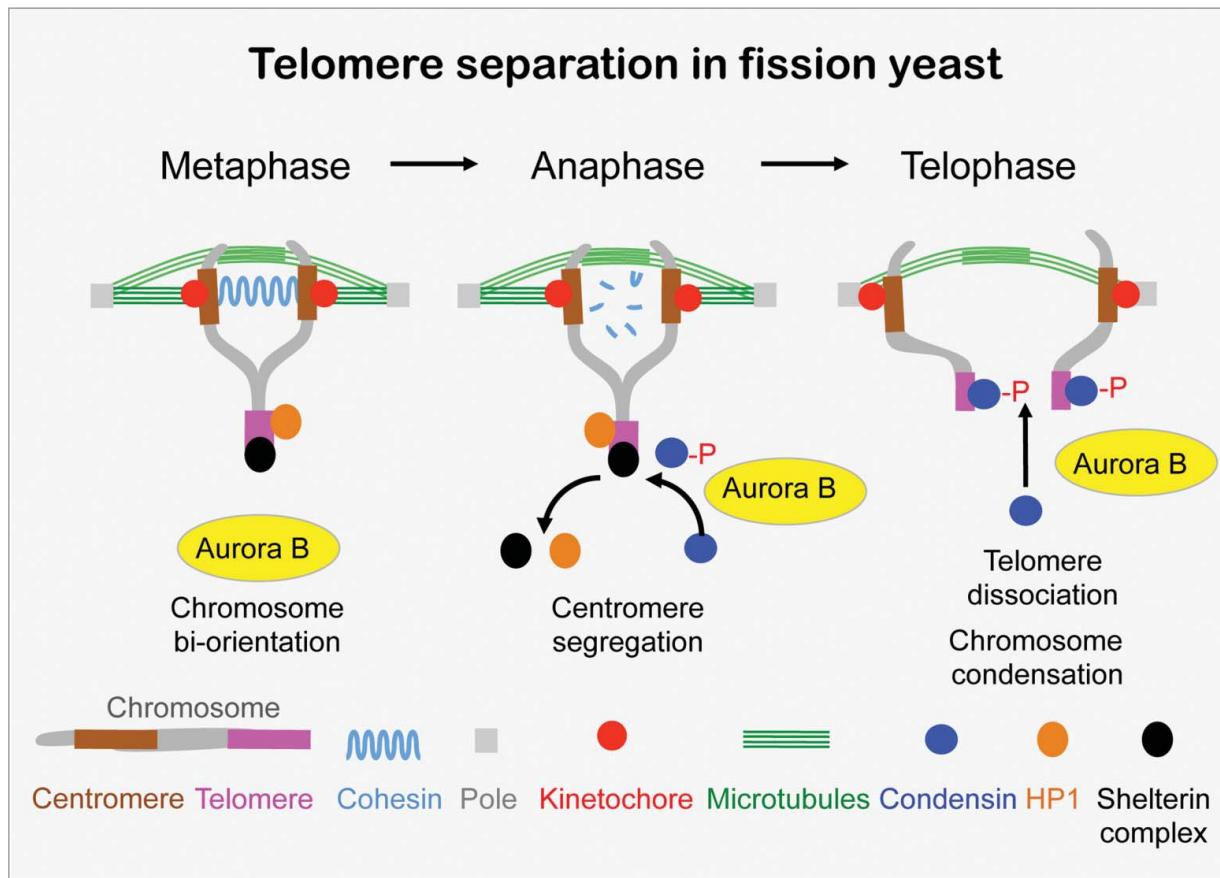
Maintaining the correct number of chromosomes is necessary for the development and survival of all organisms.<sup>1</sup> Accurate chromosome segregation is mediated by a supramolecular cellular structure, the spindle apparatus. During the past century, considerable efforts have been made to understand how the spindle assembles into this supramolecular structure and how microtubules are connected to centromeres, non-coding regions of the chromosome consisting of heterochromatin.<sup>2</sup> The centromere is required for the attachment of chromosomes to the microtubules of the mitotic apparatus, thus allowing faithful chromosome segregation. Precise coordination of mitotic events is essential to prevent the formation of aneuploid cells, a phenotype frequently observed in cancers and genetic diseases. Chromosomal instability (CIN) results from chromosome segregation defects such as merotelic attachment (a chromosome attached to both poles), but can also be caused by the presence of dicentric chromosomes. Most attachment defects are corrected before sister chromatid separation through a mechanism involving the evolutionarily conserved Aurora B kinase, whose function at centromeres has been widely described.<sup>3</sup> Chromosome attachment defects lead to the appearance of chromatin bridges during cell division (also called anaphase bridges because they are detected in anaphase). The presence of anaphase chromatin bridges during abnormal mitosis has been extensively described since their discovery by Barbara McClintock in the late 1930s. Such abnormalities are observed during cell division in certain diseases, such as Bloom syndrome, Fanconi anemia, or cancer.

The function of telomeres, a second heterochromatin domain of the chromosome, is also required to prevent chromosome instability, since telomere shortening is involved in cancer initiation and progression. Telomere dysfunctions lead to chromosomal aberration through multiple mechanisms,

including telomere fusion, formation of dicentric chromosomes, and possibly multipolar mitosis.<sup>4</sup> Chromosome end protection in fission yeast is similar to that seen in mammals and recent studies have identified a number of proteins that form the shelterin complex and protect telomeres from degradation. In fission yeast, the Aurora B kinase interacts with 2 different heterochromatin regions of the chromosome, the centromeres and the telomeres. In this context, we examined the mechanisms of fission yeast telomere separation in mitosis and described a new role for Aurora B kinase in this process.

Aurora B localizes at centromeres where it controls chromosome bi-orientation. In metaphase, each chromosome (kinetochore, red) is attached to a bundle of microtubules (green) emanating from the centrosome (spindle pole, gray) (**Fig. 1**). In fission yeast, Aurora B is also detectable at the level of telomeres (pink), where it initially controls telomere dispersion at the beginning of mitosis (metaphase) by promoting the dissociation of HP1 proteins (heterochromatin protein 1, brown) and cohesion from telomeres (**Fig. 1**). In a second step, Aurora B promotes full telomere separation (called disjunction) at anaphase by phosphorylating a subunit of the condensin complex, Cnd2 (Condensin complex subunit 2, in blue, **Fig. 1**).<sup>5</sup>

Consistent with its role at centromeres, inhibition of Aurora B results in the appearance of centromere bi-orientation defects such as merotelic kinetochore attachments that are partially corrected in anaphase through spindle elongation forces.<sup>6,7</sup> Thus, the cell lethality observed upon Aurora inhibition is unlikely to be the consequence of centromere bi-orientation defects. Instead, we observed that cell death is caused by non-separation of telomeres, leading to the accumulation of anaphase chromatin bridges that are severed by the cytokinetic actin ring.<sup>8</sup> Interestingly, components of the Shelterin complex (**Fig. 1**: black), which is specifically involved in telomere protection, dissociate



**Figure 1.** Dual function of Aurora B kinase in mitosis in centromere and telomere separation. Schematic representation illustrating the regulation of telomere dissociation throughout mitosis. Telomere foci undergo separation in 2 discrete steps. Telomere cluster dispersion occurs during metaphase, before chromosome segregation, whereas sister chromatid telomere disjunction is achieved during mid-anaphase. Aurora B is required for both processes. In metaphase, Aurora promotes the delocalization of several telomere/subtelomere components, such as shelterin components (in black), HP1 (in brown), or cohesin Rad21. At anaphase, Aurora favors the loading of condensin (in blue).

from telomere in early mitosis.<sup>9</sup> Remarkably, we find that depletion of a Shelterin protein called Ccq1 is sufficient to suppress the loss of viability resulting from Aurora B inhibition. Thus, our findings identify a new mechanism controlling chromosome arm separation that involves telomeric heterochromatin.<sup>8</sup> How Ccq1 deletion triggers Condensin loading and chromosome arm separation after Aurora inhibition remains to be determined but a more thorough examination of Aurora B function in Ccq1-deleted cells should shed light on such questions.

In the 90s, the discovery of a relationship between cancer, aging, and telomeres opened a new avenue of research in tumor biology. With increasing cell age, chromosome segregation errors appear and telomeres shorten as a result of telomerase activity. The mechanism that we have discovered constitutes an alternative model to anaphase bridge formation due to chromosome end joining or Tankyrase activity in cancer and aging.<sup>10</sup>

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