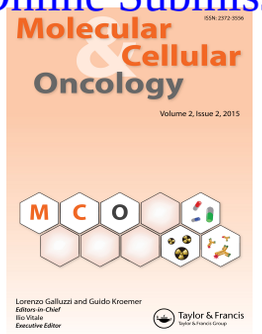

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An ATM-CHK2-INCENP pathway prevents chromatin breakage by regulating the abscission checkpoint

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ABSTRACT

In response to chromatin bridges, the chromosomal passenger complex (CPC) delays completion of cytokinesis (abscission) to prevent chromosome breakage. Here, we discuss recent findings from our lab showing that an ATM-CHK2-INCENP pathway imposes the abscission checkpoint in human cells by regulating CPC midbody-localization.

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During cell division, chromatin bridges are strings of mis-segregated chromatin connecting the anaphase poles or daughter nuclei and have been linked with genome instability and tumourigenesis.[1,2] In response to chromatin bridges in cytokinesis, cells delay abscission, the severing of the narrow intercellular canal that connects the two daughter cells, to prevent chromatin breakage or tetraploidization by regression of the cleavage furrow.[3,4] This abscission delay is called the "abscission checkpoint" in mammalian cells and requires the proper localization and catalytic activity of AURORA B kinase at the midbody (reviewed in[5]).

AURORA B is the catalytic subunit of the chromosomal passenger complex (CPC) also comprising the scaffolding protein INCENP and the non-enzymatic subunits SURVIVIN and BOREALIN.[6] In late cytokinesis, AURORA B localizes on the midbody arms and inside the Flemming body,[7] the narrow region at the midbody center where tubulin staining by immunofluorescence is blocked (Figure 1, inset), and imposes the abscission checkpoint by phosphorylating the endosomal sorting complex required for transport III (ESCRT-III) subunit charged multivesicular body protein 4 C (CHMP4C) to target CHMP4C to the midbody center to delay abscission.[5] Inhibition of AURORA B kinase activity also accelerates abscission in normally segregating cells, i.e., in the absence of trapped chromatin, indicating the abscission checkpoint functions more generally as an abscission timer.[4,7] However, the molecular mechanisms that relay chromatin bridges to the CPC have not been previously identified.

Petsalaki and Zachos showed that the DNA double-strand break signaling kinase ataxia-telangiectasia mutated (ATM) and its downstream effector checkpoint kinase 2 (CHK2) regulate the abscission checkpoint in human cancer cell lines.[8] They found that inhibition of ATM or CHK2 kinases accelerates midbody resolution in normally segregating cells and correlates with premature abscission, chromatin breakage and generation of DNA damage in cytokinesis with trapped chromatin. Mechanistically, ATM and CHK2 localize inside the Flemming body and ATM phosphorylates CHK2-threonine 68 to activate CHK2 in late cytokinesis (Figure 1). In turn, active CHK2 phosphorylates human INCENP at the newly identified site serine 91 (Ser91) to promote INCENP binding to MKLP2 kinesin, which is required for CPC-MKLP2 localization to central spindle microtubules in cytokinesis (Figure 1).[9,10] Importantly, expression of a chimeric INCENP protein that binds to AURORA B and is constitutively targeted to the midbody center, but not on the midbody arms, rescues the abscission delay in CHK2-deficient or ATM-deficient cells, showing INCENP-AURORA B localization inside the Flemming body is essential for the abscission checkpoint. By using GST-pull downs *in vitro* and reconstitution experiments with truncated proteins in cells, Petsalaki and Zachos also showed that the C-terminal 90 amino-acids of MKLP2 interact with the central midbody protein CEP55 and propose that the CPC–MKLP2 complex localizes to the midbody center through MKLP2 binding to CEP55 (Figure 1). Also importantly, the MRE11–RAD50–NBS1 (MRN) protein complex, a double-strand break sensor in the DNA damage response, localizes to the midbody and promotes ATM activation in cytokinesis with chromatin bridges, but not in normally segregating cells (Figure 1). Furthermore, expression of non-phosphorylatable mutant INCENP-Ser91A reduced cell proliferation and increased cell death,[8] suggesting inhibition of abscission checkpoint signaling can be harmful for cancer cells.

This work by Petsalaki and Zachos[8] demonstrates that AURORA B (CPC)-localization to the midbody center is required for the abscission checkpoint and identifies the molecular mechanism behind it. This study also describes a molecular pathway that signals chromatin bridges to the CPC to delay abscission and prevent chromatin bridge-breakage in cytokinesis. Furthermore, this work highlights a novel mechanism by which ATM and CHK2 could protect against genomic instability and tumorigenesis, through their role in abscission checkpoint

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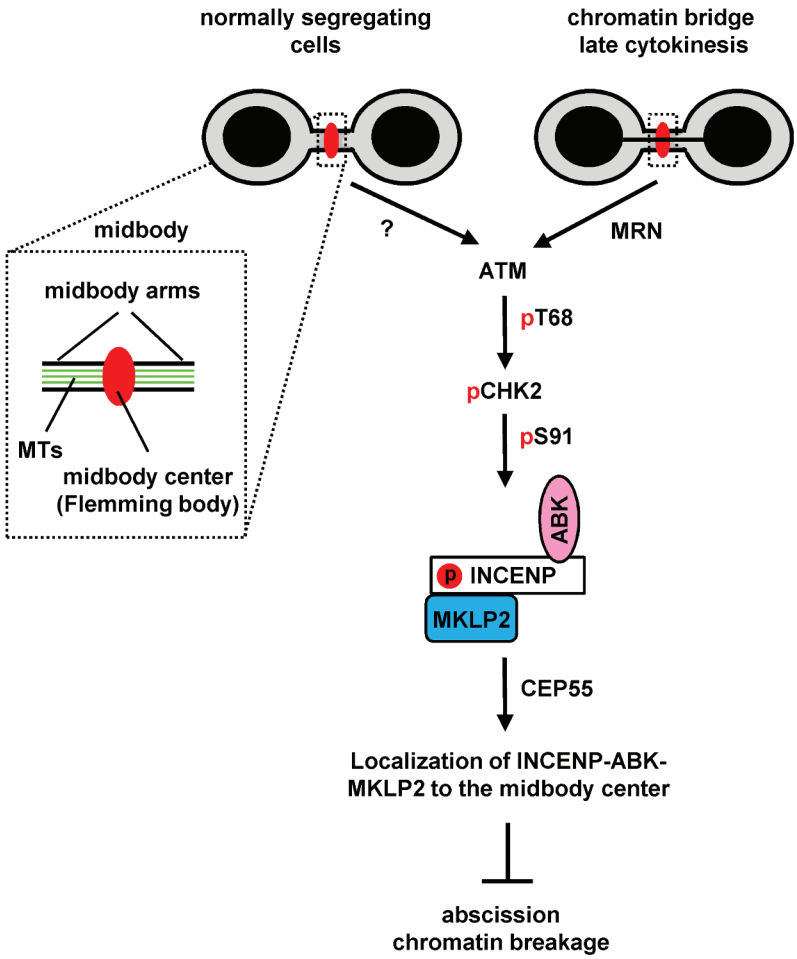

Figure 1. An ATM-Chk2-INCENP pathway imposes the abscission checkpoint by promoting chromosomal passenger complex-localization inside the Flemming body. In late cytokinesis, ATM phosphorylates CHK2-threonine 68 (T68) to activate CHK2. Active CHK2 phosphorylates INCENP-Ser91 (S91) to stabilize the INCENP-MKLP2 interaction and promote INCENP-AURORA B-localization inside the Flemming body through MKLP2-binding to the midbody protein CEP55, to delay abscission and prevent chromosome breakage. In the presence of a chromatin bridge, ATM activation requires the MRE11-RAD50-NBS1 (MRN) complex. Inset shows magnified midbody. ABK, AURORA B kinase; MTs, microtubules; p, phosphorylation.

signaling, and proposes that DNA damage and abscission checkpoint mechanisms crosstalk to maintain genome integrity.

The above findings also raise several important questions: For example, what is the mechanism of ATM activation in unperturbed late midbodies? How is the MRN complex recruited on the chromatin bridge? How is the abscission-delay signal transferred through the nuclear membrane to the CPC in the cytoplasm?[3] What happens to the chromatin bridges after MRN recruitment in checkpoint-proficient cells? And can we employ pharmacological inhibition of abscission checkpoint proteins to selectively target highly proliferating cancer cells compared with normal tissues? Future studies aimed at answering these questions will increase our understanding of abscission checkpoint mechanisms and could pave the way for manipulating the abscission checkpoint to improve cancer-cell killing in cancer patients.

Disclosure of potential conflicts of interest

The authors declare no potential conflicts of interest.

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References

1. Lens SMA, Medema RH. Cytokinesis defects and cancer. Nat Rev Cancer. 2019;19:32–45.
2. Umbreit NT, Zhang CZ, Lynch LD, Blaine LJ, Cheng AM, Tourdot R, Sun L, Almubarak HF, Judge K, Mitchell TJ, et al. Mechanisms generating cancer genome complexity from a single cell division error. Science. 2020;368(6488):e0712. doi:10.1126/science.aba0712.
3. Steigemann P, Wurzenberger C, Schmitz MH, Held M, Guizetti J, Maar S, Gerlich DW. Aurora B-mediated abscission checkpoint protects against tetraploidization. Cell. 2009;136(3):473–484. doi:10.1016/j.cell.2008.12.020.

4. Carlton JG, Caballe A, Agromayor M, Kloc M, Martin-Serrano J. ESCRT-III governs the Aurora B-mediated abscission checkpoint through CHMP4C. Science. 2012;336(6078):220–225. doi:10.1126/science.1217180.
5. Petsalaki E, Zachos G. Building bridges between chromosomes: novel insights into the abscission checkpoint. Cell Mol Life Sci. 2019;76(21):4291–4307. doi:10.1007/s00018-019-03224-z.
6. Carmena M, Wheelock M, Funabiki H, Earnshaw WC. The chromosomal passenger complex (CPC): from easy rider to the godfather of mitosis. Nat Rev Mol Cell Biol. 2012;13:789–803.
7. Petsalaki E, Zachos G. Clks 1, 2 and 4 prevent chromatin breakage by regulating the Aurora B-dependent abscission checkpoint. Nat Commun. 2016;7(1):e11451. doi:10.1038/ncomms11451.
8. Petsalaki E, Zachos G. An ATM–Chk2–INCENP pathway activates the abscission checkpoint. J Cell Biol. 2021;220(2). in press. doi:10.1083/jcb.202008029.
9. Kitagawa M, Fung SYS, Hameed UFS, Goto H, Inagaki M, Lee S. Cdk1 coordinates timely activation of MKlp2 kinesin with relocation of the chromosome passenger complex for cytokinesis. Cell Rep. 2014;7(1):166–179. doi:10.1016/j.celrep.2014.02.034.
10. Adriaans IE, Hooikaas PJ, Aher A, Vromans MJM, van Es RM, Grigoriev I, Akhmanova A, Lens SMA. MKLP2 is a motile kinesin that transports the chromosomal passenger complex during anaphase. Curr Biol. 2020;30(13):2628–2637. doi:10.1016/j.cub.2020.04.081.