Microtubule plus tips: A dynamic route to chromosomal instability

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Although chromosomal instability (CIN) is a recognized hallmark of cancer the underlying mechanisms and consequences are largely unknown. However, it is accepted that lagging chromosomes represent a major prerequisite for chromosome missegregation in cancer cells. Here, we discuss how lagging chromosomes are generated and our recent findings establishing increased microtubule assembly rates as a source of CIN.

A major characteristic of human cancer is chromosomal instability (CIN), which represents the perpetual missegregation of whole chromosomes during mitosis leading to aneuploid karyotypes. CIN gives rise to an evolving genomic heterogeneity and might thereby promote tumorigenesis, tumor progression, and the development of resistance to therapy.1 It is conceivable that subtle defects during mitosis are sufficient to cause CIN, and various mechanisms responsible for this phenotype have been proposed including defects in the spindle assembly checkpoint, supernumerary centrosomes, spindle assembly defects, defects in sister chromatid cohesion, abnormal microtubule-kinetochoore (MT-KT) attachments, pre-mitotic replication stress, and telomere maintenance (for a review see Ref.2). However, it is unclear whether these mechanisms are actually relevant in cancer.

It is, however, widely accepted that so-called lagging chromosomes, which appear during anaphase, are a major prerequisite for chromosome missegregation in human cancer cells. Lagging chromosomes result from erroneous (merotelic) MT-KT attachments that occur stochastically during the early phases of mitosis but are usually corrected before anaphase onset. In cancer cells these merotelic kinetochore attachments are not properly corrected and persist until anaphase, leading to the generation of lagging chromosomes.3 In principle, the persistence of erroneous kinetochore attachments and the subsequent generation of lagging chromosomes can arise through 2 main routes: (i) an impairment of error correction, or (ii) an increased rate of formation that overwhelms the correction machinery (Fig. 1).

Correction of erroneous kinetochore attachments involves the Aurora-B kinase and microtubule depolymerases such as MCAK and Kif2B, which localize at the MT-KT interface and destabilize incorrectly attached microtubules. Thus, error correction promotes kinetochore-microtubule turnover. Vice versa, loss of Aurora-B, MCAK, or Kif2B causes kinetochore-microtubule hyperstability leading to the generation of lagging chromosomes and CIN.4 Although hyperstable kinetochore attachments are indeed often detected in chromosomally unstable cancer cells, genes that are known to be involved in error correction appear not to be altered in human cancer. Hence, it is not yet known whether error correction per se is commonly impaired in cancer cells exhibiting CIN.

On the other hand, an increased rate of generation of erroneous kinetochore attachments might simply overwhelm a functional error correction machinery, leading to the persistence of erroneous kinetochore attachments. For example, cancer cells exhibiting supernumerary centrosomes display lagging chromosomes that are the result of increased generation of merotelic kinetochore attachments.5 Intriguingly, those cancer cells show transient multipolar mitotic spindle intermediates that reorganize into bipolar spindles by clustering the supernumerary centrosomes into 2 poles. This transient alteration in spindle geometry promotes the generation of erroneous MT-KT attachments, thus explaining the strong correlation between supernumerary centrosomes and CIN in human cancer.

In addition to supernumerary centrosomes, which are present in approximately 20–30% of human cancer cells, abnormal timing of centrosome separation before nuclear envelope breakdown might represent another important mechanism that promotes the formation of erroneous MT-KT attachments.6 However, it remains to be seen whether centrosome positioning defects are indeed widespread in human cancer.

Our recent work revealed a key trigger for the generation of lagging chromosomes and CIN that is highly relevant to
cancer. We found that an increase in microtubule plus end assembly rates within mitotic spindles is not only frequently detected in chromosomally instable colorectal cancer cells, but is also sufficient to cause transient spindle geometry defects that facilitate the generation of hyperstable kinetochore attachments and lagging chromosomes. Importantly, increased microtubule plus end assembly rates do not interfere with the cellular error correction machinery, suggesting that this mechanism causes the persistence of erroneous MT-KT attachments by overwhelming the capacity for error correction. Remarkably, restoration of proper microtubule plus end assembly by repression of the microtubule plus-end polymerase ch-TOG/CKAP5 or by treatment with low doses of Taxol suppresses spindle geometry abnormalities, the generation of lagging chromosomes, and CIN. This clearly establishes a causal relationship between increased spindle microtubule plus end dynamics, transient spindle geometry and orientation defects, lagging chromosomes, and CIN in human colorectal cancer cells (Fig. 1). Moreover, this novel route to CIN might be mediated by highly cancer-relevant genetic lesions such as loss of the tumor suppressor genes CHK2 or BRCA1, or amplification of the oncogene AURKA, genetic constitutions that are found in up to 70% of patients with colorectal cancer, in which CIN is highly prevalent. Unexpectedly, we found that the Chk2-Brc2a1 network restrains the activity of the Aurora-A kinase at mitotic centrosomes, thus establishing a role for tumor suppressors previously implicated in the DNA damage response pathway in the regulation of mitotic microtubule dynamics through negative regulation of Aurora-A.

Finally, as our work revealed options for suppressing CIN we were able to gain insights into the consequences of CIN on tumor cell physiology by comparing colorectal cancer cells with CIN and upon suppression of CIN. As a first step in this exciting direction we investigated the role of CIN in tumor growth and surprisingly found that CIN suppression accelerates tumor growth in vivo. This result was unexpected because CIN is highly prevalent in aggressive tumors. On the other hand, the fact that aneuploidy is detrimental for cell proliferation indicates that CIN might be associated with reduced tumor growth per se. Indeed, at least for colorectal cancer, a poor prognosis is associated with a high level of karyotype variability but not with a high proliferation index. This, of course, raises the question regarding the role of CIN in driving tumor progression, although it seems likely that CIN is a major driver of high adaptation and tumor evolution.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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