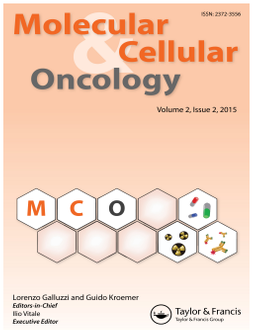

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COMMENTARY

Relevance of aneuploidy for cancer therapies targeting the spindle assembly checkpoint and KIF18A

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ABSTRACT

Aneuploidy, a common feature of cancer cells, results in increased sensitivity to the inhibition of the spindle assembly checkpoint (SAC) and the mitotic motor protein Kinesin Family Member 18A (KIF18A). We discuss the importance of drugs targeting SAC core members and KIF18A. We stress the need to assess the sensitivity to this class of drugs at appropriate time points, and propose that aneuploidy could serve as a biomarker to stratify patients for SAC-targeting treatments.

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Aneuploidy, defined as an imbalanced chromosomal composition, was associated with malignancy already more than a century ago. It is the most common genetic alteration in cancer cells, appearing in ~90% of solid tumors and affecting roughly 25% of the genome in a typical solid tumor cell,[1] yet it is an under-studied trait of cancer that remains to be exploited for clinical purposes. One reason for this is that cancer aneuploidy is notoriously difficult to model, and it is difficult to identify which of the hundreds affected genes within a given aneuploidy actually drive tumor initiation and/or progression. In addition, the cellular consequences of aneuploidy are context-specific; while aneuploidy confers a fitness disadvantage to most cells, under specific conditions cells adapt to tolerate it, and it can even promote tumorigenesis.[2,3] Despite the context-specific effects, however, a high-degree of aneuploidy can also lead to various cellular stresses – replicative, mitotic, metabolic and proteotoxic – independent of the altered chromosome.[4,5] Therefore, a major open question is whether and how we can take advantage of these stresses in order to target aneuploid cancer cells.

We recently performed a large-scale comparison of the response of near-euploid and highly aneuploid human cancer cell lines to genetic and pharmacologic perturbations.[6] We found that aneuploid cells were more resistant to drugs that inhibit the spindle assembly checkpoint (SAC), in typical 3d- and 5d-long drug assays. This trend switched, however, after prolonged drug exposure, revealing that aneuploid cells were more sensitive than euploid cells to prolonged SAC inhibition. Using single-cell DNA sequencing, live-cell microscopy and functional genetics, we demonstrated that aneuploid cells initially overcame SAC inhibition more quickly than euploid cells, but that led to the accumulation of mitotic errors such as multipolar spindles, micronuclei formation and failed cytokinesis, which ultimately led to their death.

Since aneuploid cells also had an aberrant spindle structure and altered spindle dynamics, we took a closer look at spindle-related genes and found one particular mitotic kinesin, *Kinesin Family Member 18A* (*KIF18A*), which was preferentially essential in aneuploid cells. KIF18A is a motor protein responsible for reducing chromosomal oscillatory movements, thus stabilizing chromosomes at the metaphase plate. KIF18A senses reduced kinetochore tension in the presence of abnormal microtubule–kinetochore interactions and recruits the SAC to inhibit mitotic progression and allow time for the cell to correct chromosomal attachments to the spindle.[7] We showed that loss of KIF18A had little impact on the proliferation of euploid cells, whereas aneuploid cells showed decreased proliferation, abnormal spindle geometry and dynamics, and mitotic aberrations. Lastly, overexpression of *KIF18A* sensitized aneuploid cells to SAC inhibition in a short-term assay, thus establishing a functional link between the sensitivity of aneuploid cells to SAC inhibition and their dependency on *KIF18A*.[6]

Two additional recent studies provide a complementary view of this topic. Quinton et al.[8] studied the cellular consequences of whole-genome doubling (WGD) in human cancer cell lines and similarly identified an increased dependency of WGD+ cells on the SAC and on *KIF18A*.[8] Marquis et al.[9] focused on kinesin motor proteins and reported that chromosomally unstable tumor cells specifically require KIF18A for their proliferation.[9] These three genomic features – aneuploidy, chromosome instability (CIN), and WGD – are intertwined, complicating the attempt to disentangle the effect of each of these features alone. Nonetheless, we found that the increased sensitivity of aneuploid cells to SAC inhibition remained significant in chromosomally stable aneuploid cells that have not undergone WGD.[6] Combined, the three studies suggest that the excessive number of chromosomes, characteristic of aneuploid/CIN+/WGD+ cells, makes them more vulnerable to perturbations of KIF18A and the SAC.

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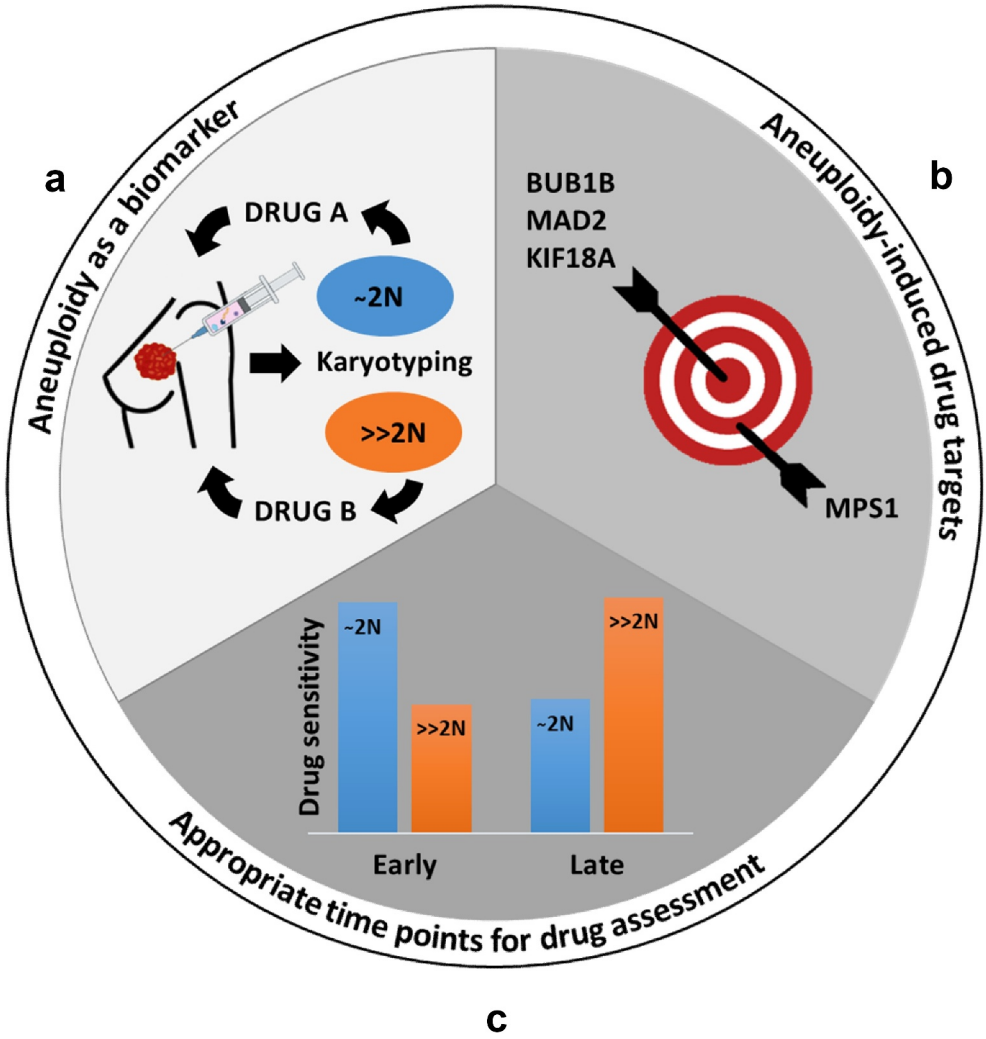

Figure 1. Impact of aneuploidy on cancer drug development (a): Tumor karyotyping could be used to identify highly aneuploid tumors and stratify patients for aneuploidy-targeting treatments. (b): Ongoing spindle assembly checkpoint (SAC) inhibition clinical trials target the SAC regulator monopolar spindle 1 (MPS1); we found aneuploid cells to be particularly sensitive to *budding uninhibited by benzimidazoles 1 Beta* (*BUB1B*), *mitotic arrest deficient 2 like 1* (*MAD2*) and *Kinesin family member 18A* (*KIF18A*) knockdown, highlighting them as potential therapeutic targets. (c): Aneuploid cells were found to be more resistant to SAC inhibitors in short-term drug assays (3–5d), but more sensitive in longer assays (14d), emphasizing that prolonged exposure is critical for the full assessment of drug sensitivity. ~ 2 n, near-diploid cells; >> 2 n, highly aneuploid cells.

Multiple SAC inhibitors are currently in clinical trials.[10] If our results hold true in clinical data, then the degree of aneuploidy and CIN may serve as a biomarker to predict patients' response to such treatments (Figure 1a). Interestingly, however, all of the SAC inhibitors that are currently in clinical trials target Monopolar Spindle 1 (MPS1) kinase, which regulates SAC assembly at the kinetochore. Although the aneuploid cells were more sensitive to pharmacological inhibition of MPS1, the gene encoding it, *TTK protein kinase (TTK)*, did not come up as more essential in aneuploid cells in the genetic screens, whereas the SAC core members *Budding Uninhibited by Benzimidazoles 1 Beta* (*BUB1B*) and *Mitotic Arrest Deficient 2 Like 1* (*MAD2*) did, and so did *KIF18A*.[6,8] These results suggest a potential benefit from targeting the SAC core members, as well as KIF18A, in order to selectively kill aneuploid cells (Figure 1b). More research is required in order to understand the exact consequences of targeting the various components of the SAC and of the proteins associated with its activity. In addition, preclinical drug testing *in vitro* usually measures cell viability after 3 to 5 days of drug exposure. However, when targeting the SAC, our results show that some effects would only become apparent at later time points. This emphasizes the need to assess the response of cells to drugs that inhibit the SAC, and potentially to additional drugs that interfere with mitosis, at time points that reflect their long-term consequence (Figure 1c).

While our findings – as well as those by Quinton et al.[8] and Marquis et al.[9]– offer a novel promising approach to cancer treatment, they have only been validated *in vitro* so far. These findings therefore ought to be validated in an *in vivo* animal model, as well as in clinical data from patients. On a molecular level, the exact mechanistic link between SAC dependency and KIF18A activity remains to be elucidated. In conclusion, we have established that aneuploidy could generate unique cellular

vulnerabilities in cancer cells, and propose that these vulnerabilities may be translated to improved drug development and patient stratification.

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Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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