

# A Review of Inducing Chromosomal Instability in Cancer Therapy

By Isabella Hu

## Author Bio

Isabella Hu is a junior at Belmont High School in MA, USA. She's always held an interest in the STEM field, from physics to math, enjoying them all. A cancer biology course this past summer inspired her to research this field where she took particular interest in looking at a relatively newer area of cancer therapy. Aside from cancer biology, she loves her current economics class and listening to music!

## Abstract

Chromosomal instability (CIN) is one of the enabling hallmarks of cancer. There are a multitude of targets for CIN including but not limited to: spindle assembly checkpoint (SAC), anaphase-promoting complex (APC), and mitotic checkpoint complex (MCC) genes. In this review we will be focusing on CIN-inducing therapies. Some of the enduring problems faced with cancer are metastatic tumor growth and resistance to gold-standard treatments such as chemotherapy. CIN-inducing therapy reduces tumor adaptability by triggering apoptosis of tumor cells with high levels of CIN, halting tumor growth, and increasing the efficacy of other chemotherapies and radiation treatments. One of the most common strategies was inhibition of Mps1, a gene important for the MCC and responsible for maintaining accurate chromosome segregation. Inhibition of this gene led to mitotic catastrophe, chromosome missegregation, aneuploidy, and ultimately cell death. Synthetic lethality was another strategy commonly used for CIN, where two mutations were utilized to induce lethal CIN. Cancer cells with specific mutations in genes such as Polo-kinase 1 and BRCA1/2 ultimately undergo apoptosis. Thus, chromosomal instability is a viable therapeutic target both for improving current treatments and for development as treatment on its own.

*Keywords:* Chromosomal Instability, Inducing CIN, Cancer Therapy, Mps1 Inhibitors, Synthetic Lethality, Treatment sensitizing, Paclitaxel, Docetaxel

## Introduction

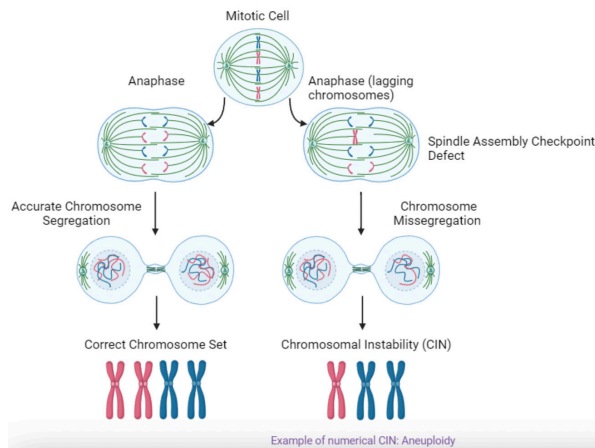


Figure 1: Chromosomal instability, spindle assembly checkpoint, mitosis

Cancer is a prevalent issue today. In 2020, there were around 18 million new cases of cancer, 10 million of which ended in death (World Health Organization, 2022). It is one of the leading causes of death around the world, rendering treatment for cancer a high-priority concern.

Characterized by its uncontrollable proliferation of cells, once left unchecked, cancerous cells can spread to various parts of the body forming lethal metastatic tumors. Chromosomal instability (CIN) is one of the enabling hallmarks of cancer. It refers to the errors that occur during chromosome segregation leading to a loss or gain of chromosomes, and sometimes aneuploidy. To maintain chromosome segregation fidelity in mitosis, cohesion must be maintained during the G2 and M phases, and precisely timed destruction of the sister chromatid cohesion must occur. These activities are regulated by cyclin-dependent kinases and the spindle assembly checkpoint (SAC). Different alterations in the various mitotic mechanisms involved, such as cohesion defects can lead to chromosomal instability (Thompson et al., 2010). Another mechanism of CIN is by mutations of SAC genes. The SAC sends signals from kinetochores to stall anaphase until all chromosomes form proper bipolar attachments to spindle microtubules, once they are properly bound the signaling switches off liberating the anaphase-promoting complex (APC). The error-correction pathway reactivates SAC signaling if a wrongly attached chromosome is found and detached.

A kinase central to this process is Mps1/TTK (referred to as Mps1 in this review) which is needed for both error correction and SAC. It is responsible for a variety of tasks including promoting the attachment of kinetochores to microtubules by regulating Aurora B activity, localizing to kinetochores, and causing events that lead to SAC activation. Mps1 also impacts APC binding and the stability of the mitotic checkpoint complex (MCC).

The SAC, error-correction pathway, and MCC are complex, meaning various impairments can lead to CIN (Pachis et al., 2018). There are two types of CIN: numerical CIN, which refers to aneuploidy and gene copy number alterations, and structural CIN, which can cause specific gene amplifications, deletions, and transformations (i.e. DNA double-strand breakage). CIN may trigger apoptosis due to how unstable the cell is or because of mitotic catastrophe. CIN-inducing therapies aim to create a high level of CIN to trigger cell death, creating a barrier to tumor growth. One of the therapies discussed in this paper is synthetic lethality. Synthetic lethality (SL) refers to the genetic or chemical combined alteration of otherwise individually viable gene pairs to target usually ‘non-druggable’ targets. Through genetic and chemical screening, a target gene is chosen and the interaction between the target gene and the altered gene creates synthetic lethality. When exploring synthetic lethality, scientists must consider drug toxicity, efficacy in different body regions, penetrance, initiation, and maintenance of the drug (Setton et al., 2021). In current research, mitotic genes were often targeted to explore therapy options. This literature review’s aim is to highlight some of the methods CIN can be used in therapy to slow or halt tumor progression. In this review, we will discuss some of the different methods of inducing CIN and how they are exploited in treatment.

## Methodology

PubMed was used to source all papers reviewed. The keywords used were formatted as follows: “chromosomal instability” cancer therapy. The filters “Last Ten Years” and “Free Full Text” were applied to focus on current CIN therapy developments. As of August 29th, 2023, the last day of looking through papers on PubMed, 341 results appeared and 24 were used in the results of this review. Literature

reviews were excluded from the results of this review. Papers focused specifically on inducing chromosomal instability were chosen.

## Results

Table 1. Papers that discussed CIN-exploiting therapy divided by method

| Method of Therapy     | Author                                                                            |
|-----------------------|-----------------------------------------------------------------------------------|
| Mps1 Inhibition       | Faisal, A., Mak, G. W. Y., Gurden, M. D. et al., 2017                             |
|                       | Stratford, J. K., Yan, F., Hill, R. et al., 2017                                  |
|                       | Szymiczek, A., Carbone, M., Pastorino, S. et al., 2017                            |
|                       | Martinez, R., Blasina, A., Hallin, J. F. et al., 2015                             |
|                       | Libouban, M. A., de Roos, J. A., Uitdehaag, J. C. et al., 2017                    |
|                       | Choi, M., Min, Y. H., Pyo, J., et al., 2017                                       |
|                       | Cunningham, C. E., Li, S., Vizeacoumar, F. S., et al., 2016                       |
| Synthetic Lethality   | Goff, L. W., Azad, N. S., Stein, S. et al                                         |
|                       | Dolly, S. O., Gurden, M. D., Drosopoulos, K. et al                                |
|                       | Nieminszczy, J., Broderick, R., Bellani, M. A., Gagos, S., & Seidman, M. M., 2019 |
|                       | Xu, H., Antonio, M. di, McKinney, S. et al., 2017                                 |
|                       | Li, J., Ohmura, S., Marchetto, A., et al., 2021                                   |
|                       | Sajesh, B. v, Bailey, M., Lichtensztejn, Z., et al., 2013                         |
|                       | Bai, H., Xia, S., Zhu, L. et al., 2022                                            |
| Treatment Sensitizing | Chinn, D. C., Holland, W. S., & Mack, P. C., 2014                                 |
|                       | Bakhoun, S. F., Kabeche, L., Wood, M. D. et al., 2020                             |
|                       | Maia, A. R. R., Linder, S., Song, J. Y. et al., 2018                              |
|                       | Scribano, C. M., Wan, J., Esboma, K. et al., 2021                                 |
|                       | Vargas-Rondón, N., Pérez-Mora, E., Villegas, V. E., et al., 2020                  |
|                       | Hsu, C.-W., Chen, Y.-C., Su, H.-H., et al., 2017                                  |
| Other Methods         | Petrov, N., Lee, H.-S., Liskovych, M., et al., 2021                               |
|                       | Oku, Y., Tareyanagi, C., Takaya, S., et al., 2014                                 |
|                       | Liu, X., Dong, C., Ma, S., et al., 2020                                           |
|                       | Ferrara, M., Sessa, G., Fiore, M. et al., 2017                                    |
|                       |                                                                                   |

### Mps1 Inhibition

The Mps1 gene, also referred to as the TTK gene, plays an important role in the chromosome alignment at the centromere during mitosis and is required for centrosome duplication. It is a critical mitotic checkpoint protein for maintaining the integrity of chromosome segregation during mitosis. Mps1 inhibitors can be applied to various cancers when inducing CIN to trigger apoptosis. TC Mps1 12 increased misaligned and lagging chromosomes in mitotic cells as well as induced premature mitotic exit in hepatocellular carcinoma cells. The induced chromosome missegregation led to CIN. Using PARP-1 as an indicator of apoptosis, it was found that HepG2 and Hep3B cells treated with TC Mps1 12 showed significant cleavage of PARP-1 suggesting

that chromosomal instability and centrosome abnormality might lead to mitotic catastrophe (Choi et al., 2017). Martinez R et al. (2015) applied Mps1 inhibition to triple-negative breast cancer, inducing knockdown by doxycycline. This knockdown led to a dose-dependent reduction in cell viability of the HCC1806 TNBC tumor cell line, and, similar to TC Mps1 12, caused chromosome missegregation and eventual apoptosis in rapidly dividing proliferative gastrointestinal compartments. Several Mps1 inhibitors were used for knockdown including MPI-047960, PF-7006, and PF-3837. Faisal et al. (2017) provided a characterization of the oral Mps1 inhibitor CCT271850. It focused more on the spindle assembly checkpoint (SAC) function which regulates accurate chromosomal segregation by delaying anaphase until all chromosomes are properly to the spindle poles. They observed SAC abrogation resulting in a large percentage of mitotic cells with unaligned chromosomes, which then led to aneuploidy. Using PARP cleavage, they concluded that apoptotic cell death induced by CCT271850 was mediated by Mps1 inhibition. Mps1 inhibition as treatment proved to be versatile as it was shown to be effective in pancreatic cancer and malignant mesothelioma, and could be administered orally, as a small-molecule inhibitor, and through siRNA-mediated depletion (Stratford et al., 2017; Szymiczek et al., 2017; Cunningham et al., 2016). Only one study discussed the effectiveness of Mps1 inhibitors based on cell type and CIN level (Libouban et al., 2017). After testing with colorectal carcinoma, adenocarcinoma, glioblastoma, osteosarcoma, and ovarian cancer cells using NTRC 0066-0, a selective and sub-nanomolar potent inhibitor, Libouban et al. found Mps 1 inhibition was more effective in aneuploid cells with no CIN phenotype.

### Synthetic Lethality

As described in the introduction, synthetic lethality is the lethal combination of two independently viable mutations. In this review, cases where SL is used to induce CIN are looked at. Cunningham et al. (2016) examined the combination of protein phosphatase 2A (PP2A) inhibition and Polo-like kinase 1 (PLK1) overexpression in various types of cancer cells including breast, prostate, pancreatic, ovarian, and glioblastoma. Interactions of PP2A with mitotic regulators including PLK1 play a role in spindle pole separation and the mitotic checkpoint. When PLK1-overexpressing cells were treated with PP2A

inhibitors, mitotic defects, and DNA damage stress were exacerbated. The slight increase in the level of  $\gamma$ -H2AX protein within 24 hours after cantharidin treatment in PLK1-overexpressing cells suggested an impaired DNA damage response. Cunningham et al. (2016) found that levels of anti-apoptotic proteins Mcl-1 and Bcl-2 were significantly reduced, signaling the possibility of apoptosis in cells with PP2A inhibition and a high level of PLK1. Another way the PLK1 was utilized was through its depletion synergistically working with high PRC1 (Protein Regulator 1) expression which was able to repress chemo-resistant Ewing Sarcoma cells by inducing CIN and mitotic catastrophe (Li et al., 2021). Another synthetic lethal combination involved the candidate gene, GAK, which played a role in mainly mitotic spindle assembly and chromosomal alignment. The silencing of this gene was combined with F-box and WD40 repeat domain-containing 7 (FBXW7) deficiency in tumor cells. (FBXW7 is an E3 ubiquitin ligase whose frequent loss of tumor suppressor function leads to increased cellular proliferation and pro-survival pathways, cell cycle deregulation, chromosomal instability, and altered metabolism).

Through an RNAi screen, it was found that GAK, with all 8 individual siRNAs, when combined with FBXW7 depletion in parental HCT116 cells led to a statistically significant increase in cell death. Further testing revealed there was an increase in cleaved PARP levels in the FBXW7 deficient but not wild-type cells with GAK protein knockdown following RNAi. PARP cleavage was used to identify whether the cells were undergoing apoptosis following GAK RNAi. This data confirmed GAK-mediated apoptosis preferentially in the FBXW7 deficient HCT116 cells as compared with wild-type cells. Following GAK RNAi, there was also a clear induction in multipolar mitosis in the cell lines, the FBXW7 cells demonstrating a two-fold increase in tri- and multipolar spindles as well as a more severe version of this phenotype compared to wild-type cells. This suggested the combination of depletion of GAK and FBXW7 induced further CIN (Dolly et al., 2017). The synthetic lethality approaches with CIN targets discussed in the other papers included: targeting superoxide dismutase 1 (SOD1) through ammonium tetrathiomolybdate (ATTM) and 2-methoxyestradiol (2ME2) treatment in RAD54B deficient colorectal cancer cells to induce apoptosis, a combined depletion of BRCA1/2 and EXD2 to create an accumulation of broken replication forks to drive

mitotic catastrophe and cell death, and exploiting the BRCA1/2 deficiency with the small molecule drug CX-5461 to induce chromosomal breaks and structural abnormalities (Sajesh et al., 2013; Nieminuszczy et al., 2019; Xu et al., 2017). Alisertib, used to inhibit Aurora Kinase A, combined with mFOLFOZ, a combination of chemo drugs, led to similar results of aneuploidy and cell death (Goff et al., 2018). Synthetic lethality allows researchers to take advantage of previously existing mutations, such as the common deficiency of BRCA1/2, in cancer cells, and exploit them to exacerbate pre-existing CIN in the cancer cells to halt tumor growth.

## Treatment Sensitizing

The most common drugs involved with inducing chromosomal instability in this paper were paclitaxel and docetaxel, both being taxane drugs. Breast cancer cell lines with intermediate CIN were found to be sensitive to taxane treatment and anthracyclines (Vargas-Rondon et al., 2020). Scribano et al. (2021) found similar results in breast cancer cells where increasing multipolar divisions in paclitaxel resulted in higher cytotoxicity and pre-existing chromosomal instability increased sensitivity for paclitaxel in breast cancer cells. More specifically, by genetically introducing centrosome amplification using tetracycline-inducible overexpression of Polo-like kinase 4 (PLK4), the number of multipolar spindles before and after anaphase increased, as well as the death of cells treated by paclitaxel. Interestingly, Mps1 inhibition also played a role in sensitizing cancer cells. It enhanced sensitivity to radiotherapy and enhanced chromosomal instability increasing the cell line's sensitivity to microtubule-targeting drugs such as vincristine or paclitaxel (Canovas et al., 2018). Canovas et al. (2018) also found when p38a inhibition was paired with either paclitaxel or docetaxel, the levels of cell death were increased, proving that the combination of p38a inhibition with taxane-based chemotherapy increased missegregation, DNA damage, and aneuploidy in cancer cells. This all led to tumor regression. Another Mps1 inhibitor, Cpd5, increased the sensitivity KBIP-B11 cells had to paclitaxel, as well as speeding up the mitotic arrest.

The combination of paclitaxel and Cpd-5 induced severe aneuploidy and resulted in more cell death after 48 and 72 hours of drug treatment. The two drugs gave rise to more segregation defects



due to an increase in cell divisions with multipolar spindles, leading to a higher level of apoptosis (Maia et al., 2018). Docetaxel treatment efficacy, on the other hand, increased when cells were concurrently exposed to MK-5108, an Aurora Kinase A inhibitor. In 10 out of the 11 cell lines, Chinn et al. (2014) tested, concurrent application of docetaxel and MK-5108 resulted in greater sustained growth inhibition. Aside from taxane drugs, etoposide, a drug that induces DNA damage, was also discussed. In salivary adenoid cystic carcinoma, the gold-standard treatment was usually radiotherapy or surgical resection, both of which still led to local, recurring metastasis. To combat this, Bai et al. (2022) found a synthetically lethal treatment of etoposide and suppressed polymerase theta (POLQ) that demonstrated greater efficacy in halting tumor growth compared to etoposide alone. Bakhoun et al. (2015) also showed the role of CIN in radiation treatment. They found that GFP-Kif2b overexpression, suppressing numerical CIN, showed an increase in resistance to radiation treatment, likely due to cell death resultant being suppressed as a byproduct. Consequently, in a patient cohort with increased chromosome missegregation rates in mitosis, ionizing radiation had greater potency, notably with a decreased repair efficiency of double-strand breakages.

## Other Methods

Various other ways of inducing CIN to slow or halt tumor growth were presented as well. Sometimes, knockdown of PLK1 or depletion of Citron Kinase (CIT-K) was enough to initiate cell, or cytokinesis failure for the latter. Both of these methods were successfully applied in colorectal cancer cells. Oku et al. (2014) investigated small molecule inhibitors that cause mitotic chromosome segregation errors, narrowing down to Rho-associated coiled-coil kinase (ROCK), whose inhibition induced centrosome fragmentation and apoptosis in T Leukemia cells. Drugs were another viable option for inducing CIN. SM15, a cytotoxic analog, inhibited the correction of erroneous attachments of polar spindles giving rise to cell death by mitotic catastrophe and apoptotic cell death from interphase (Ferrara et al., 2017). Pt-tpy, Pt-vpym, and Pt-cpym were also drugs that induced CIN, however, instead they induced telomere aberrations which were an important dysfunction leading to CIN. Inducing chromosomal instability and cell cycle arrest through miRNA was another method discussed, specifically on how to deliver this miRNA to the site

of action (Liu et al., 2020). Having these various methods to induce CIN and eventually lead to cell death provides researchers with many paths to explore to mitigate tumor growth and limit tumor adaptability.

## Conclusion

CIN has great potential as a therapeutic target. In this review, it was found that inhibitors of CIN genes exacerbated the state of CIN in the cell lines which gave rise to apoptosis. Inducement of CIN was also commonly used with another treatment or drug, oftentimes it was the higher level of CIN that increased the treatment or drug's efficacy. The results of the studies are promising however several questions arise from a lack of current research. (1) What determines the level of CIN that a cell can survive? (2) How can we determine when that level no longer contributes to tumor adaptability but becomes lethal? (3) How can we account for these specific differences between cell and tumor types? (4) How can we determine which mechanism/pathway of CIN to target? Is there a need to identify one that can be applied to multiple cancers, or should our focus continue to be split over various targets? CIN-exploiting therapies have proven to be helpful in drug-resistant cancer developments and it remains important to continue exploiting that weakness in cancers. By continuing to approach treatments with a mindset open to combining therapies, doctors, scientists, and researchers can improve the lives and outcomes of cancer patients.

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