7. Discussion, summary and future perspectives
Chapter 7

**SUMMARY**

The main challenge of cancer therapy is to attain successful tumor clearance, while ensuring low toxicity in healthy tissues. To achieve this, differences between cancerous and non-cancerous cells must be fully understood and therapeutically exploited.

Early examples of exploiting a therapeutic window between normal and cancer cells involve the traditional cancer treatments chemo- and radiotherapy. The efficacy of these treatments is mainly based on enhanced toxicity in cancer cells owing to their uncontrolled cell growth. Since then, multiple novel strategies have been developed that target cancer cell characteristics, to improve selective eradication of these cells. These characteristics include:

1. ‘Oncogene addiction’, in which tumors have become dependent upon specific oncogenic signaling. Examples of such signaling pathways are the EGFR/map kinase signaling pathway and BCR-ABL pathways, inhibition of which causes selective lethality in cancer cells, in which these pathways are ‘driving’ tumor cell proliferation.

2. ‘Synthetic lethality’, in which tumor cells have lost the function of a specific gene which makes them reliant on a second gene or pathway for survival. The prototypical example of synthetic lethality is the synergistic effects of PARP inhibitors in tumors harboring mutations in the \( BRCA1 \) and \( BRCA2 \) genes.

3. ‘Non-oncogene addiction’, wherein tumors become reliant for their survival on genes that are not oncogenes, including certain metabolic and DNA repair pathways. An example hereof is the observation that tumors with high levels of replication stress become dependent on genome maintenance pathways to resolve DNA lesions induced during replication.

All above-mentioned modes of targeted therapies have originated from mechanistic insights of how tumor cells are re-wired, and how these processes provide therapeutically actionable vulnerabilities. Unfortunately, tumors almost invariably develop resistance to targeted agents, of which PARP inhibitors are not an exception.\(^{(1)}\) In order to prevent the emergence of treatment resistant cancer cells, it is essential to improve current synthetically lethal approaches, and to find new selective cancer killing strategies.

To this end, the aim of this thesis was to:

1. Better understand the underlying synthetically lethal mechanisms of PARP inhibitors in HR-deficient cancer cells, and to use these insights to develop new combination strategies.

2. Target replication stress to selectively kill cancer cells.

In chapter 1, a general introduction to the thesis with corresponding aims was provided. To answer the question how replication stress (RS) arises and whether it can prove to be a target for cancer therapy, a literature study was performed in chapter 2. Here, we discussed the various factors that result in RS, and provided an overview of the mechanisms that cells employ to respond to replication stress. Finally, we discussed how such response mechanisms could be targeted. Possible treatment strategies that are discussed involve: targeting of cell cycle checkpoint kinases, mitotic processing of replication intermediates, DNA structure-specific resolvases, and immune-checkpoint inhibition to treat genomically instable cancers harboring replication stress.

In chapter 3 and 4, we studied the effects of PARP inhibition in tumor cells lacking functional \( BRCA1 \) or \( BRCA2 \), and tested combination strategies to potentiate the effects of
PARP inhibitor treatment. Firstly, in chapter 3 we observed PARP inhibitors to impair replication fork stability in cancer cells that are defective for HR. We found replication-induced DNA damage to be transmitted into mitosis, and to result in the formation of chromatin bridges and lagging chromosomes during anaphase. If cells could not resolve chromatin bridges, they failed to complete cytokinesis. This directly resulted in cell death, or indirectly induced cell death as multinucleated cells were formed that were unable to support clonogenic survival. Interestingly, the presence of multinucleated cells was also observed in vivo in Brca2−/−;p53−/− and Brca1−/−;p53−/− mammary mouse tumors treated with PARP inhibitors. Lastly, we observed that upon mitotic bypass through depletion of EMI1, HR-deficient cells were rescued from PARP inhibitor-induced cytotoxicity, indicating that mitotic progression is essential for PARP inhibitor efficacy. Our data therefore shed light on the mechanism of PARP inhibitor cytotoxicity in HR-deficient cancer cells. In the future, these findings could guide us towards combination strategies to potentiate PARP inhibitors in HR-deficient tumors.

In chapter 4, we utilized our earlier insights on PARP inhibitor cytotoxicity. Since replication stress-induced mitotic aberrancies were found to be responsible for PARP inhibitor toxicity, we aimed to explore ways to potentiate PARP inhibitors. To this end, we combined PARP inhibitors with inhibitors of ATR, a checkpoint kinase with a central role in the response to replication. We observed that ATR inhibition acted synergistically with the inhibition of PARP. We found this to hold true for both BRCA2-depleted cells and Brca2 knock-out models. This synergy could not be explained by a reduction in fork stability, as ATR inhibition did not further impair PARP inhibitor-induced fork degradation. Interestingly, however, ATR inhibition induced premature mitotic entry, resulting in mitotic aberrancies and genomic instability. In line with these data, delaying mitotic entry by CDK1 inhibition prevented the formation of both chromatin bridges and lagging chromosomes, as well as genomic instability. Together, these data show that the effects of ATR inhibition in potentiating PARP inhibitors are related to a role for ATR in regulating cell cycle control.

It is well established that enhanced expression of oncogenes is observed in numerous cancers, and that high levels of specific oncogenes induce replication stress. In chapter 5, we tested whether replication stress can be selectively targeted in cancer cells harboring high oncogene levels. We first developed models in which we could induce replication stress. Specifically, we engineered RPE-1 TP53WT and TP53mut cells with doxycycline-inducible constructs of Cdc25a and Cyclin E1. As expected, overexpression of Cdc25a and Cyclin E1 resulted in slower replication. Furthermore, enhanced expression of oncogenes increased the sensitivity to inhibitors of the ATR and WEE1 checkpoint kinases. Furthermore, enhanced expression of Cdc25a and Cyclin E1 resulted in more chromatin bridges and lagging chromosomes in mitosis. Interestingly, in conditions where oncogene expression enhanced sensitivity to ATR and WEE1 inhibition, treatment with ATR and WEE1 inhibitors exacerbated mitotic aberrancies. Conversely, in cell lines in which oncogene expression did not lead to ATR and WEE1 inhibitor sensitivity, we did not see an enhancement of mitotic aberrancies. These findings were confirmed using live-cell microscopy, which again showed
induction of mitotic abnormalities upon ATR and WEE1 inhibition in cells overexpressing oncogenes. These findings suggest that the abnormalities seen in mitosis are responsible for drug sensitivity. Combined, our data indicate that oncogene-induced replication stress causes mitotic aberrancies, and that cells overexpressing Cyclin E or Cdc25A can be targeted using ATR and WEE1 inhibitors.

In Chapter 6, we investigated whether Rif1, a down-stream target of 53BP1, retains its DNA damage response (DDR) function during mitosis. We observed no recruitment of Rif1 to irradiation-induced damage foci during mitosis. Instead, we uncovered that Rif1 localized to so-called ultra-fine DNA bridges (UFBs) in anaphase. Additionally, we found that Rif1 recruitment to UFBs depended on the DNA translocase PICH, and was independent of 53BP1 or BLM. Rif1 was shown to facilitate the resolution of UFBs. Furthermore, loss of Rif1 induced nucleoplasmic bridges, RPA70-positive UFBs as well as nuclear bodies in the following G1 phase. Thus, we report a previously undescribed function of Rif1 in mitosis, where it plays a role in resolving UFBs thereby ensuring genomic integrity.

**DISCUSSION and FUTURE PERSPECTIVES**

**Replication stress results in mitotic aberrancies**

In chapter 3, we aimed to elucidate the molecular mechanisms underlying PARP inhibitor cytotoxicity, and to identify possible new combination strategies. We observed high levels of replication stress in HR-deficient cancer cells following inhibitor treatment. Specifically, we observed compromised fork stability and increased FANCD2 foci during replication. Surprisingly, we found DNA lesions to remain unresolved in S or G2 phase and to be propagated into mitosis. Ultimately, these unresolved DNA lesions resulted in chromosome segregation defects, cytokinesis failure and cell death. Our findings reiterated that replication lesions can be transmitted into mitosis.

Surprisingly, our data also pointed towards progression through mitosis, with replication stress and accompanying mitotic aberrancies, as a mechanism of PARP inhibitor cytotoxicity. Although we focused on the mitotic transmission of PARP inhibitor-induced lesions, it is likely that other replication-induced DNA lesions can also be transmitted into mitosis, and thereby affect cell fate. A number of interesting unanswered questions remain, and are addressed below.

What type of DNA lesions cause chromatin bridges and lagging chromosomes?

In chapter 3, we learned that the presence of DSBs alone does not explain the observed segregation defects in mitosis. Indeed, cisplatin treatment induced a striking increase in gamma-H2AX, relative to PARP inhibition in BRCA2 depleted cells. However, less chromatin bridges were observed with this treatment. Another interesting finding was that interference with PARP function per se was not required for the generation of mitotic bridges, as siRNA depletion of PARP failed to induce chromatin bridges. Instead, the trapping of PARP, where the PARP protein is non-covalently bound to DNA, is likely required to induce these effects. These observations are in line with the trapping capacity/potency of PARP inhibitors to be correlated with increased cell killing potential.

Based on our observations and those of others, we propose a model wherein trapped PARP molecules
prevent successful replication of DNA. As a consequence, DNA is not timely replicated, causing cells to enter mitosis with under-replicated regions. Subsequently, under-replicated regions of DNA induce chromatin bridges. An important aspect of this model is that the DNA lesions should go unnoticed by the G$_{2}$/M cell cycle checkpoint, preventing cells repairing these lesions. Indeed, we found that the reduction of PARP inhibitor-induced fork degradation partly rescued chromatin bridge formation, further strengthening our model. Upon replication fork stalling, newly synthesized DNA is degraded by nucleases, ultimately resulting in more under-replicated regions. However, we found that combined PARP and ATR inhibition exacerbated mitotic segregation defects by accelerated mitotic entry, while rescuing PARP inhibitor-induced fork degradation. Possibly, the decrease in fork degradation observed by PARP and ATR inhibition could result in less under-replicated DNA and would therefore be able to slightly reduce chromatin bridge formation as seen by inhibition of MRE11. However, the excessive premature mitotic entry, and accompanying decrease in replication, would ultimately result in a net increase of under-replicated regions thereby increasing instead of decreasing chromatin bridge formation. Indeed, delaying mitotic entry through inhibition of CDK1, led to reduced chromosome segregation defects.\cite{5}

These findings show that, following PARP inhibitor treatment, HR-deficient cells require time to finish replication prior to mitotic entry. Taken together, these studies point to a model in which chromatin bridges, and possibly lagging chromosomes, are formed when cells fail to complete DNA replication in a timely fashion.

\textbf{‘Are mitotic bridges specific for PARP inhibitors in HR-deficient cells?’}

If our model as explained above is true, other treatments that impair DNA replication or induce premature mitotic entry would likely also induce chromatin bridges. In line with this hypothesis, DNA cross-linking agents like cisplatin and oncogene-induced replication stress (chapter 5) also enhanced chromatin bridges and lagging chromosomes, albeit to different degrees. The observed lower amounts of DNA lesions upon cisplatin treatment could likely be attributed to robust G$_{2}$/M checkpoint activation, in contrast to a very minor G$_{2}$/M checkpoint activation in response to PARP inhibition.

\textbf{‘Why do ATR and PARP inhibition act antagonistically on fork degradation?’}

Possibly, our finding that PARP inhibitor-induced replication fork degradation is reversed by ATR inhibition can be explained by the shared role of PARP and ATR in regulating replication fork reversal.\cite{6,7}

Indeed, reversed forks are the assumed substrate of the nucleases known to degrade stalled forks. Prevention of fork reversal would thus prevent fork degradation from occurring.\cite{8-11}

Although similar findings were recently discovered by others, the underlying mechanism of how ATR affects fork reversal is incompletely understood and warrants further research.\cite{12}

\textbf{‘What is the effect of PARP inhibition on DNA replication?’}

Initially, PARP inhibition was suggested to lead to an accumulation of single-strand DNA breaks (SSBs), which would be converted into toxic double-strand DNA breaks (DSBs) in replicating cells.\cite{13,14} The dependency of cells to repair replication-born DSBs through HR, was thus suggested as a
mechanism underlying the observed synthetic lethality of PARP inhibition in HR-defective cancer cells. More recently, the PARP trapping capacity of PARP inhibitors was demonstrated to correlate with the cytotoxicity of PARP inhibitors in HR-deficient cells. 

This observation suggests that trapped PARP-DNA complexes are a source of DNA lesions, rather than the accumulation and subsequent conversion of SSBs into DSBs.

In a very recent paper, PARP inhibition was found to result in faster replication. This finding is in clear contrast with the dogma that PARP inhibition impairs replication. In contrast however, Mendoza et al also described PARP inhibitor-treated cells to divide slower and be enriched in late S-phase when difficult-to-replicate regions are replicated. This finding in the same paper, is in line with our findings in chapter 4 and indicates PARP inhibition to slow cell cycle progression. Therefore, it is possible that upon PARP inhibition, general replication kinetics are accelerated, whereas replication at difficult-to-replicate regions is impaired. Subsequently, this impairment of replication results in more under-replicated regions in mitosis with consequent chromatin bridge formation. Furthermore, it is important to realize that there are important methodological differences in the assessment of replication speed. Instead of treating cells with PARP inhibitors during incubation of cells with synthetic nucleotides, cells were pre-treated with PARP inhibitors, which were subsequently washed off prior to synthetic nucleotide incorporation. Using this set-up, the impact of PARP inhibition on replication restart instead of ongoing replication dynamics is measured, which greatly affects the interpretation. Indeed, release of cells treated with PARP inhibitor in late S-phase is likely to induce faster replication rates, but does not preclude a role for PARP inhibition in causing under-replication.

‘Why do under-replication DNA regions not activate the G\textsubscript{2}-M checkpoint?’

Another interesting finding is that under-replicated regions do not appear to activate the G\textsubscript{2}-M checkpoint, in contrast to DSBs. Indeed, cells suffering from replication stress are found to enter mitosis, while they still are in the process of replicating their DNA. G\textsubscript{2}-M checkpoint arrest can be initiated by ATM/Chk2 or the ATR/Chk1 route. Under-replicated regions are likely not recognized via the ATM/Chk2 route as they are not clear DNA ends. However, it is surprising that ATR-Chk1 does not induce a G\textsubscript{2}-M arrest, since under-replicated regions consist of single stranded DNA stretched which are known to activate ATR. In chapter 4 we indeed observe ATR activation upon PARP inhibition in BRCA2-depleted cells. Possibly, ATR is either not activated to a sufficient extent or is in some way prevented from inducing G\textsubscript{2}-M arrest. The former explanation is in line with findings in chapter 4 where in BRCA2 depleted cells, a low dose of PARP inhibitor induces strong levels of replication stress yet no G\textsubscript{2}-M arrest. In contrast, a much higher concentration of PARP inhibitor did induce G\textsubscript{2}-M checkpoint arrest. The precise answer why cells enter mitosis with under-replicated regions, that impair genomic integrity and may even induce cell death, is currently not understood and warrants further research.

Consequences and processing of mitotic DNA damage

When mitotic DNA damage is not resolved timely, chromatin bridges or ultrafine bridges can be formed. Whereas an increase in the formation
of DNA bridges could be caused by mechanisms discussed above, an increase in DNA bridges could also be caused by a reduction in their resolution. This was shown to hold true both for bulky chromatin bridges and UFBs. Indeed, upon the induction of replication stress by depletion of BRCA2, loss of the resolving nuclease MUS81 was reported to cause more chromatin bridges.\(^{(19)}\)

In chapter 6, we observed that loss of Rif1, in addition to PICH and BLM, was involved in UFB resolution. Therefore, while we have gained important insights into the complex mechanisms that cause the formation and resolution of DNA bridges, there are still many important questions unanswered for which more research is required to fill the gaps.

In addition to gaining a better understanding of how mitotic DNA lesions arise, it is key to grasp the consequences of such lesions. In chapters 3–7, we showed that a failure to resolve chromatin bridges or UFBs can result in damaged DNA in daughter cells. Such genomic abnormalities manifest as micronuclei, cytokinesis failure and cell death in the case of bulky chromatin bridges. Exactly how mitotic DNA damage is able to trigger cell death is currently unclear. One possibility involves differential wiring of the apoptosis machinery during mitosis. Specifically, it could be that apoptosis is activated at a lower threshold following mitotic entry. Evidence for such re-wiring has previously been presented. Mitotic kinases, notably CDK1, were reported to modify both pro- and anti-apoptotic proteins, including Bcl-XL, Bcl-2, Mcl-1 as well as several caspases.\(^{(20)}\) However, mitosis-specific modifications of these components of the apoptosis machinery appeared to make cells more resistant rather than susceptible to apoptosis. Additionally, some of the reported pro-apoptotic effects during mitosis are only instigated during prolonged mitotic spindle checkpoint arrest, and therefore do not necessarily reflect the situation of cells entering with unresolved DNA lesions.\(^{(21)}\)

Another possibility involves replication-mediated joint DNA molecules being transformed into more toxic DNA lesions, such as DSBs, during mitosis. Indeed, replication-mediated DNA lesions that remain unresolved until mitotic entry are acted upon by the MUS81/EME nuclease,\(^{(3)}\) probably as part of a complex of multiple structure-selective nucleases.\(^{(22)}\) Processing of DNA lesions does not necessarily lead to an accumulation of toxic DNA structures, since nuclease-mediated processing of mitotic DNA lesions is an initial step in their resolution. However, PARP inhibitor treatment in the context of HR deficiency might lead to an overwhelming load of DNA lesions, beyond the capacity of mitotic repair. Alternatively, efficient processing of mitotic DNA lesions may be hampered in cells, in which HR and PARP are both inactivated. Additionally, physical tension exerted onto chromatin bridge DNA by spindle force could be responsible for cell death, either directly or through the generation of DSBs. Alternatively, cytokinesis failure and consequent formation of multinucleated cells might constitute another way through which cells could eventually generate toxic DNA lesions which lead to cell death.\(^{(23)}\) Indeed, in our study or reports of others, multinucleated cells that arise after failed cytokinesis failed clonogenic outgrowth and eventually died.\(^{(24,25)}\)

Likely, multiple of the abovementioned mechanisms occur in parallel to instigate cell death in the situation of mitotic DNA damage. This notion is supported by our pleiotropic phenotypes: whereas subsets of PARP inhibitor-treated cells die prior to completing mitosis, others fail to undergo
cytokinesis, leading to multinucleation and subsequent cell death. Notably, a failure to resolve UFBs does not seem to frequently result in severe phenotypes including multinucleation and cell death. Rather, UFBs resolution failure was shown to induce micronuclei and 53BP1 bodies, which do affect genome integrity, but do not potently induce cell death. Understanding the nature of the apoptotic cues in mitosis will prove pivotal for exploiting this knowledge to potentiate therapeutic strategies relying on mitotic catastrophe for anti-cancer cytotoxicity.

The role of mitotic transmission of DNA lesions in cancer cell fate

Mitotic catastrophe is frequently thought to be responsible, at least partly, for cytotoxicity of current cancer treatments. However, it has proven difficult to identify whether mitotic progression and accompanying mitotic aberrancies are the cause or merely a consequence of cell death. By using live cell microscopy in chapter 3 and 5, we observed consequences of mitotic defects in real-time. This provided a strong association between chromatin bridges and acute cell death, and indirect induction of cell death through the formation of multinucleated cells. Furthermore, mitotic chromatin bridges induced by oncogene overexpression were only observed in cells that underwent cell death later on. Regardless, these observations provide associations rather than causal relationships.

We attempted to resolve this issue by using -to our knowledge for the first time- forced mitotic bypass induced by EMI1 depletion as a tool to assess the contribution of mitotic progression to cell death. Specifically, we implemented this tool to test the contribution of mitotic progression to the cytotoxicity of PARP inhibitors in HR-deficient cells. Our data showed that depletion of EMI1 efficiently induced mitotic bypass, as judged by the appearance of cells with >4n DNA content. Simultaneously, EMI1 depletion rescued PARP inhibitor cytotoxicity. In this context, it is important to realize that EMI1 may have additional roles, and might alter the cellular response to DNA damage through additional mechanisms. For instance, it would be interesting to see what the effect is of introducing F-box domain mutations of EMI1 in BRCA2-deficient cells. Also, it would be interesting to compare the effects of EMI1 depletion in BRCA1-deficient versus BRCA2-deficient cells, since resistance to PARP inhibitors has previously been shown to have different mechanisms in these different genotypes. Notably, the majority of secondary mutations (e.g. in 53BP1, REV7, RIF1) that restore HR in BRCA1-deficient cells, where not able to restoring HR in BRCA2-deficient models.

Likewise, our approach of forced mitotic bypass could be used to test the influence of mitotic progression on other cytotoxic agents. To this end, it would prove insightful to test the effects of EMI1 depletion in the context of treatment with cytotoxic drugs that interfere with DNA replication, and are known to induce cell death acutely. Such treatments should still be effective or increasingly effective upon EMI1 depletion, since EMI1-depleted cells are still able to replicate. For instance, using live cell microscopy a drug panel could be tested with or without functional EMI1 to assess the role of mitotic progression in the cytotoxicity of these agents.

Replication stress-induced mitotic aberrancies and cancer treatment

We have established that chromosome miss-segregation can act as a mechanism...
of cytotoxicity in cancer therapy. An important next step is to assess the possible implications for cancer treatment. Already, our observation that mitotic defects and progression through mitosis was underlying PARP inhibitor cytotoxicity in chapter 3, was the basis to test a rational combination strategy in chapter 4. Specifically, we found that inhibition of the replication stress response kinase ATR acts synergistically with PARP inhibitors in killing HR-deficient cancer cells. This synergy was caused by premature mitotic entry, resulting in enhanced chromosome segregation defects and cell death. Similarly, in chapter 5, cells harboring oncogene-induced replication stress were selectively killed through induction of mitotic aberrancies upon inhibition of ATR or WEE1. It might thus be interesting to test whether tumors that overexpress Cyclin E1, or other replication stress-inducing oncogenes, show sensitivity to ATR or WEE1 inhibitors. This is relevant, as ATR or WEE1 inhibitors are currently being tested in clinical trials, and development of selection criteria for patient inclusion is warranted. Of specific interest in this context are Cyclin E1-overexpressing tumors, including triple-negative breast cancers and high-grade ovarian cancers, because these tumors lack actionable targets, and overall these patients have a poor prognosis. Currently, clinical trials are ongoing to select patients with Cyclin E1-overexpressing tumors for treatment with WEE1 inhibitors (Clinicaltrials.gov NCT03253679). Since WEE1 and ATR inhibitors seem to trigger cell killing in cells harboring replication stress, combining PARP with WEE1 inhibitors could act synergistically in HR deficient models, as was seen with PARP and ATR inhibition in chapter 4.

To further improve upon the above-mentioned strategies, in which mitotic aberrancies are induced to trigger cell death, we propose three mechanisms which warrant further investigation:

1. Replication stress could be therapeutically enhanced by agents that interfere with DNA replication (e.g. cisplatin) to induce a further overload of under-replicated regions in mitosis. Alternatively, this approach could result in replication catastrophe in S-phase, and may induce mitotic catastrophe through chromosome miss-segregation, or delayed cell death after induction of multinucleation.

2. Aggravation of replication stress-induced mitotic aberrancies by using tubulin poisons (e.g. taxanes), or through therapeutic inactivation of resolvase pathways (e.g. GEN1 and MUS81-EME1). However, while likely, it is currently unclear whether the increased cell death seen upon enhancing chromosome segregation defects are due to enhanced mitotic catastrophe. Therefore, more mechanistic insight is required. Additionally, it will be insightful to test the effects of inhibiting multiple resolvase pathways in combination with different replication stress-inducing agents.

3. Immune-checkpoint blockade of cancers that present with high levels of lagging chromosomes. For a long time, it is known that lagging chromosomes or unresolved DNA breaks can give rise to micronuclei. The nuclear membranes that surrounds micronuclei frequently rupture. As a result, micronucleus DNA is released into the cytoplasm, where it can activate the pattern-recognition receptor cyclic GMP–AMP synthase (cGAS). Subsequently, cGAS induces pro-inflammatory signaling via the stimulator of interferon genes (STING). Interestingly, mouse tumors were successfully cleared by
the immune checkpoint inhibitor anti-PD-L1 in cells that had micronuclei and STING signaling, but not in tumors in which STING was inactivated. While preliminary, these data indicate that lagging chromosomes activate the cGAS-STING pathway, resulting in tumor clearance following PDL-1 inhibitor treatment. These results warrant the analysis of immune checkpoint inhibitor combination treatments, in which cytoplasmic DNA is induced through WEE1, ATR or PARP inhibition.

CONCLUDING REMARKS

A better understanding of the mitotic ‘death cues’ that underlie replication stress-induced mitotic aberrancies will aid in the development of improved cancer treatments. Although mitotic catastrophe in response to DNA damage induction has been reported for decades, molecular cues that are responsible for mitotic catastrophe remain elusive, and additional research is warranted to uncover the mechanisms underlying this phenomenon.

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