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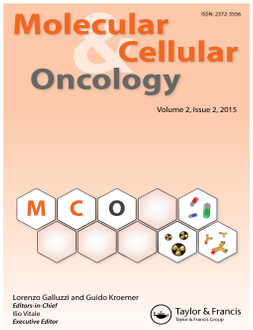

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AUTHOR'S VIEW

Never tear us a-PARP: Dealing with DNA lesions during mitosis

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ABSTRACT

Tumors defective in homologous recombination (HR) are highly sensitive to poly ADP-ribose polymerase (PARP) inhibition, however the cell biological mechanisms underlying this synthetic lethality remain elusive. We recently identified that PARP inhibitor-induced DNA lesions persist until mitosis, subsequently causing mitotic chromatin bridges, multinucleation and apoptosis. Here, we discuss the implications of these findings.

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BRCA1 and BRCA2 are essential in achieving error-free repair of DNA double stranded breaks (DSBs) through homologous recombination (HR). Mutations in HR genes, therefore, result in defective genome maintenance and predispose to tumourigenesis, primarily in breast and ovarian tissues. The resulting HR-defective tumors appeared highly sensitive to inhibitors of PARP,[1,2] resulting in the successful clinical development of PARP inhibitors for patients with BRCA1/2 mutant cancers. Unfortunately, however, patients often develop resistance to PARP inhibitors and relapse. To identify possible new combination strategies that improve PARP inhibitor therapy, molecular insight into the mechanism of PARP inhibitor cytotoxicity in HR-deficient tumor cells is required.

Exactly how cancer cells with defective HR die following PARP inhibition remains incompletely clear. Initially, loss of PARP was reported to cause single stranded DNA break (SSB) accumulation, owing to the role of PARP in base excision repair (BER).[1,2] High levels of SSBs would then, through the course of DNA replication, lead to DSB formation, which in HR-deficient cells ultimately results in cell death. However, the role of PARP inhibitors in BER and ensuing SSB accumulation is debated, suggesting that other functions of PARP and HR genes are involved in cell death induction.[3] Specifically, HR components as well as PARP were found to have important functions in the protection and restart of replication forks.[4,5]

We recently showed that HR-deficient cancer cells indeed have compromised fork stability when treated with PARP inhibitors, and accordingly present with high levels of FANCD2 foci during replication.[6] Surprisingly, these DNA lesions appear to remain unresolved in S or G2 phase, and instead are propagated into mitosis, resulting in chromatin bridge formation in anaphase.[6] Of note, using live cell imaging we observed that PARP inhibitor-induced chromatin bridges led to multinucleation and cell death.

Our findings reiterate that replication lesions can be transmitted into mitosis.[7] Although we focused on the mitotic transmission of PARP inhibitor-induced lesions, it is highly likely that numerous other replication lesions can ultimately be transmitted into mitosis, and through this phenomenon affect cell fate (Fig. 1). In this Author's View, we will further discuss our findings and implications thereof.

Consequences and processing of mitotic DNA damage

Exactly how mitotic DNA damage triggers cell death is unclear. One possibility involves differential wiring of the apoptotic machinery during mitosis, or that apoptosis is activated at a lower threshold following mitotic entry. Indeed, mitotic kinases, notably Cyclin-dependent kinase-1 (Cdk1), were reported to modify pro- as well as anti-apoptotic proteins, including Bcl-X_L, Bcl-2, Mcl-1 and several caspases.[8] However, multiple mitosis-dependent modifications of the apoptosis machinery make cells 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.

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,[7] probably as part of a complex of multiple structure-selective nucleases.[9] 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 with inactivated HR and PARP.

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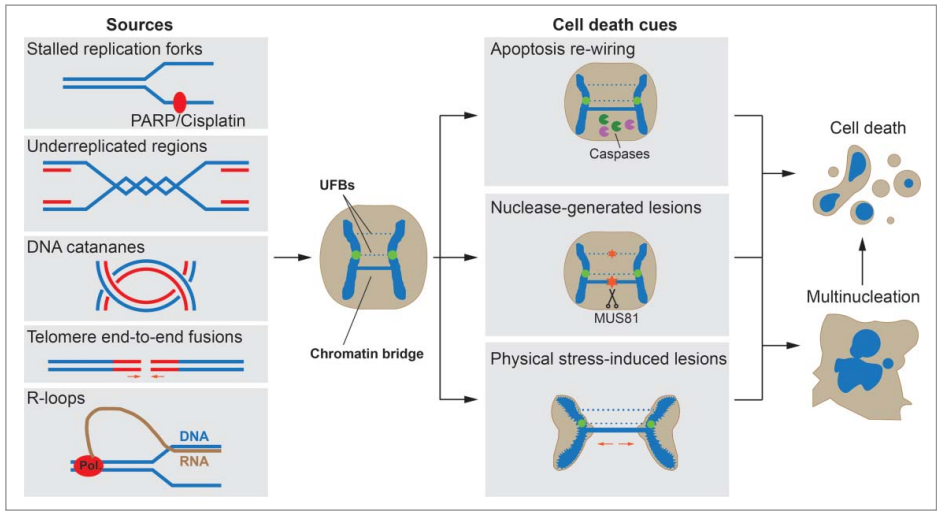

Figure 1. Dealing with unresolved DNA lesions during mitosis. In cancer cells, overexpression of oncogenes, but also treatment with PARP inhibitors or other cytotoxic agents, causes DNA replication lesions, including stalled replication forks. In addition, replication stress can leave some regions underreplicated and results in DNA catananes. Alternatively, telomere artition can lead to end-to-end fusions, and the replication machinery (DNA polymerases, 'Pol') can collide with DNA:mRNA hybrid molecules (R-loops). When replication-mediated lesions remain unresolved until mitosis, they result in the formation of ultra-fine bridges (UFBs) and bulky chromatin bridges. If unresolved, DNA bridges can cause multinucleation and cell death. Potential 'cell death cues' have been described, but their molecular wiring remains largely elusive.

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 cells could eventually generate toxic DNA lesions which lead to cell death.[10]

Likely, multiple of the abovementioned mechanisms occur in parallel to instigate cell death. A notion which is supported by our finding that subsets of PARP inhibitor-treated cells die prior to completing mitosis, whereas others fail to undergo cytokinesis, leading to multinucleation and subsequent cell death. Understanding 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, as least partly, for cytotoxicity of current cancer treatments. Our report, to our knowledge, for the first time uses forced mitotic bypass induced by depletion of Early Mitotic Inhibitor-1 (EMI1), as a tool to assess the contribution of mitotic progression to cell death. We implemented this tool to test the contribution of mitotic progression to the cytotoxicity of PARP inhibitors in HR-deficient cells. However, this approach can be applied similarly to test other agents. We showed that, for instance, cisplatin, also induces mitotic chromatin bridges in a HR-deficient cancer cells.[6] Additionally, oncogene-induced replication stress also results in under-replicated lesions, and it would therefore be interesting to see whether mitotic catastrophe is observed in tumors with oncogene-induced replication stress. Later findings would fit a model in which mitotic catastrophe presents a possible mechanism clearing cells upon chromosome missegregation, genetic instability and tumourigenesis. Since the cytotoxicity of PARP inhibitors in HR-deficient cells is promoted by mitotic progression, it is interesting to speculate that cancer cells harboring DNA replication lesions maintain viable by arresting the cell cycle. Targeting of DNA damage checkpoint kinases, including WEE1, could be used to abrogate cell cycle arrest, push PARP inhibitor-treated cells into mitosis, and promote cell death.

In summary, a better understanding of the mitotic 'death cues' that underlie the cytotoxicity of PARP inhibitors, and possible many other anti-cancer agents, will aid in directing 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.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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