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The interplay of DSB repair and cell cycle control

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The DNA damage response pathways involve processes of double-strand break (DSB) repair and cell cycle checkpoint control. The coordinated interplay of these mechanisms is crucial for the maintenance of the genomic integrity as the progression through critical cell cycle phases with unrepaired DSBs can promote chromosome aberration formation.
We recently demonstrated that the G1/S and G2/M checkpoints both have limitations. The G1/S checkpoint is very sensitive to DSBs and can exclude cells harboring a single DSB from the actively proliferating population. However, full G1/S checkpoint induction after ionizing radiation (IR) is a slow process requiring about ~4 h. Consequently, a time window is provided in which many cells enter S phase with high numbers of unrepaired DSBs, progress through S phase and exhibit elevated numbers of DNA damage foci and chromosome breaks in G2 and mitosis. Live cell imaging provided the opportunity to consolidate these findings by following single cells throughout S phase. Here, the possibility to track single GFP-53BP1 foci provided new insight into the dynamics of DSB repair and the formation of new DSBs in the context of replication.
In contrast to the G1/S checkpoint, the G2/M checkpoint is initiated very rapidly but cells are released from G2 arrest prematurely before DSB repair is completed. Since DSB repair in G2 involves HR processes we speculated that cells enter mitosis with unresolved HR intermediates like Holliday Junctions. There is increasing evidence that in mitosis such structures can be resolved by Mus81- and Gen1-dependent mechanisms. However, using immuno-fluorescence microscopy, chromosomal approaches as well as live cell imaging technology we observed that some breaks are transferred into telophase and the subsequent G1 phase. We observed that cells which were irradiated in G2 and divided in the presence of unrepaired DSBs fail to efficiently repair the breaks in G1. This observation may suggest that structural alterations occur at the DSB ends during mitosis which render the breaks more difficult to repair in G1. We are currently elucidating the molecular processes which occur during Holliday Junction resolution in mitosis.
In summary, both the G1/S and G2/M checkpoints have serious limitations, albeit different in nature, which likely contribute to the development of genomic instability.

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