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A direct role for HIPK2 in homology-directed DNA repair and the regulation of PARP inhibitor sensitivity

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Our cells are under continuous attack by exogenously and endogenously evoked DNA damage resulting in different types of DNA lesions. DNA double-strand breaks (DSBs) are the most deleterious type of genome damage and are in principle repaired by two pathways, non-homologous end-joining (NHEJ) and homologous recombination (HR). Homology-directed repair of DSBs efficiently counteracts genome instability and cancer formation. Moreover, cancer cells frequently show defects in DNA repair and particularly HR-deficiency of cancer cells can be therapeutically exploited since such cells are sensitized to poly(ADP-ribose) polymerase inhibitor (PARPi) treatment.

Work from us and others has established the tumour suppressor Homeodomain Interacting Protein Kinase 2 (HIPK2) as a central player in DNA damage-induced cell fate control. Upon DSB induction by ionizing radiation (IR), HIPK2 is activated by a mechanism involving checkpoint kinase ATM and site-specific HIPK2 autophosphorylation, and triggers cell death through the p53 pathway. Although the cell death regulatory function of HIPK2 in response to irreparable DNA damage is well-established, its function upon repairable DNA damage remains largely obscure.

Intriguingly, our unpublished data identified a direct role for HIPK2 in homology-directed DSB repair. We found that HIPK2 forms a protein complex with DSB repair factors BRCA1 and 53BP1, and physically accumulates at IR-induced DSBs in an ATM-regulated manner. DSB reporter assays and Sister chromatid exchange analysis revealed an essential role for HIPK2 in DSB repair by HR. Mechanistically, we found that HIPK2 binds and site-specifically phosphorylates BRCA1, thereby regulating BRCA1 protein stability. Accordingly, HIPK2 depletion or pharmacological inhibition of HIPK2 results in declined BRCA1 levels and potentiates IR sensitivity and PARPi toxicity in BRCA1-proficient cells. Together, our results identify a direct role of HIPK2 in HR repair, and suggest HIPK2 inhibition as novel strategy to sensitize BRCA1-proficient cancer cells to PARPi.

Keywords:
DNA repair; homologous recombination; PARP inhibitor; HIPK2