A unified mechanism for PARP inhibitor-induced PARP1 chromatin retention at DNA damage sites in living cells

Poly(ADP-ribose) polymerase (PARP) inhibitors (PARPis) not only suppress PARP1 catalytic activity but also prolong its association to damaged chromatin. Here, through live-cell imaging, we quantify the alterations in PARP1 dynamics and activity elicited by seven PARPis over a wide range of concentrations to deliver a unified mechanism of PARPi-induced PARP1 chromatin retention. We find that gross PARP1 retention at DNA damage sites is jointly governed by catalytic inhibition and allosteric trapping, albeit in a strictly independent manner-catalytic inhibition causes multiple unproductive binding-dissociation cycles of PARP1, while allosteric trapping prolongs the lesion-bound state of PARP1 to greatly increase overall retention.

Importantly, stronger PARP1 retention produces greater temporal shifts in downstream DNA repair events and superior cytotoxicity, highlighting PARP1 retention, a complex but precisely quantifiable characteristic of PARPis. Our approach can be promptly repurposed for interrogating the properties of DNA-repair-targeting compounds beyond PARPis.