New Mechanistic Insights into PARP1-mediated DNA Damage Response

PARP1 is a major poly(ADP-ribose) transferase that plays an important role in DNA damage repair. PARP1 has been shown to be a DNA single-strand and double-strand break sensor protein that helps rapidly recruit many downstream DNA repair proteins to damaged DNA sites in a poly(ADP-ribose) dependent manner. Here I will talk about a new mechanism of PARP1-mediated DNA damage response. We recently identified and provided the structural evidence that PARP1 interacts with Timeless - a classic subunit of the replication fork protection complex. We demonstrated that rapid and transient accumulation of Timeless at laser-induced DNA damage sites requires PARP1 but not poly(ADP-ribose)ylation and that Timeless is co-trapped with PARP1 at DNA lesions upon PARP inhibition. Furthermore, we show that Timeless and PARP1 interaction is required for efficient homologous recombination repair. Our study provides implications for understanding the mechanism of the clinically active PARP inhibitors and raise a new possibility to develop alternative PARP1-targeted therapy for cancer treatment.