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Regulation of PARP1 activity by its protein partners

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Poly (ADP-ribose) polymerase 1 (PARP1) is catalysis poly(ADP-ribose) (PAR) at DNA damage sites to recruit DNA repair factors. PARP1 is playing key role in regulation of multiple processes in high eukaryotes and interacts with DNA and RNA binding proteins. Among proteins relocated on damaged DNA, the nuclear RNA-binding protein FUS is one of the most abundant, raising the issue about its involvement in DNA repair. The reconstituted PARP-1/PAR/damaged DNA system was analyzed by atomic force microscopy in the presence of FUS. We demonstrated FUS recruitment at DNA damage sites via PAR binding, and observed assembly of dynamic compartments in which damaged DNA is concentrated (Singatulina et al., Cell Rep, 2019; Sukhanova et al., IJMS, 2021). FUS contains disordered prion-like domains and its interaction with PAR is a driving force in formation of membrane less compartments by liquid-liquid phase separation. We anticipate that FUS facilitates DNA repair through the transient compartmentalization of damaged DNA. This process permits to select damaged DNA from undamaged one and attracts DNA repair proteins. The hydrolysis of PAR by PARG dissociates these compartments, which in turn promotes the turnover of DNA repair in cell. Y-box-binding protein 1 (YB-1) is a multifunctional positively charged protein that interacts with DNA or RNA and poly(ADP-ribose) (PAR). YB-1 contains a disordered Ala/Pro-rich N-terminal domain (A/P domain), a cold shock domain (CSD) and an intrinsically disordered C-terminal domain (CTD) containing several clusters of positively and negatively charged amino acid residues. The C-terminal domain plays a critical role in YB-1 binding to nucleic acids, including polymer poly(ADP-ribose). YB-1 was shown functionally interacts with poly(ADP-ribose) polymerase 1 (PARP1) which catalyzes the synthesis of a poly(ADP-ribose) and protein poly(ADP-ribosyl)ation, including auto-poly(ADP-ribosyl)ation, during genotoxic stress. It was shown by us that Yb-1 stimulates PARP1 activity (Naumenko et al., Biomolecules, 2020). We studied the functional role of disordered C-terminal domain of YB-1 in the regulation of poly(ADP-ribose) synthesis by PARP1 *in vitro*. We demonstrate that the PARP1-dependent poly(ADP-ribose) synthesis rate is increased in the presence of YB-1 and is strongly controlled by the interaction of CTD (YB-1) with poly(ADP-ribose). Moreover, we show that both decrease of chain length or increase of branching frequency of poly(ADP-ribose) have an effect on the poly(ADP-ribose) binding affinity of YB-1 and YB-1-mediated stimulation of PARP1 enzymatic activity. These findings provide interesting insights into the regulation of PARP1 activity with poly(ADP-ribose) binding proteins containing charged amino-acid residues in disordered domains (Naumenko, Biomolecules, 2021). YB-1 is expressed in malignant tumors and may influence sensitivity to anticancer drugs. Therefore, our study shed light on the role of PARP1 and RNA binding proteins containing prion-like domains in stimulation of PARP1 activity and in the formation of dynamic liquid compartments, which can facilitate DNA repair by concentrating damaged DNA and repair proteins.

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