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Regulation of poly(ADP-ribose) polymerase 1 activity by Y-box-binding protein 1

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Motivation and Aim: The poly (ADP-ribose) polymerase 1 (PARP1) is considered as one of the key regulators of mammalian DNA damage response. PARP1 catalyzes synthesis of poly(ADP-ribose) (PAR) by transferring of ADP-ribose units from NAD^+ onto target proteins resulting in their mono- or poly(ADP-ribosyl)ation (MARylation or PARylation). It is currently believed that RNA-binding proteins can be involved in the DNA repair and regulation of PARP1's functions in cell responses to genotoxic stress. One of these proteins is the multifunctional Y-box binding protein (YB-1). YB-1 is considered as PARP1-interacting partner and is a target for the covalent PARylation both *in vitro* and *in vivo*.
Methods and Algorithms: We studied the YB-1-dependent regulation of PARP1 activity *in vitro* using biochemical approaches and single molecular method, such as atomic force microscopy.
Results and Conclusion: In the present study, we analyzed the regulation of PARP1 activity with YB-1 via its ability to bind PAR (damaged DNA) and be trans-PARylated. YB-1 consists of an alanine/proline-rich (AP) domain, a cold-shock domain (CSD), and an unstructured C-terminal domain (CTD) carrying clusters of negatively and positively charged residues. An unstructured C-terminal part of YB-1 involved in an interaction with PAR behaves similarly to full-length YB-1 in modulation of PAR synthesis, indicating that both DNA and PAR binding are involved in the regulation of PARP1 activity by YB-1. To determine molecular mechanism by which YB-1 regulates PARP1 activity, we generated YB-1 mutants which lacks clusters of positively charged amino acids in the C-terminal domain and PARP1 mutants synthesizing highly branched or short PAR polymers. We found a correlation between the positive charge of the YB-1 CTD and its ability to interact with PAR and damaged DNA and to be trans-PARylated. Furthermore, PAR structural features such as frequency of branching and chain length were observed to influence noncovalent binding of YB-1 and to have a strong influence on YB-1 trans-PARylation.
Thus, the CTD can be considered a specific PAR-interacting module that plays a critical role for binding of YB-1 to PAR.
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