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HPF1 can promote opposite effects on different stages of PARP1 and PARP2 autoPARylation and histone modification

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Poly(ADP-ribose) (PAR) composed of linear and/or branched repeats of ADP-ribose is synthesized by enzymes called poly(ADP-ribose) polymerases (PARPs) that utilize NAD+ as a substrate to modify themselves (automodification) or target molecules (heteromodification) [1, 2]. Poly(ADP-ribosyl)ation (PARylation) catalyzed by polymerases (PARPs) is one of the immediate cellular responses to DNA damage.

The best studied PARP family member, PARP1, is the abundant nuclear protein involved in multiple cellular processes, among them, DNA repair regulation. PARP1 serves as a sensor of the DNA lesions usually induced by ionizing irradiation and oxidative stress and signals to recruit the appropriate proteins to the sites of damage [3, 4]. PARP2 was also discovered as an enzyme that catalyzes the synthesis of PAR [5]. PARP2 shares significant homology with PARP1 in the catalytic domain structure, but differs in the domain architecture due to the absence of zinc fingers and BRCT domain8. Roles of PARP1 and PARP2 in base excision repair and single-strand break repair were intensively studied. Overlapping functions of PARP1 and PARP2 in regulation of these processes were shown by using model DNA duplexes as well as nucleosomes [6, 7]. PARP2 synthesizes shorter PAR chains than PARP1 does and also inhibits PARP1-catalyzed PAR synthesis via hetero-oligomerization of the two PARPs [8]. It has been shown that removal of histone H3 is largely suppressed in PARP2-deficient cells21. Thus, PARP1 and PARP2 can perform both overlapping and specific functions in maintaining genome stability, and these enzymes cooperate in the regulation of cellular processes.

A new histone PARylation factor (HPF1) which modulates PARP1/2 activity was discovered recently. HPF1 switches the PARP1/2 PARylation specificity to serine residues by completing their active sites. This joint active site of HPF1-PARP complex involved in the PARylation of histones [9]. It was shown that HPF1 enhances NAD+-hydrolysis catalyzed by PARP1 and leads to the shortening of synthesized PAR. However, the general picture of HPF1 interaction with PARP only begins to clear up. In the presented study, we demonstrate for the first time that HPF1 can stimulate the autoPARylation of PARP1/2 and the heteroPARylation of histones in the context of nucleosomes. Interestingly, stimulation is promoted by the incomplete serine-specificity switch. We have shown that only a large excess of HPF1 over PARPs can switch the activities to NAD+ hydrolysis. HPF1 more efficiently stimulates PARP2, compared with PARP1 and the effect of stimulation is dependent on the structure of DNA damage. We suggest a specific role of PARP2 in the ADP-ribosylation-dependent modulation of chromatin structure. We provide evidence that HPF1 can promote opposite effects on

different stages of the PARP1/2-catalyzed reaction: it stimulates early stages and inhibits elongation by shielding of amino acid residues important for PAR chain elongation [9]. The dual regulatory function of HPF1 may contribute to maintenance of PARP activity at the level required for its function in the DNA damage response signaling and repair, independently on the NAD+ concentrations. The suppression is most likely predominant function of HPF1 at the normal NAD+ concentration in the nucleus (100 μM) to prevent negative consequences of PARP hyperactivation. The stimulatory action of HPF1 might regulate PARP activity under stressed conditions, when the sustained PARP activity leads to NAD+ depletion [10].

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