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HPF1 stimulates PARP1 and PARP2 to autoPARylation and histone modification

Tatyana A. Kurgina [1], Nina A. Moor [1], Mikhail M. Kutuzov [1], Konstantin N. Naumenko [1], Alexander A. Ukraintsev [1], Olga I. Lavrik [1,2]

[1]Institute of Chemical Biology and Fundamental Medicine, SB RAS, Novosibirsk, Russia.
[2]Novosibirsk State University, Novosibirsk, Russia.

Poly-ADP-ribosylation (PARylation) is an essential post-translational modification of biomolecules. Poly(ADP-ribose)polymerase 1 and 2 (PARP1/2) are the main enzymes, that synthesize PAR in a nucleus. These enzymes and PARylation catalyzed by them are involved in many biological processes, including DNA damage response. The PARP1/2 proteins serve as sensors for detecting DNA lesions and the signal performed with these enzymes is necessary to repair DNA damages [1]. A new histone PARylation factor (HPF1) which modulates PARP1/2 activity was discovered recently. By completing the active site of PARP1/2, HPF1 switches the PARylation specificity to serine residues. Thereby, HPF1 functions in the complex with PARP1/2 involved in the PARylation of histones [2]. It was shown that HPF1 leads to the shortening of synthesized PAR, and enhances NAD+-hydrolysis catalyzed by PARP1. 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. 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 [3]. Moreover, we show that HPF1 more efficiently stimulates PARP2, compared with PARP1 and the effect of stimulation is dependent on the structure of DNA damage. The HPF1-dependent histone PARylation catalyzed by PARP2 is specifically stimulated by a 5'-dRP containing BER DNA intermediate [4]. We suggest a specific role of PARP2 in the ADP-ribosylation-dependent modulation of chromatin structure in the DNA-damage response. The work was supported by grants from RSF 21-64-00017

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