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PARPs and PARGs orchestrate the assembly/disassembly of FUS/Poly(ADP-ribose) compartments at DNA damage sites and FUS translocation to cytoplasmic stress granules

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Motivation and Aim: The stability of the genome is controlled by a complex machinery of repair that counteracts DNA damage, the major guilty in cancer and ageing related diseases [1]. After DNA damage, mammalian cells trigger a cascade of events that starts from poly(ADP-ribose)polymerases (PARPs) recruitment to site of DNA damage. Nuclear PARPs, PARP1 [2], recognize damaged DNA and synthetize long and branched poly(ADP-ribose) polymers (PAR) resulting in covalent modification of itself and other DNA binding proteins [2]. The protein poly(ADP-ribosyl)ation (PARylation) is a reversible post-translational modification. PAR polymers covalently attached to acceptor proteins is hydrolyzed by poly(ADP-ribose) glycohydrolase (PARG), which makes protein PARylation a reversible post-translational modification [2]. Recently, PARylation has been shown for RNA binding proteins, which accumulate in DNA regions damaged by short laser beam exposures raising issues about their putative role in DNA repair [3]. Here we focus our attention on the RNA binding protein FUS (fused in sarcoma) during genotoxic stress. FUS is one of the most abundant RNA-binding proteins that can be PARylated after exposure to genotoxic stress and interact with PAR. However, the role of the PAR dependent FUS accumulation at damaged DNA in the cellular response to genotoxic stress remains unclear.
Methods and Algorithms: To address the above-mentioned issue, we developed an original approach based on a single molecule analyzes by atomic force microscopy (AFM). Such approach enables to visualize the molecular assemblies formed by FUS at DNA damage sites after PARP1 activation *in vitro*. In cells, we used immunofluorescence, immunoblotting and RNA interference to detect intracellular compartmentalization of FUS after exposure to genotoxic stress.
Results: In vitro, we found that FUS is recruited to DNA damage sites by binding to PAR and subsequently forms large molecular assemblies thus concentrating damaged DNA into compartments and demonstrated their reversibility through the hydrolysis of PAR by PARG.
Conclusion: We suggest that PAR-dependent relocation of FUS may participate to an adapted translational response to DNA damages.
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