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DNA DAMAGE RESPONSE

DNA takes a break with SUMO

> the E3 SUMO ligases PIAS1 and PIAS4 have an important role in the mammalian DDR pathway

During the DNA damage response (DDR), repair proteins such as the E3 ubiquitin ligase breast cancer type 1 susceptibility protein (BRCA1) accumulate at DNA double-stranded breaks (DSBs), and ubiquitylation at these sites helps recruit further repair proteins. Small ubiquitin-related modifier (SUMO) — which is attached to proteins by a pathway involving the E1 enzyme SAE1, the E2 enzyme UBC9 (also known as UBE21) and an E3 ligase (such as PIAS1 and PIAS4) — has also been implicated in the DDR, but its role was unclear. Galanty *et al.* and Morris *et al.* now report that PIAS1 and PIAS4 promote DNA repair and are required for BRCA1 E3 ubiquitin ligase activity at DSBs.

Both groups show that UBC9, SUMO1, SUMO2 and SUMO3 accumulate at DSBs in mammalian cells in a PIAS1- and PIAS4-dependent manner. Furthermore, depletion of PIAS1 and PIAS4 causes a decrease in DSB repair by homologous recombination and non-homologous end joining, indicating a functional role for these E3 SUMO ligases in DNA repair.

So, what is the function of SUMO and PIAS proteins at DSBs and how do they contribute to DNA repair? During the DDR, histone H2AX is phosphorylated in the chromatin surrounding DSBs, which results in the recruitment of repair factors, such as tumour suppressor p53-binding protein 1 (TP53BP1) and the E3 ubiquitin ligases BRCA1, RNF8 and RNF168, to damaged DNA. Galanty *et al.* show that PIAS1 and PIAS4 are recruited to DSBs by their SAP domains and mediate the association of TP53BP1, BRCA1 and RNF168 with damage sites. They also find that TP53BP1 and BRCA1 are sumoylated in response to ionizing radiation, and that these sumoylation events are promoted by PIAS1 and PIAS4. Morris *et al.* independently show that PIAS1 and PIAS4 promote BRCA1 sumoylation at sites of DNA damage in hydroxyurea-treated cells, and that sumoylation of BRCA1 *in vitro* increases its E3 ubiquitin ligase activity.

The ubiquitylation of histones H2A and H2AX at sites of DNA damage, which mediates the recruitment of further repair proteins, is mediated by the E3 ubiquitin ligases BRCA1, RNF8 and RNF168. Galanty *et al.* show that depletion of PIAS4 reduces histone H2A ubiquitylation at DSBs and impairs the recruitment of RNF168 to these sites of damage. Morris *et al.* show that depletion of PIAS1, PIAS4 or BRCA1 reduces the level of BRCA1-dependent ubiquitylation at DSBs, and that PIAS1 and PIAS4 are required for the accumulation of RNF168 and ubiquitin conjugates generated by RNF168 at damage sites. These data provide further evidence that SUMO and ubiquitin function together at DSBs to promote DNA repair.

Collectively, these studies reveal that the E3 SUMO ligases PIAS1 and PIAS4 have an important role in the mammalian DDR pathway by regulating the recruitment of key DNA repair proteins to DSBs, the sumoylation of TP53BP1 and BRCA1, and the E3 ubiquitin ligase activity of BRCA1.

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ORIGINAL RESEARCH PAPERS Galanty, Y. *et al.* Mammalian SUMO E3-ligases PIAS1 and PIAS4 promote responses to DNA double-strand breaks. *Nature* **462**, 935–939 (2009) | Morris, J. R. *et al.* The SUMO modification pathway is involved in the BRCA1 response to genotoxic stress. *Nature* **462**, 886–890 (2009)