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Histone ADP-ribosylation controls early multi-scale chromatin dynamics upon DNA damage

ADP-ribosylation signaling by PARP1 is a key early event of the DNA damage response (DDR). PARP1 recruitment occurs within seconds upon DNA damage, triggering the accumulation of ADP-ribose binding repair factors and regulating chromatin architecture at sites of DNA damage. Histones, which are the second main target of this signaling pathway after PARP1 itself, are ADP-ribosylated, causing a rapid and transient relaxation of damaged chromatin. Although it has recently been proposed that this first remodeling event favors the access of further repair proteins to DNA lesions, it has not been characterized yet how exactly the ADP-ribosyl signaling shapes chromatin during the DDR at a nucleosome scale. Furthermore, new findings have described mono-ADP ribosylation as a second wave of PARP signaling, however its role in chromatin remodeling remains unclear.

In this project, we aim to uncover how ADP-ribosylation modulates chromatin folding immediately after DNA damage nearby lesions and to unveil its potential functions in the DDR. To this end, we characterize chromatin architecture at multi- scale levels in live human cells: from the fiber itself to single histones. We use an innovative set-up based on single-molecule imaging combined with laser-micro- irradiation. We develop machine learning approaches to extract diffusion parameters from our experimental single particle tracking data. Our results show that chromatin motion is dramatically increased as early as 30 seconds after irradiation. Interestingly, this effect is transient as chromatin recovers its initial mobility 10 minutes after irradiation. This increased dynamic is restricted to chromatin located within the irradiated area, suggesting a specific response to DNA damage. Notably, these changes in chromatin dynamics occur at both the chromatin fiber and nucleosome scales and correlate with PARP1-dependent chromatin remodeling. We have therefore characterized chromatin dynamics in conditions where ADP-ribosylation is inhibited (PARPi), persistent (PARGi, ARH3KO) or when PARP1 is fully or partially suppressed (PARP1 mutants). We demonstrate that multi-scale dynamic changes of damaged chromatin depend on mono- and poly ADP-ribosylation of histones and play an essential role in the choice of repair pathway.

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