PARP1-DNA co-condensation drives DNA repair site assembly to prevent disjunction of broken DNA ends

Nagaraja Chappidi[1], Thomas Quail[2,3,5,6,7], Simon Doll[1,3,7], Laura T. Vogel[4], Suren Felekyan[4], Ralf Kühnemuth[4], Claus A. M. Seidel[4], Jan Brugues[2,3,5], Marcus Jahnel[1,3], Titus M. Franzmann[1], Simon Alberti[1 *]

Affiliations

1. Biotechnology Center (BIOTEC), Center for Molecular and Cellular Bioengineering, Technische Universität Dresden, Tatzberg 47/49, 01307 Dresden, Germany
2. Max Planck Institute of Cell Biology and Genetics (MPI-CBG), Pfotenhauerstr. 108, 01307 Dresden, Germany
3. Cluster of Excellence Physics of Life, TU Dresden, Arnoldstraße 18, 01307 Dresden, Germany
4. Department of Molecular Physical Chemistry, Heinrich Heine University, Universitätsstraße 1, 40225 Düsseldorf, Germany
5. Max Planck Institute for the Physics of Complex Systems (MPI-PKS), Nöthnitzer Str. 38, 01187 Dresden, Germany
6. Cell Biology and Biophysics Unit, European Molecular Biology Laboratory, Meyerhofstraße 1, 69117 Heidelberg, Germany
7. These authors contributed equally.

***Corresponding author:**

Simon Alberti (simon.alberti@tu-dresden.de)

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Abstract

DNA double-strand breaks (DSBs) are repaired at DSB sites. How DSB sites are assembled and how broken DNA is prevented from separating is not understood. Here we uncover that the synapsis of broken DNA ends is mediated by the DSB sensor protein poly(ADP) ribose (PAR) polymerase 1 (PARP1). Using quantitative bottom-up biochemistry, we reconstitute functional DSB sites and show that DSB sites form through co-condensation of PARP1 multimers with DNA. The co-condensates exert mechanical forces to physically keep DNA ends together and become enzymatically active for localized PAR synthesis. PARylation promotes release of PARP1 from DNA ends and the concomitant recruitment of effector proteins, such as Fused in Sarcoma (FUS), which stabilizes broken DNA ends against spatial separation, revealing a finely orchestrated order of events that primes broken DNA for repair. We provide a comprehensive molecular model for the hierarchical assembly of DSB condensates to explain DNA end synapsis and the subsequent recruitment of effector proteins for DNA damage repair.