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The orchestration of NHEJ factors at DNA double-strand breaks by the Ku70/Ku80 heterodimer

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Double Strand Breaks (DSB) are among the most toxic DNA lesion for the cells. A default during the repair process can lead to chromosomic aberrations, genes rearrangements and cancers. Without sister chromatid, the non-homologous end-joining (NHEJ) represent the major pathway of DSB repair in eukaryote cells. The ring-shaped Ku70/80 heterodimer rapidly senses broken DNA ends forming a recruiting hub (1, 2). Through protein-protein contacts eventually reinforced by protein-DNA interactions, the Ku-DNA hub attracts a series of specialized protein. To repair simple DSBs, such as 5’ phosphorylated blunt-ended DNA ends, the only additional requirement is the activity of DNA Ligase 4 (LIG4) in complex with its co-factor, the XRCC4 homodimer. Ku and LIG4/XRCC4 form the minimal core machinery of the c-NHEJ that can further be stimulated by the XLF or PAXX homodimers. We combined structural, biochemical and cellular analyses to unveil the role of Ku-Binding Motifs (KBM) present on several NHEJ factors. We determined crystal and CryoEM structures of Ku70/80/DNA complexes with different KBM motifs and unveiled their relative position on the heterodimer (3, unpublished data). We characterized the competition and synergies between these KBM motifs and used separation of function mutants of these KBM to precise the role of these interaction both in terms of recruitment at the DSB sites and in terms of repair efficiency. We then contributed to analyse the role of these KBM motifs in the context of the NHEJ super-complexes formation.

References

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