Non-catalytic Roles for XPG with BRCA1 and BRCA2 in Homologous Recombination and Genome Stability - DTU Orbit (19/12/2018)

Non-catalytic Roles for XPG with BRCA1 and BRCA2 in Homologous Recombination and Genome Stability

XPG is a structure-specific endonuclease required for nucleotide excision repair, and incision-defective XPG mutations cause the skin cancer-prone syndrome xeroderma pigmentosum. Truncating mutations instead cause the neurodevelopmental progeroid disorder Cockayne syndrome, but little is known about how XPG loss results in this devastating disease. We identify XPG as a partner of BRCA1 and BRCA2 in maintaining genomic stability through homologous recombination (HRR). XPG depletion causes DNA double-strand breaks, chromosomal abnormalities, cell-cycle delays, defective HRR, inability to overcome replication fork stalling and replication stress. XPG directly interacts with BRCA2, RAD51, and PALB2, and XPG depletion reduces their chromatin binding and subsequent RAD51 foci formation. Upstream in HRR, XPG interacts directly with BRCA1. Its depletion causes BRCA1 hyper-phosphorylation and persistent chromatin binding. These unexpected findings establish XPG as an HRR protein with important roles in genome stability and suggest how XPG defects produce severe clinical consequences including cancer and accelerated aging.

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