BLM helicase determines the choice of the DNA repair pathways in a cell cycle dependent manner

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Mutations in tumor suppressor BLM helicase cause Bloom Syndrome (BS). BS patients are characterized by predisposition to multiple types of cancer. It was found that BLM helicase was recruited in a biphasic manner to multiple annotated DSBs extending from 80 bps to 9 kb from the break site. BLM recruitment was dependent on the presence of NBS1, MRE11 and ATM. While ATM activity was essential for BLM recruitment in the early phase, it was dispensable in the late phase when MRE11 exonuclease activity and RNF8 mediated ubiquitylation of BLM are key the determinants. Interaction between polyubiquitylated BLM and NBS1 was essential for the helicase to be retained at the DSBs. The helicase activity of BLM was essential for the recruitment of key HR and c-NHEJ factors onto the chromatin in S- and G1 phase, respectively. During repair phase BLM inhibited HR in S-phase and c-NHEJ in G1 phase. Consequently, inhibition of helicase activity of BLM enhanced the rate of DNA alterations. Overall it was determined that BLM utilized its pro- and anti-repair functions to maintain genome stability.