

S008 How heterochromatin influences DNA double strand break repair in mammalian cells

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DNA non homologous end joining (NHEJ) represents the major DSB repair mechanism in mammalian cells. ATM, Artemis and the damage response mediator, 53BP1, MDC1, BRCA1 and the MRN complex, are required for a component of NHEJ that repairs ~ 15 % of radiation-induced DSBs in G0/G1 phase. We considered that ATM/Artemis may function in end-processing of DSBs that have complex DNA ends prior to rejoining by NHEJ. Examination of DNA damaging agents that introduce DSBs of varying complexity revealed that the requirement for ATM did not exceed 25 % of introduced DSBs. Thus, the correlation between DSB complexity and ATM/Artemis dependency is weak. Instead, we observed that most DSBs that remain in the presence of an ATM inhibitor are located within the periphery of heterochromatin. Our findings suggest that heterochromatin represents a barrier to DSB repair, which ATM overcomes via phosphorylation of Kap1, a heterochromatic building factor. siRNA of Kap1, HDAC1/2 or HP1 relieves the requirement for ATM in DSB repair. ATM is required for the slow component of DSB repair. Our findings provide strong evidence that DSBs within heterochromatin are repaired with slow kinetics.