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An ATM dependent checkpoint that inhibits spindle assembly

E Smith, V Costanzo

Cancer Research UK, Clare Hall Laboratories, South Mimms, United Kingdom

Protein kinases, ATM and ATR monitor the occurrence of damage to DNA and are key players of the damage response transduction pathways. DNA damage recruits and activates ATM/ATR integrating a coordinated response to minimise the deleterious effects of DNA damage and preserve the integrity of the genome. In response to DNA damage, ATM/ATR initiate a signal transduction pathway leading to cell cycle arrest, DNA repair and apoptosis. We demonstrated the presence of an ATM dependent DNA damage checkpoint that disrupts spindle assembly in mitosis following chromsome breakage in *Xenopus Laevis* egg extract. The checkpoint is abrogated by caffeine and partially by specific ATM inhibitor, KU55933. The checkpoint has no apparent association with spindle assembly regulators, MPF, Plk, Aurora kinases A/B or the RCC1-Ran GTP pathway. Instead, we identified a novel centrosome protein named X-CRA1 (Centrosomal protein Regulated by ATM/ATR) as a target of the mitotic ATM dependent checkpoint. We demonstrated that X-CRA1 is required for organised spindle assembly, with possible involvement in centrosome duplication. Interestingly, X-CRA1 delocalises from centrosomes in the presence of DNA damage, suggesting a possible mechanism through which centrosomes contribute to maintaining genome integrity during mitosis. Further studies will focus on characterizing the ATM dependent checkpoint that actively disassembles or inhibits mechanisms that actively promote spindle maintenance by targeting centrosome protein X-CRA1.