

**M002** Role of protein kinases in maintenance of genome stability and DNA repair

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ATM (ataxia telangiectasia (A–T)–mutated) and ATR (ATM and Rad3–related) belong to the PI(3)–kinase-like kinase (PIKK) family of protein kinases. Mutations in these kinases cause genome instability and disease. ATR is an essential protein; knockout mice die during embryogenesis probably because cells sustain a high level of DNA damage during DNA replication. Cells with hypomorphic mutations in ATR show severe sensitivity to genotoxins and defects in DNA damage and DNA replication checkpoints. ATM and ATR are highly conserved; in yeast Mec1 (ATR) is essential because stalled replisomes collapse and cannot restart. A range of cellular targets of ATM and ATR have been identified. However, the molecular bases for the aspects of the regulation of replisome stability and DNA repair by ATM and ATR are not yet clear. In this light, we recently found that phosphorylation of budding yeast Slx4 by the Mec1 and Tel1 kinases (yeast orthologues of ATR and ATM, respectively) at a single residue is essential for efficient DNA flap cleavage by the Rad1-Rad10 nuclease during DNA repair *in vivo*. The identification of multiple roles for Slx4 in responding to DNA damage, other than assisting Rad1-Rad10-dependent DNA cleavage, will be discussed. Recent progress in understanding the mode of action of Slx4 at the molecular level will be also be presented and the identification of human SLX4 and its regulation of XPF-ERCC1, the human equivalent of Rad1-Rad10, will be described.