

**P013** ATM activation and signalling under hypoxic conditions  
**Ester M. Hammond**

*The Gray Institute for Radiation Oncology and Biology,  
University of Oxford.*

The ATM kinase has been shown previously to respond to the DNA-damage induced by reoxygenation following hypoxia by initiating a Chk 2-dependent cell cycle arrest in the G<sub>2</sub> phase. Here we show that ATM is both phosphorylated and active during exposure to hypoxia in the absence of DNA damage detectable by either Comet assay or 53BP1 focus formation. Hypoxia-induced activation of ATM correlates with oxygen concentrations low enough to cause a replication arrest and is entirely independent of HIF 1 $\alpha$  status. In contrast to damage-activated ATM, hypoxia-activated ATM does not form nuclear foci but is instead diffuse throughout the nucleus. The hypoxia-induced activity of both ATM and the related kinase, ATR, is independent of NBS1 and MRE11, indicating that the MRN complex does not mediate the DNA-damage response to hypoxia. However, similar to the DNA damage response there is a requirement for the mediator protein, MDC1, to amplify the ATM response to hypoxia. Our findings clearly demonstrate that there are alternate mechanisms for activating ATM that are both stress specific and independent of the presence of DNA breaks. Our data clearly indicate that the tumour micro-environment and in particular hypoxia can initiate a DNA damage response in the apparent absence of actual damage.