

S009 RNF8 and RNF168 orchestrate the response to DNA double-strand breaks

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The DNA double-strand break is the most cytotoxic lesion and elicits a complex cellular response that comprise the activation of a signal transduction cascade controlled by kinases of the PI(3) kinase-like kinase family ATM, DNA-PKcs and ATR. I will present the results of a genome-scale RNA interference screen that led to the identification of the RNF8 and RNF168 E3 ubiquitin ligases as key regulators of the chromatin-based response to DNA double-strand breaks. RNF8 and RNF168 act downstream of ATM, H2AX and MDC1 to promote the recruitment of multiple proteins to the site of DNA damage, including the BRCA1 tumor suppressor and the DNA repair protein 53BP1. I will present our latest model of the action of RNF8 and RNF168. Moreover, we have found that RNF168 is mutant in a novel radiosensitivity and immunodeficiency syndrome, termed RIDDLE, thereby implicating regulatory ubiquitylation in response to DNA damage as a physiologically important response.