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MAIN FIELDS OF RESEARCH; ABSTRACT

Maintaining genome stability is crucial for all living cells and organisms. The repair of the most cytotoxic DNA lesions, namely DNA double-strand breaks (DSB), is based on a variety of factors that modify chromatin structure, such as kinases and ubiquitin ligases. A key event is represented by the non-canonical ubiquitination of histone H2A on the K15 site (H2AK15Ub), mediated by the ubiquitin ligase RNF168. H2AK15Ub acts as a docking site for the recruitment of the downstream effectors 53BP1 and BRCA1, which promote DNA repair by either non-homologous end joining (NHEJ) or homologous recombination (HR), respectively. Although the RNF168 pathway is functionally implicated in determining the repair pathway choice, the mechanism underlying this fine regulation is still missing. Another level of complexity has been recently added to the ubiquitin code by the discovery that ubiquitin itself undergoes PTMs such as acetylation and phosphorylation.
Our research aims at characterizing the potential role of ubiquitin phosphorylation in the context of the DNA damage response (DDR). Interestingly, our data indicate that ubiquitin phosphorylation modulates the dynamics of chromatin ubiquitination during DDR activation. Furthermore, we found that ubiquitin phosphorylated at a specific site impairs 53BP1 *foci* accumulation upon genotoxic stress, suggesting that phosphorylation on this site potentially interferes with 53BP1 recruitment to damaged chromatin, thereby regulating repair pathway choice. By using a phospho-ubiquitin specific antibody, we found a potential role of this modification in finely tuning the accumulation of 53BP1 to chromatin structure. Future studies are needed to further investigate the molecular mechanism of ubiquitin phosphorylation in the regulation of genome stability by controlling 53BP1 accumulation at chromatin structures, offering novel potential therapeutic strategies for cancer treatment.

SPECIAL TECHNIQUES AND EQUIPMENT

Confocal and fluorescence microscopy, quantitative image-based cytometry (QIBC), in vitro ubiquitination assay, generation of phospho-specific antibody, functional assays investigating genome stability (chromosomal aberrations, repair pathway choice, telomere fusions), FACS