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MAIN FIELDS OF RESEARCH; ABSTRACT

The DNA double stranded (DSBs) breaks are potent threats to the maintenance genome stability. To deal with this, cells elicit a complex response triggered by protein kinases, leading to the hierarchical accumulation of signalling and repair factors, which are largely under the control of reversible protein ubiquitination on the chromatin surrounding the DSB sites. Key players in this process are the ubiquitin ligases RNF8 and RNF168, which ultimately ubiquitinate H2A type histones and promote the accumulation of 53BP1 and BRCA1. These factors are responsible to activate downstream events for DSB repair, either by non-homologous end joining (NHEJ) or homologous recombination (HR), respectively. One of the cell-intrinsic mechanism that acts in maintaining the balance between robust DSB signal transduction and HR repair involves the RING finger protein 169 (RNF169), a paralog of RNF168. RNF169 maintains the balance by limiting the accumulation of 53BP1 at the damaged chromosomes, by competing for the binding to ubiquitinated histones H2A. In addition to its role in DSBs signalling and repair, RNF169 was also recently suggested to have potential roles in DNA replication stress. Despite its initial characterization indicated that RNF169 is a potentially active ubiquitin ligase, no targets have been identified so far. By employing a state-of-the-art portfolio of techniques, the research project aims at investigating and characterizing the ubiquitinating activity of RNF169 towards novel substrates, and at understanding how RNF169 – and its substrates – affect the replication process during stress conditions. The accomplishment of this research project will broaden our understanding of this poorly characterized ubiquitin ligase, by elucidating the role of RNF169 and its substrates in DNA replication and genome stability.

SPECIAL TECHNIQUES AND EQUIPMENT

DNA fiber assay, Chromatin extraction, Immunofluorescence, Recombinant protein production, in-vitro assays, Co-IP