Cell Cycle 14:13, 1999; July 1, 2015; © 2015 Taylor & Francis Group, LLC

USP7 saves RIDDLE for the end

Comment on: Zhu Q, et al. USP7 deubiquitinase promotes ubiquitin-dependent DNA damage signaling by stabilizing RNF168. Cell Cycle 2015; 14(9):1413–25; PMID:25894431; http://dx.doi.org/10.1080/15384101.2015.1007785

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Double strand breaks (DSBs) are one of the most cytotoxic DNA lesions known and therefore pose a constant threat to genomic integrity.[1] If left unrepaired, DSBs can lead to mutations and chromosomal aberrations which are often associated with cancer. Eukaryotic cells employ a sophisticated DNA damage response (DDR) to protect their genome from DNA damage, such as DSBs. During the DDR to DSBs, one of the most distinctive hallmarks of the response is the ordered assembly of damage signaling and repair proteins into multi-protein complexes in the vicinity of the DSB. The accumulated proteins form so-called ionizing radiation-induced foci (IRIF), which are detectable by immunofluorescence microscopy. Over the last decade, the list of proteins residing in IRIF has been rapidly expanding, and now includes ATM, NBS1, phosphorylated H2AX, MDC1 (mediator of DNA-damage checkpoint 1), E3 ubiquitin (Ub) ligase RNF8, RNF168, MOF, ubiquitinated H2AX/A, BRCA1 and 53BP1 among others.[2] It is widely recognized that the recruitment/accumulation of these DDR factors or factor complexes is initially triggered by ATM-dependent phosphorylation of H2AX, which is instrumental for the recruitment of MDC1. The MDC1 protein in turn recruits RNF8, which in concert with RNF168, initiates the crucial Ub-dependent signaling cascade.

The ubiquitin ligase RNF168 was identified as a key factor in forming 53BP1 IRIF and RNF168 gene mutations were shown to be responsible for RIDDLE syndrome.[3] This human genome instability syndrome manifests diverse clinical features, such as radiosensitivity, immunodeficiency, facial dysmorphism, and mild motor control and learning difficulties. Some of these features are also common to ataxia-telangiectasia patients. Studies have shown that RNF168 is an E3 Ub ligase that ubiquitinates histones H2A and H2AX at lysines (K) 13 and 15 (K13/15),[4] which are distinct from the first H2A ubiquitination sites identified and found at K118/119. The poly K63-Ub chains at K13/15 on H2A/X are the result of subsequent RNF8-catalyzed Ub chain extension. Both BRCA1 and 53BP1 bind to polyubiquitinated H2A/X. BRCA1 is recruited in a RAP80-Abraxas-BRCA1-BRCC36 complex in which RAP80 is capable of binding Ub moieties through the Ub-interacting motif (UIM) domain, while 53BP1 recognizes nucleosomes containing dimethylated H4K20 and ubiquitinated H2A through its Tudor domain and ubiquitination-dependent recruitment (UDR) motif, [5] respectively. While much remains to be unraveled about this Ub-dependent signaling pathway, we know that BRCA1 and 53BP1 determine the DSB repair pathway choice between homologous recombination (HR) and non-homologous end joining (NHEJ).

Although the RNF8 and RNF168-mediated Ub-dependent signaling cascade is critically important for the eukaryotic cell's ability to cope with the burden of DSBs, how the cell regulates RNF8 and RNF168 is largely unknown. Both TRIP12 and UBR5 were identified as negative regulators of RNF168,[6] however, whether RNF168 is a direct substrate of these E3 ligases is unknown. Against this backdrop, in their newest studies, Zhu *et al.* show that the USP7 deubiquitinase enzyme promotes Ub-dependent DNA damage signaling by stabilizing RNF168. [7] They provide substantial evidence that USP7 deficiency curbs Ub-dependent signaling during the DDR to both UVR and IR-induced DNA damage. Zhu and colleagues further demonstrate that USP7 interacts with and deubiquitinates RNF168. It had previously been documented that USP7 regulates Ring1B and Bmi1 Ub ligases,[8] 2 components of Polycomb repressive complex 1 (PRC1), which are also DDR participants, generating monoubiquitinated H2A at K118/119 (uH2A). Zhu *et al* have combed through the tangled relationship of H2A monoubiquitination and H2A/X polyubiquitination with bypass experiments, which estimated the contribution of USP7-mediated RNF168 regulation to the Ub-dependent signaling cascade. A similar approach previously helped to define RNF8 and RNF168 as targets of HSV-1 encoded ICP0 E3 Ub ligase. In general, the study has revealed that USP7 is a new regulator of Ub-dependent signaling cascade.

The study has also raised some interesting questions and possibilities. For example, BRCA1 and Chk1 are both down regulated in USP7-deficient cells. Are BRCA1 and Chk1 also substrates of USP7? With a growing number of USP7 targets and inhibitors now identified, the testing of USP7 as a plausible therapeutic target for cancer warrants close attention.

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