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Autophagy regulates DNA repair through SQSTM1/p62

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ABSTRACT

Macroautophagy/autophagy is primarily a degradative pathway that clears malfunctioning cellular components in response to various types of stress. Recent studies have indicated that autophagy also plays an important role in maintaining genome stability. Loss of autophagy is associated with increased damage to DNA, inappropriate amplification of genomic regions and abnormal chromosome number. In a recent paper by Wang et al. the authors uncover a mechanism through which autophagy regulates the ubiquitination of chromatin. In particular, the autophagy receptor and substrate SQSTM1/p62 inhibits the E3 ligase RNF168-dependent ubiquitination of histone in response to DNA double-strand breaks. Dysregulation of this process leads to a reduced ability to repair DNA and a corresponding increase in the sensitivity of cells to radiation-induced damage.

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Based on confocal microscopy Wang et al. found that transfection of HCT116 cells with siRNA against *SQSTM1* leads to abundant nuclear conjugated ubiquitin foci.[1] An analysis of chromatin protein extracted from HeLa cells, revealed that SQSTM1 knockdown increases chromatin poly-ubiquitination. Conversely, overexpression of SQSTM1 has the opposite effect, reducing this DNA-damage-induced chromatin ubiquitination. Increased poly-ubiquitination of histone H2A is also observed with SQSTM1 knockdown, whereas, knockdown of either NBR1 or WDFY3/ALFY, 2 autophagic proteins that have functions similar to SQSTM1, has no obvious effect on chromatin ubiquitination, suggesting that SQSTM1 is a specific negative regulator of this DNA-damage-induced response.

Next, the authors showed that irradiation cannot induce chromatin ubiquitination in autophagy-defective cells, but this failure is rescued by SQSTM1 knockdown, suggesting that excess SQSTM1 in autophagy-defective cells causes reduced chromatin ubiquitination. RNF168 catalyzes the poly-ubiquitination of damaged DNA.[2] Wang et al. observed that RNF168-dependent K63 ubiquitination of H2AFX/H2AX or chromatin is suppressed by co-expression of SQSTM1. They next used co-immunoprecipitation to demonstrate that the interaction between SQSTM1 and RNF168 involves the SQSTM1 LIM-binding (LB) domain; SQSTM1 suppression of RNF168-dependent poly-ubiquitination is mediated by a direct interaction between the 2 proteins, and requires the LB domain. Along these lines, the authors showed that the ligase activity of RNF168 is inhibited when SQSTM1 binds the LB domain. Furthermore, the RNF168 motif interacting with ubiquitin (MIU1) corresponds to the SQSTM1 binding site. Finally, a discharge assay suggests SQSTM1 interferes with the transfer of ubiquitin from the E2 rather than the binding of RNF168 to the E2 enzyme.

The repair of double-strand breaks typically involves homologous recombination or non-homologous end-joining.[3] Accordingly, the authors examined the effect of SQSTM1 on these 2 pathways and found that a reduced efficiency of homologous recombination that resulted from the inhibition of autophagy is rescued by SQSTM1 knockdown. In addition, the downstream recruitment of repair factors including BRCA1, UIMC1/RAP80 and RAD51 is impaired with SQSTM1 overexpression or loss of autophagy, but again can be recovered by SQSTM1 knockdown. These data collectively suggest that autophagy deficiency leads to impairment of DNA repair factor recruitment in an SQSTM1-dependent manner.

The authors also looked at DNA repair kinetics and found a delay of DNA repair dependent on SQSTM1. Lastly, Wang et al. examined cancer cell growth and found that the colony formation rate is substantially reduced in the presence of excess SQSTM1. Similarly, the cancer cell survival rate following irradiation is reduced in a SQSTM1-dependent manner when autophagy is inactivated by the deletion of *ATG3*. In summary, these findings provide novel insights into the crosstalk between DNA repair and autophagy, and could potentially shed light on studies of neurodegenerative diseases as well as possible avenues for anticancer therapeutics.

Disclosure of potential conflicts of interest

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