THE EXOSOME AND THE MAINTENANCE OF GENOME INTEGRITY

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ABSTRACT

The RNA exosome acts on different RNA substrates and plays important roles in RNA metabolism. The fact that short non-coding RNAs are involved in the DNA damage response led us to investigate whether the exosome plays a role in DNA repair. We have shown that the exosome catalytic subunit RRP6/EXOSC10 is recruited to DNA double-strand breaks (DSBs) in *Drosophila* S2 cells and human HeLa cells exposed to either ionizing radiation or I-PpoI endonuclease cleavage. DIS3, the other catalytic subunit of the nuclear exosome, is also recruited to DSBs, whereas the exosome core subunit EXOSC7 is not. Depletion of different exosome subunits does not interfere with the phosphorylation of the histone variants H2Av (*Drosophila*) or H2AX (humans), but depletion of RRP6/EXOSC10 impairs the recruitment of the homologous recombination factor RAD51 to the damaged sites, without affecting RAD51 levels. The recruitment of RAD51 to DSBs in S2 cells is also inhibited by overexpression of RRP6-Y361A–V5, a catalytically inactive RRP6 mutant. Furthermore, cells depleted of RRP6 or EXOSC10 are more sensitive to radiation, which is consistent with RRP6/EXOSC10 playing a role in DNA repair. RRP6/EXOSC10 can be co-immunoprecipitated with RAD51, which links RRP6/EXOSC10 to the homologous recombination pathway in animal cells. Taken together, our results suggest that a 3'-5' ribonucleolytic activity is required for efficient DNA repair.