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Faculty of Biology Paper of the Month: January 2014

Awarded to Graduate Student Hanan Khoury

Khoury H., Guttmann-Raviv N., Ipenberg I., Huggins D., Jeyasekharan A.D.,and Ayoub N.. PARP1-dependent recruitment of KDM4D histone demethylase to DNA damage sites promotes double-strand break repair. 2014. PNAS doi:10.1073/pnas.1317585111

Abstract:
Members of the lysine (K)-specific demethylase 4 (KDM4) A–D family of histone demethylases are dysregulated in several types of cancer. Here, we reveal a previously unrecognized role of KDM4D in the DNA damage response (DDR). We show that the C-terminal region of KDM4D mediates its rapid recruitment to DNA damage sites. Interestingly, this recruitment is independent of the DDR sensor ataxia telangiectasia mutated (ATM), but dependent on poly (ADP-ribose) polymerase 1 (PARP1), which ADP ribosylates KDM4D after damage. We demonstrate that KDM4D is required for efficient phosphorylation of a subset of ATM substrates. We note that KDM4D depletion impairs the DNA damage-induced association of ATM with chromatin, explaining its effect on ATM substrate phosphorylation. Consistent with an upstream role in DDR, KDM4D knockdown disrupts the damage-induced recombinase Rad51 and tumor protein P53 binding protein foci formation. Consequently, the integrity of homology- directed repair and non-homologous end joining of DNA breaks is impaired in KDM4D-deficient cells. Altogether, our findings implicate KDM4D in DDR, furthering the links between the cancer-relevant networks of epigenetic regulation and genome stability.