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KDM4D crosstalks with PARP1 and RNA at DNA DSBs

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Genomic DNA is continuously damaged by external and endogenous factors, resulting in diverse DNA lesions. Impairment in responding to these lesions may result in genomic instability and trigger tumorigenesis. Luckily, cells have evolved the DNA damage response (DDR), which is a sophisticated network that detects, signals and repairs DNA damage. DDR machinery relies on post-translational modifications, including phosphorylation, ubiquitination and methylation. In response to DNA double-strand breaks (DSBs), many DDR proteins accumulate at sites of broken DNA. DSBs are mainly repaired by either homologous recombination (HR) or non-homologous end joining (NHEJ) repair pathways.[1] Besides DDR proteins, emerging evidence implicate small non-coding RNAs (ncRNAs) in DDR. Some ncRNAs act at DSBs and mediate recruitment of DDR factors to breakage sites, while others modulate the expression of DDR factors.[2]

The lysine-demethylase 4 family (KDM4) consists of 4 members, KDM4A-D, which specifically demethylate H3K9me2/me3, H3K36me3 and H1.4K26. KDM4A-D proteins function in several cellular processes, including DNA replication, differentiation and gene expression regulation.[3] Recently, KDM4D was demonstrated to act in the DDR and modulate DSB repair.[4,5] KDM4D depletion impairs the chromatin association of the master protein kinase, ATM. This defective chromatin localization impairs the DDR-induced phosphorylation of histone H2AX (Ser139), KAP1 (Ser824) and Chk2 (Thr68). Additionally, KDM4D depletion impairs focus formation by Rad51 and 53BP1, which are associated with HR and NHEJ, respectively. Accordantly, KDM4D depletion sensitizes cells to ionizing radiation. Collectively, KDM4D is required for efficient DSB repair via both HR and NHEJ pathways.[4]

In accordance with the role of KDM4D[4] in the DDR, KDM4D is rapidly and transiently recruited to sites of DNA damage. This accumulation was observed using several approaches: First, KDM4D is recruited to laser-microirradiated sites.[4,5] Second, it accumulates at a single DSB, induced by I-SceI endonuclease. Third, KDM4D binding to sequences surrounding the I-SceI recognition site is increased in cells harboring a DSB at this site. Fourth, KDM4D chromatin association is augmented upon DNA damage induction. The C-terminus of KDM4D (residues 313-523) mediates the recruitment to DSBs. Interestingly, KDM4D demethylase activity is unnecessary for its accumulation at DNA damage sites,[4] opposing to the requirement for KDM4B demethylase activity for its recruitment to sites of DNA damage.[5] This difference may result of dissimilar structure and substrate specificity between the 2 demethylases.[3]

The recruitment of several DDR proteins to DNA damage sites is mediated by different key DDR proteins, such as ATM and PARP1.[1] Noteworthy, KDM4D recruitment is independent of ATM activity but is PARP1-dependent. Indeed, KDM4D undergoes ADP-ribosylation (PARylation) by PARP1, and 4 evolutionary conserved residues, E357/R450/R451/R455 are essential for this PARylation. Mutating these residues impairs KDM4D recruitment and leads to defective DSB repair by HR.[4]

In a recent paper published in Cell Cycle, Khoury-Haddad et al., further investigated the mechanism that regulates KDM4D accumulation at breakage sites. They found that KDM4D binds poly (ADP-ribose) (PAR) moieties *in vitro*. KDM4D PAR-binding region was mapped to residues 350-474.[6] This region contains the residues (E357/R450/R451/R455) that are essential for KDM4D PARylation and assembly at sites of DNA damage.[4] A fragment of KDM4D (residues 1-474), containing the PAR-binding domain (residues 350-474), showed a minor and transient accumulation at DNA damage sites. Furthermore, KDM4D lacking the PAR-binding domain (Δ350-474) did not accumulate at DNA damage sites, indicating that residues 350-474 of KDM4D are essential for KDMD4 recruitment to DNA damage sites.[6] It is yet to be determined whether the binding of KDM4D to PAR moieties is critical for its recruitment to DNA damage sites. Moreover, further studies are needed to reveal PARP1-depenedent KDM4D partners at DSB sites.

Furthermore, they tested the effect of KDM4D-RNA interaction on its recruitment to DNA damage sites,[6] since KDM4D chromatin localization is RNA-dependent. Mutating His115/219, Arg222/225/228/236/123 and Lys127 of KDM4D results in loss of RNA and chromatin binding.[7] This mutant, which can no longer bind RNA, failed to accumulate at DNA damage sites, indicating that KDM4D-RNA interaction is required for its DNA damage accumulation.[6]

Altogether, these studies implicate PARP1 and yet unidentified RNA molecules in regulating KDM4D function in the DDR.

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