REGIONAL CENTRE FOR BIOTECHNOLOGY

Seminar series

MOF and histone H4 acetylation at lysine 16 are critical for DNA damage response and double-strand break repair.

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Abstract

The brains of ataxia telangiectasia (AT) patients display an aberrant loss of Purkinje cells (PCs) that is postulated to contribute to the observed deficits in motor coordination as well as in learning and cognitive function. AT patients have mutations in the ataxia telangiectasia mutated (ATM) gene [Savitsky et al. (1995) Science 268:1749–1753]. We have also reported that Purkinje cell (PC)-specific deletion of the mouse males absent on the first (mMof) gene (Cre−), which encodes a protein that specifically acetylates histone H4 at lysine 16 (H4K16ac) and influences ATM function, is critical for PC longevity (Kumar et al; 2011). The human MOF gene encodes a protein that specifically acetylates histone H4 at lysine 16 (H4K16ac). Here we show that reduced levels of H4K16ac correlate with a defective DNA damage response (DDR) and double-strand break (DSB) repair to ionizing radiation (IR). The defect, however, is not due to altered expression of proteins involved in DDR. Abrogation of IR-induced DDR by MOF depletion is inhibited by blocking H4K16ac deacetylation. MOF was found to be associated with the DNA-dependent protein kinase catalytic subunit (DNA-PKcs), a protein involved in non-homologous end-joining (NHEJ) repair. ATM-dependent IR-induced phosphorylation of DNA-PKcs was also abrogated in MOF-depleted cells. Our data indicate that MOF depletion greatly decreased DNA double-strand break repair by both NHEJ and homologous recombination (HR). In addition, MOF activity was associated with general chromatin upon DNA damage and colocalized with the synaptonemal complex in male meiocytes. Thus MOF, through H4K16ac (histone code), has a critical role at multiple stages in the cellular DNA damage response and DSB repair.