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Extended Abstract

A new protein interaction of the SETD1A methyltransferase complex: Linking epigenetic regulation to the DNA damage response

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Abstract

SETD1A is a component of an histone methyltransferase assembly, analogous to the S. cerevisiae Set1/COMPASS complex. In mammalian cells, SET1/MLL histone methyltransferase (HMT) complexes methylate H3K4, resulting in an epigenetic mark generally associated with increased transcription. While the SET domain-containing proteins are believed to be non-redundant, the SET1/MLL complexes contain shared subunits such as WDR5 (WD repeat domain 5), RBBP5 (Retinoblastoma-binding protein 5), ASH2L (Absent, small or homeotic)-like), and HCF1 (host cell factor 1), as well as factors that may be unique to specific complex isoforms. Defects in SETD1A have been linked to a number of human diseases, including cancer and schizophrenia. It is the main catalytic component of a multiprotein complex that methylates lysine 4 of histone H3, a histone mark associated with gene activation. In humans, six related protein complexes with partly nonredundant cellular functions share several protein subunits but are distinguished by unique catalytic SET-domain proteins. To further investigate the role of SETD1A, we mapped the physical interactions of the protein under endogenous conditions in two cell lines (HEK and NT2). We were able to confirm the identity of known interactors within the SETD1A-complex and validated the interaction of a new interactor, Rad18. Rad18 is a ubiquitin ligase involved in DNA repair pathways. Size exclusion chromatography was used to confirm that the interaction with Rad18 occurs in an distinct complex to SETD1A-complex. Depletion of both SETD1A & RAD18 lead to reduce the expression of both proteins, suggesting that SETD1A regulates RAD18 expression. Notably, depletion of both SETD1A and RAD18 shows a defect in the monoubiquitylation of PCNA (Ub-PCNA) in the presence of DNA damage agent (MMC).This newly defined function for SETD1A could be a novel therapeutic target for cancer drug development and therefore detailed structural analysis of the SETD1A domain and its interaction with RAD18 will be illuminating and potentially important for future drug development. Epigenetic research has rapidly evolved into a dynamic field of genome biology. Chromatin regulation has been proved to be an essential aspect for all genomic processes, including DNA repair. Chromatin structure is modified by enzymes and factors that deposit, erase, and interact with epigenetic marks such as DNA and histone modifications, as well as by complexes that remodel nucleosomes. In this review we discuss recent advances on how the chromatin state is modulated during this multi-step process of damage recognition, signaling, and repair. Moreover, we examine how chromatin is regulated when different pathways of DNA repair are utilized. Furthermore, we review additional modes of regulation of DNA repair, such as through the role of global and localized chromatin states in maintaining expression of DNA repair genes, as well as through the activity of epigenetic enzymes on non-nucleosome substrates. Finally, we discuss current and future applications of the mechanistic interplays between chromatin regulation and DNA repair in the context cancer treatment.

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