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A New Chromatin-Cytoskeleton Link in Cancer

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Abstract

The set domain containing 2 (SETD2) histone methyltransferase, located at 3p2, specifically trimethylates lysine 36 of histone H3 (H3K36me3). H3K36me3 is an active mark involved in transcriptional elongation and RNA processing, and a key regulator of DNA repair. In fact, SETD2 is the only methyltransferase that “writes” the H3K36me3 mark. Recent results from Park et al have found a new role for SETD2 in the methylation of K40 of α -tubulin. Loss of SETD2 abolishes methylation of K40 of α -tubulin, and results in a dysfunctional mitotic spindle and abnormalities in cytokinesis. Thus, SETD2 links chromatin and cytoskeleton homeostasis through its methyltransferase activity. These studies have important implications on the role of SETD2 mutations in promoting genomic instability and tumor progression.

Introduction

Defects in chromatin modifying proteins have come to define distinct subsets of both rare and common cancers. Defects in SWI/SNF chromatin remodeling complexes, for example, occur in approximately 20% of all cancers (1). Loss-of-function of one of these complex members, *SMARCB1* (SNF5/INI1/BAF47), defines rare, but very aggressive, malignant rhabdoid tumors (MRT) (2, 3) and renal medullary carcinomas (RMC) (4–6). In the kidney, in addition to MRTs and RMCs, renal cell carcinoma (RCC) is also characterized by defects in chromatin modifiers. Over 95% of clear cell RCCs exhibit 3p loss, resulting in co-deletion of a cluster of chromatin modifier genes on the short arm of chromosome 3: the histone methyltransferase *SETD2*, the SWI/SNF component *PBRM1*, and the histone deubiquitinase *BAP1* (7, 8). Subsequent “second-hit” mutations in these genes result in loss-of-function, and contribute to progression of RCC, and in the case of *SETD2* and *BAP1*, are associated with aggressive tumors and the lethal phenotype (7, 9).

SETD2 in Cancer

SETD2 is a histone methyltransferase responsible for the H3K36me3 methyl mark on histones (10). In addition to rare cancers such as clear cell RCC, glioblastoma multiforme and pancreatic cancers, which are significantly associated with inactivating mutations of *SETD2*, a significant frequency of SETD2 alterations is observed in several more common

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tumors (Figure 1), including melanoma (11), bladder and lung cancer (cbiportal), which also exhibit alterations in other chromatin modifiers such as the SWI/SNF complex SMARCA4 ATP-ase subunit (12).

New Functions for SETD2 in Cancer

Park et al. have now discovered a new function for SETD2 and revealed a previously unknown linkage between the epigenome and the cytoskeleton (13). They found that in addition to histones, SETD2 also methylates α -tubulin, and that methylation is a new post-translational modification of microtubules. They showed that SETD2 directly binds α -tubulin, and can methylate α -tubulin in an *in vitro* methyltransferase assay. They were able to generate an antibody to the site of methylation on microtubules, lysine 40, and using this α -TubK40me3 antibody, showed that methylation occurred on dynamic microtubules during mitosis and cytokinesis. Importantly, they also showed that this microtubule methyl mark was required for genomic stability, as loss of SETD2 caused chromosome segregation errors, micronuclei and polyploidy. Thus, loss of genomic stability is a new mechanism by which defects in SETD2 and possibly other chromatin modifiers can drive oncogenesis.

In support of the importance of SETD2 function at the cytoskeleton, Park et al. examined the impact of SETD2 loss on the epigenome and found minimal impact on gene expression, and no consistent changes between two different lines of kidney cells in which SETD2 had been inactivated. More importantly, they identified a domain on SETD2, which was required for microtubule methylation but not histone methylation (Figure 2). Taken together, this data indicates that SETD2 function as a chromatin and cytoskeleton modifier can be separated. In addition, as pathogenetic mutations are found in the SRI domain of SETD2 in clear cell RCC, cytoskeleton defects could also be contributing to the neoplastic phenotype.

This report also raises the possibility that chromatin modifiers have consequences beyond perturbation of the epigenome and genomic stability that are important in cancer. Certainly other chromatin modifiers, such as EZH2, have been shown to have non-histone targets (14, 15), although none yet have been linked to the cytoskeleton. Furthermore, SETD2 mutations may provide a link between transcriptional events in the nucleus, and cytoskeletal events and their cell biology consequences. The cytoskeleton plays a key role in invasion and metastasis. Although the impact of SETD2 loss on migration and motility has not yet been explored, other chromatin modifiers have been linked to the metastatic phenotype. Loss of the histone demethylase KDM6B/JMJD3, for example, enhances aggressiveness of pancreatic cancer cells (16), and the BAF57 member of the SWI/SNF complex confers a pro-metastatic migratory phenotype on prostate cancer cells (17). SET1A, a member of the COMPASS complex histone methyltransferase (18) is upregulated breast cancer tumors and cell lines, and ablation of *SETD1A* leads to a decrease in migration and invasion *in vitro* and to a decrease in metastasis in nude mice (19). While these authors linked this phenotype to altered epigenetic regulation of expression of genes such as matrix metalloproteinases, it would now be important to explore whether these, and other chromatin modifiers, could also be acting at the cytoskeleton.

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Figure 1. Frequency of SETD2 alterations in human tumors
A search of tumors with SETD2 alterations distributed by frequency identifies both rare and commons tumors with alterations in this gene (cBioPortal).

Figure 2. Distribution of mutations in SETD2

Mutations predicted to inactivate SETD2 occur throughout the protein, and cluster in the functional methyltransferase set domain. The SRI domain is also a site for pathogenic SETD2 mutations (from cBioPortal).