Signaling

Major finding: Nuclear IκBα binds to histones H2A and H4 and facilitates Polycomb-dependent HOX gene silencing.

Clinical relevance: Nuclear IκBα accumulation decreases with squamous cell carcinoma progression.

Impact: IκBα has a noncanonical nuclear function that is critical to skin homeostasis and development.

CHROMATIN-BOUND IκBα MEDIATES POLYCOMB ACTIVITY

The only known activity of IκB proteins is the cytoplasmic sequestration and inhibition of NF-κB. IκB proteins have been found in the nucleus, but their functional significance is unclear. Mulero and colleagues evaluated IκBα localization in human tissues and observed nuclear IκBα staining in the skin, particularly in keratinocytes. Both cytoplasmic and nuclear IκBα could be detected, but phosphorylation and SUMOylation of IκBα were specifically required for its nuclear accumulation. The phosphorylated, SUMOylated nuclear form of IκBα specifically interacted with histones H2A and H4, but not NF-κB, indicating that IκBα can directly bind chromatin in an NF-κB–independent manner. Chromatin immunoprecipitation sequencing in primary human keratinocytes revealed that IκBα binds near promoter and enhancer regions of genes associated with embryonic development and differentiation, including homeobox (HOX) genes. IκBα-occupied loci were also enriched for high levels of the repressive histone H3 lysine 27 trimethylation mark, and overlapped with Polycomb repressive complex (PRC) binding sites. Consistent with these findings pointing to a noncanonical role of IκBα in Polycomb-dependent gene silencing, nuclear IκBα physically interacted with the PRC2 subunit SUZ12, the simultaneous binding of both proteins to IκBα targets was associated with decreased gene expression, and mutation of the *Drosophila* IκB homolog enhanced the Hox-related extra sex combs phenotype of Polycomb mutant flies independently of the *Drosophila* NF-κB homolog. Given that deregulated HOX expression occurs in squamous cell carcinomas, which develop from keratinocytes, the authors assessed IκBα localization in transformed keratinocytes and found that nuclear IκBα accumulation was lost in association with decreased PRC2 binding and massive upregulation of IκBα target genes. Moreover, depletion of nuclear IκBα correlated with squamous cell carcinoma progression. These findings point to a role of nuclear IκBα in developmental gene regulation and suggest that loss of nuclear IκBα may be oncogenic. ■

Mulero MC, Ferres-Marco D, Islam A, Margalef P, Pecoraro M, Toll A, et al. Chromatin-bound IκBα regulates a subset of Polycomb target genes in differentiation and cancer. Cancer Cell 2013;24:151–66.

Genomic Instability

Major finding: Overexpression of the H3K9/36me3 demethylase KDM4A induces gain of 1q12, 1q21, and Xq13.1.

Mechanism: KDM4A promotes DNA rereplication by displacing HP1γ and recruiting the replication machinery.

Impact: The local chromatin state can determine the susceptibility of certain genomic loci to copy gains.

KDM4A PROMOTES SITE-SPECIFIC COPY NUMBER GAIN

Recurring amplifications of specific genomic loci are observed in human cancers, but the factors that predispose to copy number gains are poorly understood. Given previous findings showing that focal amplification events occur during S phase and that lysine (K)-specific demethylase 4A (KDM4A), an H3K9/36me3 demethylase, regulates DNA accessibility and replication timing, Black and colleagues hypothesized that KDM4A could provide a link between local chromatin structure and copy number variation. Analysis of *KDM4A* copy number and expression level in The Cancer Genome Atlas revealed that amplification and overexpression of *KDM4A* occurred in 18.9% of tumors overall and in 46% of ovarian cancers. Stable overexpression of KDM4A did not induce large-scale genomic instability but instead resulted in a specific increase in KDM4A occupancy at chromosome 1q12 and focal amplification of this locus in 14% of cells. Gain of 1q12 was specifically dependent on KDM4A, required KDM4A enzymatic activity, and could be suppressed by overexpression of the H3K9me3 methyltransferase SUV39H1 or the H3K9me3-binding protein heterochromatin protein 1γ (HP1γ). Interestingly, 1q12 copy gain was not stably inherited but was generated during S phase of each cell cycle before being eliminated by the end of G2. KDM4A directly bound and recruited the MCM complex and DNA polymerase to 1q12 and induced rereplication of this locus in association with decreased H3K9me3 and HP1γ occupancy, suggesting that KDM4A can induce site-specific copy number gain by altering local chromatin structure and recruiting the DNA replication machinery. In primary tumors, *KDM4A* amplification was not only correlated with gain of 1q12 but was also correlated with gain of 1q21 and Xq13.1, which were likewise found to be rereplicated in KDM4A-overexpressing cells. Although the reason why these particular loci are amplified upon KDM4A overexpression remains unclear, these findings establish that deregulation of a chromatin modulator can result in site-specific copy number abnormalities. ■

Black JC, Manning AL, Van Rechem C, Kim J, Ladd B, Cho J, et al. KDM4A lysine demethylase induces site-specific copy gain and rereplication of regions amplified in tumors. Cell 2013;154:541–55.

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