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Role of the SMYD3 histone methyltransferase in tumorigenesis

Local or global effects?

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Tumorigenesis is often accompanied by changes in the enzymes that catalyze posttranslational modifications of histone tails, leading to alterations in chromatin structure and gene expression.[1] For example, several histone methyltransferases (HMT) responsible for either activating or repressive methylation marks have been implicated in cancer progression, suggesting that these enzymes may be promising targets for oncology drug discovery. However, an unresolved issue is the specificity of these methylation events and the gene targets responsible for their associated tumor phenotypes. Furthermore, their impact may be on chromatin structure at the global level, or rather may be focused on localized effects on key specific gene promoters.

Histone methylation events control transcriptional activity by modulating chromatin structure and the accessibility of transcription factors and RNA polymerase II at promoters. Methylation can be associated with transcriptional activation (i.e., H3K4, H3K36 and H3K79) or with transcriptional repression (i.e., H3K9, H3K27 and H4K20). The HMT SMYD3 (SET and MYND domain containing protein 3) is particularly interesting, as its SET domain is crucial for histone lysine methylation activity, and its MYND-type zinc-finger domain (zf-MYND) can bind to specific DNA motifs.[2] Moreover, SMYD3 was reported to be overexpressed in several cancers, including colorectal, hepatocellular and breast cancer cells, and was also identified in gene signatures in metastatic pancreatic tumors.[3,4] However, the effects of SMYD3 on histone modification and gene expression relevant to tumor progression remains relatively unclear.

SMYD3 was initially reported to methylate lysine 4 of histone H3 (H3K4).[2] However, recent studies have questioned this function and proposed H4K20 or H4K5 as SMYD3 substrates.[5,6] Indeed, SMYD3 knockdown led to global decreases in H4K5me without affecting total cellular H3K4 methylation levels.[6] However, it remains possible that specific localized events on selective promoters might contribute to SMYD3-driven tumorigenesis.

We recently provided evidence for this hypothesis by showing that SMYD3 binds to the proximal promoter region of the gene encoding MMP-9, a matrix metalloprotease involved in tumor cell invasion and metastasis.[7] The silencing of *SMYD3* expression caused a selective decrease in H3K4 methylation on the *MMP-9* promoter and reduced gene expression. We used in vitro invasion assays and in vivo zebrafish xenotransplantation models to demonstrate a functional impact on the invasiveness and metastatic behavior of human tumor cells.[7] MMP family members degrade extracellular matrix (ECM) components and activate growth factors. Elevated levels of MMP-9 are detected in multiple human cancers, such as breast, colon, brain and lung cancer, and inflammatory diseases, such as multiple sclerosis and rheumatoid arthritis. Clinical trials using MMP inhibitors have been hampered by problems with selectivity, so it remains a challenge to develop strategies to target the epi-regulation of *MMP-9* expression.[8] In our hands, SMYD3 levels did not have an effect on global H3K4 methylation but appeared to impact selective promoter regions.[7] As metastasis is responsible for most cancer-related death, it remains a significant challenge to dissect the precise series of epigenetic events in tumor progression. Our discovery that the SMYD3 histone methyltransferase regulates the epigenetic expression of an essential pro-metastatic gene *MMP-9* offers a target to develop therapeutic strategies aimed at preventing cancer progression. Future studies exploring the crosstalk between H3K4, H4K20 or H4K5 methylation events will likely throw new light on the local or global impact of SMYD3 in cancer cells.

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