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Characterization of the SMYD Family of Lysine Methyltransferases: *Reflections upon Key Findings and Therapeutic Implications*

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Abstract: It has been almost two decades since studies upon the SET-MYND (SMYD) family of lysine methyltransferases were first initiated following the serendipitous discovery of the SMYD1 gene. In that time, much has been learned about the roles of the SMYD family in processes ranging from embryogenesis to tumorigenesis. Herein, we reflect upon the implications of the ongoing characterization of the SMYD family with regard to the growing landscape of therapeutic targets.

Introduction

In 1995, Hwang and Gottlieb reported the discovery of the SMYD1 gene as an unanticipated finding during their study of the CD8b promoter[1]. According to their report, unexpected promoter activity, distinct from that of CD8b, was identified upstream of the CD8b gene. Further analysis ultimately revealed that the second promoter activity was associated with a gene that is transcribed opposite to that of CD8b. The newly detected gene was thus reported with the designation, "Bop," for "CD8b opposite." It was not for another decade, when a second member of the family was reported[2], that the official nomenclature for the Bop family was revised to account for the unique presence of both a SET (Suppressor of variegation, Enhancer of Zeste, Trithorax)[3] and MYND (Myeloid-Nervy-DEAF1)[4-6] domain. Since then, the SMYD family has been characterized as key regulators of cellular processes whose aberrant expression can lead to pathological consequences.

SMYD1

Following a targeted deletion of SMYD1, Gottlieb *et al*. ultimately determined that it is essential in *cardiomyocyte differentiation* and *cardiac morphogenesis*[7]. Absence of SMYD1 reduces the expression of key transcription factors associated with the right ventricle of the heart, leading to *ventricular hypoplasia*. In a murine model, this is embryonically lethal at day 9.5. The transcriptional regulation imparted by SMYD1 was later shown to be facilitated by the methylation activity of its SET domain[8]. This finding, along with the more recent elucidation of the SMYD1 structure[9], provide a foundation upon which future advances may lead to therapeutics for the clinical management or, perhaps, prevention of human heart defects involving the underexpression of SMYD1. Given the timing of events dependent upon proper expression of SMYD1 during embryogenesis, likely pathways for gene therapeutic intervention are dependent upon significant advances in gene therapy technologies.

SMYD2

The initial characterization of SMYD2 indicated that it too catalyzes methylation in a highly specific, SET-dependent manner[10]. That study also revealed that SMYD2, like SMYD1, is highly expressed in the heart. However, targeted deletion of SMYD2 in a murine model showed that it is dispensable in the heart[11]. The greatest therapeutic potential associated with SMYD2 is likely related to its role in the SET-mediated methylation and repression of the tumor suppressor, p53. More recently, the retinoblastoma tumor suppressor has also been identified as a target of SMYD2. Thus potential therapeutics involving SMYD2 will likely have oncogenic applications via spatial and/or temporal control SMYD2-mediated catalysis. Studies highlighting the structural basis for

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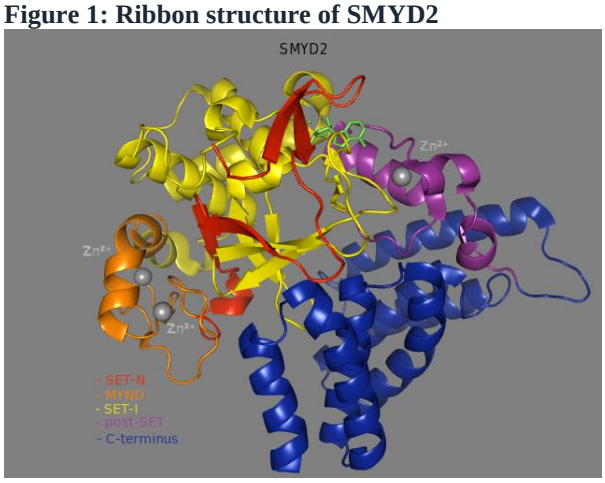
SMYD2-mediated methylation of p53[12-13] provide a framework for such translational research.

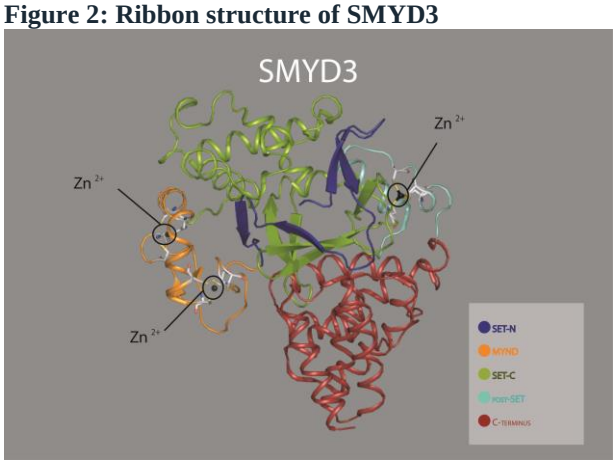
Figure 1: Ribbon structure of SMYD2



SMYD3

SMYD3 has been shown to catalyze trimethylation of H4-K20[14], H4-K5[15], and H3-K4[2] and monomethylation of vascular endothelial growth factor receptor 1[16]. SMYD3 has also been implicated as a proto-oncogene in colorectal, hepatocellular and breast carcinomas[17-20] by virtue of its over-expression and promoter-associated polymorphisms in malignant cells. Thus, catalytic inhibition of aberrantly expressed SMYD3 is the target of most ongoing attempts to develop therapeutics involving this SMYD family member. Targeting of its catalytic domain has been facilitated by the availability of three independent SMYD3 crystal complexes[14, 21-22].

Figure 2: Ribbon structure of SMYD3



Further potential for therapeutic applications associated with SMYD3 are manifest in the recent findings that a degenerate tetratricopeptide repeat (TPR)-like domain encoded in the SMYD3 C-terminal domain (CTD) mediates physical interaction with the nuclear chaperone, HSP90[23]. In the same study, it is further demonstrated that the CTD of SMYD3 is essential for its basal HMTase activity and that the TPR-like structure facilitates HSP90-enhanced catalysis. Finally, impairment of the SMYD3-HSP90 association results in SMYD3 mislocalization within the nucleus and its consequent loss of chromatin association. This, in turn, results in reduction of SMYD3-mediated cell proliferation and inhibition of its oncogenic activity. These findings highlight the potential for a novel approach to impeding HSP90-driven malignancy in SMYD3-overexpressing cells which would exhibit a reduced toxicity profile over current HSP90 inhibitors.

SMYD4 and SMYD5

SMYD4 and SMYD5 have yet to be comprehensively characterized. However, data from Expressed Sequence Tags suggests that they are expressed in a wide range of normal, tumor, and diseased tissues[24]. This broad range of expression presents the potential for future applications targeting the expression or catalytic mechanisms of SMYD4 and/or SMYD5 in the clinical management of human disease.

Conclusions

The SMYD Family is a group of cell regulators that function primarily through SET-mediated methylation of target proteins. Future research on SMYD proteins, with strong emphasis on the distinct organismal context, will further elucidate key biological functions of SMYD family proteins along with the implications of their aberrant activities. Such emphases may reveal new paradigms for framing future therapeutics targeting the expression and/or catalytic activity of the SMYD family.

Acknowledgments

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