Smyd2 Vs Smyd3: Structure based analysis of small molecule binding selectivity

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Often, proteins belonging to the same family elicit distinct downstream bioactivities yet tend to have similar substrate/cofactor binding pockets with high sequence conservation. This makes it challenging for selective binding of small molecules to protein of interest during drug development. In order to better understand the dynamics of small molecule binding in homologous proteins, we did a structural comparative study of Smyd-small molecule complexes.

Smyd (1-5) proteins are members of the protein methyltransferase family containing conserved SET and Zinc-finger MYND domains. *In vivo*, Smyd2 is known to methylate histone H3 and p53 and Smyd3, on the other hand, methylates histone H3 and MAP3 Kinase2. Overexpression of Smyd2 has been reported in esophageal squamous primary carcinomas and Smyd3 is overexpressed in colorectal and hepatocellular carcinoma.

Bay-598 is a substrate competitive probe of Smyd2 with >100-fold selectivity over other histone methyltransferases. Smyd3-Bay598 complex structure reveals a binding pocket that is similar to Smyd2. X-ray crystal structure of Smyd3-Bay598 complex along with biophysical studies was performed to dissect the structural basis for the high selectivity of Smyd2 to Bay-598.