

Cfp1/Cps40 stabilizes MLL complex formation through multi-valent interactions

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The SET1 family of methyltransferases (SET1A/B, MLL1-4) are responsible for the methylation of Lys-4 on histone H3 (H3K4), a post-translational modification that is predominantly localized in the promoter and enhancer regions of actively transcribed genes. Moreover, mis-regulation or mutations of members of SET1 family of PKMTs is now recognized as a hallmark of cancers. Members of the SET1 family of methyltransferases require several regulatory subunits to efficiently methylate histone H3. These subunits include DPY30/Cps25, WDR82/Cps30, WDR5/Cps35, Cfp1/Cps40, RbBP5/Cps50 and Ash2L/Cps60. Once bound to SET1, these proteins form a protein complex referred to as COMPLEX ASSociated to SET1 (COMPASS) whose role is to fully activate the methyltransferase activity of SET1. While previous structural studies highlighted important molecular underpinnings underlying the interaction of COMPASS subunits¹⁻³, they failed to capture the overall architecture of COMPASS. In addition, owing to the low resolution of a Cryo-EM structure of COMPASS⁴, an in-depth understanding of the structural determinants controlling the formation and regulation of COMPASS remains elusive.

Here we present the purification and partial *in vitro* reconstitution of COMPASS from *Chaetomium thermophilum*. Biochemical evidence suggest that Cps40 is able to regulate the COMPASS activity through interacting with regions found at the N-terminus of SET1 catalytic domain as well RbBP5/Cps50 and WDR5/Cps35 likely prompting these subunits to shape the SET domain into an active conformation. These results pave the way for further in-depth understanding of COMPASS's structure and regulation, especially the Cfp1/Cps40's role in COMPASS biology.

1) Sarvan, S. et al. Nat. Struct. Mol. Biol. 18, 857–9 (2011).

2) Zhang, P. et al. Genes Dev. 29, 123–8 (2015).

3) Avdic, V. et al. Structure 19, 101–8 (2011).

4) Takahashi, Y. et al. Proc. Natl. Acad. Sci. U. S. A. 108, 20526–31 (2011)