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Cryo-EM structures of human PRMT5:MEP50 complex reveal chemical basis for designing high-specificity inhibitors

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Protein arginine methyltransferase 5 (PRMT5) has emerged as a promising oncogenic drug target. Multiple PRMT5 inhibitors are currently in differential stages of clinical trials for different cancer types. So far, all inhibitors against PRMT5 share an intrinsic limitation that their inhibitory efficiency decreases significantly in the presence of 2-methylthioadenosine (MTA). MTA is a cofactor analog of PRMT5 and is accumulated by 5-10 folds in a major fraction of cancer cells containing mutated MTA phosphorylase (MTAP) genes in patients. To overcome this problem, we urgently need PRMT5-specific inhibitors that specifically inhibit its enzyme activity in the presence of MTA accumulation. In this study, we took advantage of virtual screening to identify a pharmacophore and used it for structure-based drug design against PMRT5. We were able to design and synthesize specific inhibitors for PRMT5 and determined structures of PRMT5:MEP50 using single-particle cryo-electron microscopy. We tested the effect of newly identified inhibitors on PRMT5 and found that one of them is ~5 fold higher in enzyme inhibition in the presence of MTA than without MTA. Structural comparison of the apo and inhibitor bound PRMT5 complexes shows that binding of an inhibitor in the catalytic pocket pushes against the cofactor binding site, leading to positive cooperativity in the binding of the inhibitor and MTA. The PRMT5-inhibitor structure provides fresh structural insights into the design and development of better small molecule inhibitors against PRMT5.

References

Afonine, P.V., Poon, B.K., Read, R.J., Sobolev, O.V., Terwilliger, T.C., Urzhumtsev, A., and Adams, P.D. (2018). Real-space refinement in PHENIX for cryo-EM and crystallography. Acta Crystallogr D Struct Biol *74*, 531-544.

Alinari, L., Mahasenan, K.V., Yan, F., Karkhanis, V., Chung, J.H., Smith, E.M., Quinion, C., Smith, P.L., Kim, L., Patton, J.T., *et al.* (2015). Selective inhibition of protein arginine methyltransferase 5 blocks initiation and maintenance of B-cell transformation. Blood *125*, 2530-2543.

Andreu-Perez, P., Esteve-Puig, R., de Torre-Minguela, C., Lopez-Fauqued, M., Bech-Serra, J.J., Tenbaum, S., Garcia-Trevijano, E.R., Canals, F., Merlino, G., Avila, M.A., *et al.* (2011). Protein arginine methyltransferase 5 regulates ERK1/2 signal transduction amplitude and cell fate through CRAF. Sci Signal *4*, ra58.

Antonysamy, S., Bonday, Z., Campbell, R.M., Doyle, B., Druzina, Z., Gheyi, T., Han, B., Jungheim, L.N., Qian, Y., Rauch, C., *et al.* (2012). Crystal structure of the human PRMT5:MEP50 complex. Proc Natl Acad Sci U S A *109*, 17960-17965.

Banasavadi-Siddegowda, Y.K., Welker, A.M., An, M., Yang, X., Zhou, W., Shi, G., Imitola, J., Li, C., Hsu, S., Wang, J., *et al.* (2018). PRMT5 as a druggable target for glioblastoma therapy. Neuro Oncol *20*, 753-763.

Biggar, K.K., and Li, S.S. (2015). Non-histone protein methylation as a regulator of cellular signalling and function. Nat Rev Mol Cell Biol *16*, 5-17.

Burgos, E.S., Wilczek, C., Onikubo, T., Bonanno, J.B., Jansong, J., Reimer, U., and Shechter, D. (2015). Histone H2A and H4 N-terminal tails are positioned by the MEP50 WD repeat protein for efficient methylation by the PRMT5 arginine methyltransferase. J Biol Chem *290*, 9674 9689.

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