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Molecular enzymology of DNA methyltransferases – conformational changes and allosteric regulation

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DNA methylation is an essential epigenetic chromatin modification. The setup and maintenance of DNA methylation patterns depends on the coordinated activity of DNA methyltransferases (DNMTs) and their allosteric regulation by interacting proteins, other chromatin modifications and post-translational modifications. I will present novel assays for DNMTs including single enzyme assays to study their mechanism and conformationally locked mutants to study allosteric effects. Based on this, recent data regarding the regulation and targeting of DNMTs by allosteric effect will be presented. Moreover, I will present insights into the mechanism of DNMTs regarding target site location, specificity and processivity.

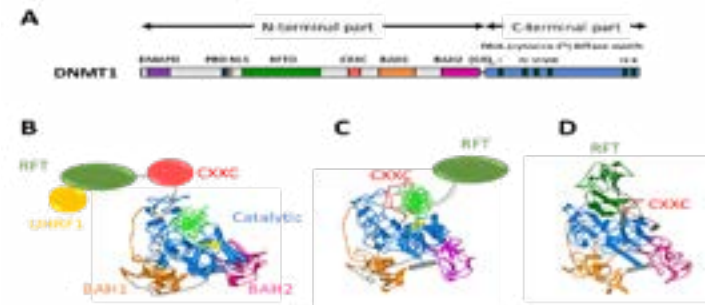

Figure 1: Domain structure and 3D structure of DNMT1. A) Domain structure of DNMT1 (for descriptions of the domains refer to the main text). B-D) Different structures of DNMT1 with AdoHcy shown in yellow and DNA in light green. B) Structure with DNA bound in the active site. UHRF1 (yellow) stabilizes the active conformation of DNMT1. C) Structure with unmethylated DNA bound to the CXXC domain. D) Apoenzyme structure with the RFT domain blocking of the active site.

Recent Publications

1. Lungu et al. (2017) Modular fluorescence complementation sensors for live cell detection of epigenetic signals at endogenous genomic sites. Nature Communications 8:649.
2. Maier, Möhrle and Jeltsch (2017) Design of synthetic epigenetic circuits exhibiting positive feedback, memory effects and reversible switching, Nature Communications 8:15336.
3. Jurkowska and Jeltsch (2016) Allosteric control of mammalian DNA methyltransferases - a new regulatory paradigm. Nucleic Acids Res. 44:8556-8575.
4. Bashtrykov, et al. (2014) The UHRF1 protein stimulates the activity and specificity of the maintenance DNA methyltransferase DNMT1 by an allosteric mechanism. J. Biol. Chem. 289:4106-15.
5. Jeltsch and Jurkowska (2014) New concepts in DNA methylation. Trends Biochem Sci. 39:310-18.

Biography

Albert Jeltsch completed his PhD working on the mechanism of restriction endonucleases at University of Hannover in 1994. Afterwards, he started to study DNA methyltransferases at Justus-Liebig University Giessen and at Jacobs University Bremen. Since 2011, he is a Professor of Biochemistry at the University Stuttgart. He received the Gerhard-Hess award (DFG) and BioFuture award (BMBF). He has long standing expertise in Biochemical study of DNA and protein methyltransferases, methyl lysine reading domains and in rational and evolutionary protein design. His work has been published in more than 250 publications in peer reviewed journals and he is in the editorial boards of several journals.

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