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ABSTRACTS

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Fundamental Biocatalysis

General Aspects

Functional role of DNMT3a DNA methyltransferase mutations observed in acute myeloid leukemia

Gromova E.S.[1], Khrabrova D.A.[1], Kirsanova O.V.[1], Loiko A.G.[1], Tolkacheva N.A.[1], Cherepanova N.A.[2]

[1]*Chemistry Department, Moscow State University, 119991, Moscow, Russia*

[2]*Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA 01605*

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DNA methylation of cytosine residues in CpG sites is an epigenetic modification that plays an important role in the regulation of gene expression and in other biological processes. In mammals, DNA methylation is introduced by *de novo* DNA methyltransferase (MTase) Dnmt3a. Recently genomic studies on acute myeloid leukemia (AML) have demonstrated that a gene encoding for human DNMT3A (human enzyme is denoted by capital letters) is frequently mutated with striking prevalence of R882H mutation. R882H has been extensively studied and its potential carcinogenic effect has been suggested. We investigate the role of the other missense mutations in DNMT3A catalytic domain found in AML (S714C, R635W, R736H, R771L, P777R, and F752V) using accordingly mutated murine Dnmt3a catalytic domain (Dnmt3a-CD) and 30-mer CpG-containing DNA substrates as model system. Human and murine enzymes have identical primary structures of the catalytic domain. *In vitro* methylation assays showed the 3-5-fold reduced activity for R181L (R771L), S124C (S714C) and P187R (P777R) mutants. The most pronounced reduction of the activty was observed for F152V (F752V), R45W (R635W) and R146H (R736H). Further, the effect of these mutations on individual steps of the methylation reaction was studied. R181L (R771L), S124C (S714C) and P187R (P777R) preserve the ability to bind DNA as it was shown by similar dissociation constants for the Dnmt3a-CD/DNA complexes. In the case of R45W (R635W) and R146H (R736H) a complete loss of DNA binding properties was observed. Finally, the ability of the DNMT3A partner protein DNMT3L to restore the methylation activities of S124C (S714C) and R181L (R771L) was revealed. Hence, mutation in DNMT3A leads to diverse levels of activity and interaction with Dnmt3a partners. Strikingly, all the mutations except S124C (S714C) are not located in the DNMT3A catalytic loop. The contribution of the studied specific residues to molecular mechanism of DNMT3a-mediated DNA methylation was suggested. The role of aberrant DNMT3a activity in AML was discussed on the basis of our knowledge of how these mutations affect methylation function. Collectively, these data together with previously studied R790 and R792 DNMT3a mutants [1] suggest functional impairment of DNMT3a during pathogenesis.

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1. O.V. Lukashevich, N.A. Cherepanova, R.Z. Jurkovska, A.Jeltsch and E.S. Gromova, ***BMC Biochemistry*** (2016) 17:7 (1-10).