Epigenomic and transcriptional effects of Dnmt3b mutations in human ICF syndrome-derived B cell lines

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Immunodeficiency, Centromeric region instability, Facial anomalies (ICF) syndrome (OMIM 242860), is a human autosomic recessive disease due to mutations in the Dnmt3b gene, characterized by inheritance of aberrant patterns of DNA methylation and heterochromatin defects (1). How mutations in Dnmt3B and the resulting deficiency in DNA methyltransferase activity result mainly in immunodeficiency has not been clarified yet. Patients show variable agammaglobulinemia and a reduced number of T cells, making them prone to infections and death before adulthood. It is already known that the expression of several genes and microRNAs is deregulated in ICF lymphoblastoid cell lines (LCLs), being both up- and down-regulated (2,3). Surprisingly, subtle but significant reduction of promoter methylation was seen in only few analyzed upregulated genes and approximately half of them were marked with loss of repressive histone modifications, particularly H3K27 trimethylation, and gain in transcriptionally active H3K9 acetylation and H3K4 trimethylation marks, while an extensive change of histone modifications of upregulated miRNAs was always observed.

It is clear that Dnmt3B mutations affect not only DNA methylation, but also several other expression regulators. In order to assess to what extent these mutations affect the epigenetic landscape of the whole genome we examined the global DNA methylation profile using the Infinium assay from Illumina, the genome-wide mapping of 3meK4H3, 3meK27H3 and RNA Polymerase II (Pol II) by chromatin immunoprecipitation-sequencing (ChIP-seq) and correlated those to mRNA transcriptome (obtained by RNA-seq) and to microRNA expression (by previous microarray results) in ICF and control LCLs. We found a positive correlation between active genes, binding of Pol II and 3meK4H3 binding and an opposite correlation with 3meK27H3 binding and DNA methylation as expected. Moreover, we identified several regions of interest, which are differentially enriched between the patient and the controls. The complete results will be shown in the poster.

Beyond its relevance to ICF syndrome, by addressing the impaired DNMT3B functions in abnormal epigenome cases and how these reflect to the transcriptomes of the affected cells, these data will provide new insights in the field, unravelling the physiological contribution of DNMT3B to the epigenetic network.

References

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