Professor Ulrich Mahlknecht

Editor-in Chief

*Clinical Epigenetics*

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Dear Professor Ulrich Mahlknecht,

Enclosed please find out our recent research paper entitled “Genome-wide DNA methylation patterns in CD4+ T reveal significant contribution of DNA methylation to rheumatoid rthritis”. Rheumatoid arthritis (RA) has been demonstrated as a complex disease which is involved with genetic and epigenetic aberrant. Current study has showed the genetic variation could only explained 20%-50% of the heritability of RA. It is a urgent task to identify missing heritability of RA which would bring insight to the pathological mechanism and therapy to RA. In the present study, performed a genome-wide DNA methylation study in CD4+ T cells in 12 rheumatoid arthritis patients and 12 matched normal healthy controls. 810 hypomethylated and 392 hypermethylated CpG sites in RA CD4+ T cells compared to normal controls were identified with the multiple test correction. 383 hyper methylated and 785 hypomethylated genes were found in RA patients. Cluster analysis based on significantly differential methylated loci showed distinct separation between RA and normal controls, indicating that these methylation difference reflected the biology difference of CD4+ T-cell between RA and normal. Gene ontology analysis showed alternative splicing and phosphoprotein were significantly aberrant in RA patients, indicating the abnormal of transcript alternative splicing and protein modification mediated by DNA methylation might play important role in the pathogenesis of rheumatoid arthritis. What’s more, the result showed human leukocyte antigen (HLA) region was frequently hypo-methylated in RA patients, including HLA-DRB6, HLA-DQA1 and HLA-E. What’s more, large number differential CpG loci between RA and normal were found to be significantly associated with some important clinical characteristic of RA, such as course of a disease (COD), swollen joint count (SJC), tender joint count (TJC), patient global assessment (PGA) and disease activity score in 28 Joints (DAS 28). Genome-wide DNA methylation patterns revealed significant DNA methylation change in CD4+ T cells from patients with rheumatoid arthritis. Our study showed the significant contribution of DNA methylation to rheumatoid arthritis and provided large number of candidate aberrant DNA methylation regions which can be investigated in the RA clinical and bench research.

All authors have agreed the current version of the manuscript. The manuscript has not been submitted to elsewhere for considering publication.

Thanks for your editorial help in advance.

Sincerely,

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