

Epigenetic changes in T-cell and monocyte signatures and production of neurotoxic cytokines in ALS patients

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Abstract

We have investigated transcriptional and epigenetic differences in peripheral blood mononuclear cells (PBMCs) of monozygotic female twins discordant in the diagnosis of amyotrophic lateral sclerosis (ALS). Exploring DNA methylation differences by reduced representation bisulfite sequencing (RRBS), we determined that, over time, the ALS twin developed higher abundances of the CD14 macrophages and lower abundances of T cells compared to the non-ALS twin. Higher macrophage signature in the ALS twin was also shown by RNA sequencing (RNA-seq). Moreover, the twins differed in the methylome at loci near several genes, including *EGFR* and *TNFRSF11A*, and in the pathways related to the tretinoin and H3K27me3 markers. We also tested cytokine production by PBMCs. The ALS twin's PBMCs spontaneously produced IL-6 and TNF- α , whereas PBMCs of the healthy twin produced these cytokines only when stimulated by superoxide dismutase (SOD)-1. These results and flow cytometric detection of CD45 and CD127 suggest the presence of memory T cells in both twins, but effector T cells only in the ALS twin. The ALS twin's PBMC supernatants, but not the healthy twin's, were toxic to rat cortical neurons, and this toxicity was strongly inhibited by an IL-6 receptor antibody (tocilizumab) and less well by TNF- α and IL-1 β antibodies. The putative neurotoxicity of IL-6 and TNF- α is in agreement with a high expression of these cytokines on infiltrating macrophages in the ALS spinal cord. We hypothesize that higher macrophage abundance and increased neurotoxic cytokines have a fundamental role in the phenotype and treatment of certain individuals with ALS.—Lam, L., Chin, L., Halder, R. C., Sagong, B., Famenini, S., Sayre, J., Montoya, D., Rubbi L., Pellegrini, M., Fiala, M. Epigenetic changes in T-cell and monocyte signatures and production of neurotoxic cytokines in ALS patients.