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Estrogen receptor-alpha regulates epigenetic changes on genomic regulatory regions: potential biomarkers in multiple sclerosis outcomes

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Background: Estrogen immunomodulation is associated with a reduction of relapse rate among women with multiple sclerosis (MS) during the third trimester of pregnancy. Estrogen Receptor-alpha (ERa) may regulate the differentiation of T cell subtypes, particularly of T regulatory (Treg) and Th17 cells.

Goals: Identification and validation of cell-type-specific genomic regulatory regions able to influence the proportion of Treg / Th17 cells of MS patients during pregnancy.

Material and methods: Peripheral blood mononuclear cells (PBMC) from 13 pregnant women patients 8 pregnant (8 MS and 5 healthy) were collected during the 3rd trimester of pregnancy and post-partum. Cell-type-specific regulatory regions have been identified by data integrative analysis on FoxP3 and RORc loci, coding for lineage-determining transcription factor of Treg and Th17 cell differentiation. Epigenetic modifications and ERa binding enrichment were evaluated by chromatin immunoprecipitation assay. RORc and FoxP3 promoter and genomic regulatory regions have been selected by bioinformatic analysis. In vitro analyses on purified Th17 and Tregs treated with E2 were conducted.

Results: ERa binds on RORc and FoxP3 promoter and genomic regulatory regions. On the third trimester of pregnancy, we observed that on Treg cells H3K4me3 on FoxP3, gene activation marker, is enriched more than H3K27me3, gene silencing marker; the ratio of H3K4me3/ H3K27me3 changed, in a similar way, in the post-partum. In vitro, the E2 treatment, induces, on cell-type-specific regulatory regions of purified and polarized Th17 cells the enrichment of H3K27me3, gene silencing marker, on RORc and the enrichment of H3K4me3, gene activation marker, of FoxP3.

Conclusion: ERa binds to regulatory regions of Foxp3 and RORC, driving the balance of Treg/Th17. This effect of E2 is confirmed in vitro. This result in a larger population of pregnant and non pregnant patients, could lead to the identification of new epigenomic biomarkers for monitoring disease outcomes and interferon treatment efficacy.

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