

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

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

**This is a pre print version of the following article:**

*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/1757444> since 2020-10-01T14:59:24Z

*Publisher:*

SAGE PUBLICATIONS LTD

*Terms of use:*

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

**Abstract:** P948

**Type:** Poster

**Abstract Category:** Pathology and pathogenesis of MS - Genetics /Epigenetics and Pharmacogenetics

**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.

**Disclosure:**

This study is partially supported by grant from Merck Italy, an affiliate of Merck KGaA, Darmstadt, Germany.

Dr Clerico received personal compensation from Biogen Idec and Merck Serono for public speaking, editorial work and advisory boards.

Dr Cutrupi has nothing to disclose

Dr. Iannello has nothing to disclose

Dr. Ferrero has nothing to disclose

Dr. Cordero has nothing to disclose

Dr. Rolla has nothing to disclose

Dr. Annibali is an employee of Medical Affairs Division of Merck, Italy

Dr. De Bortoli has nothing to disclose

Dr Durelli received personal compensation from Biogen Idec and Merck Serono for public speaking, editorial work and advisory boards.