**75. Methylation and Transcriptome Signatures of Monocytes Reveal Novel Pathways Involved in Giant Cell Arteritis Pathogenesis**

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**Background:** Giant cell arteritis (GCA) is an immune-mediated large-vessel vasculitis with a complex etiology mediated by the interplay between both genetic and epigenetic factors. Several immune cells have been linked to its pathophysiology, including CD14+ monocytes that are crucial in the systemic and local inflammatory processes. Considering that the integration of -omics data has proven to be effective in yielding insight into our understanding of the molecular bases of complex diseases, we aimed to perform an integrative analysis of DNA methylation and gene expression profiling of CD14+ monocytes in GCA.

**Methods:** CD14+ monocytes were positively sorted by flow cytometry from whole blood of 31 healthy controls and 82 GCA patients within three different clinical status (active, in remission with glucocorticoid (GC) treatment, and in remission without treatment). Subsequently, DNA methylation profiling with the Illumina Infinium Methylation EPIC array and RNA-sequencing were carried out for an epigenome- and transcriptome-wide association study, respectively. MatrixEQTL R package was used to determine the correlation among DNA methylation changes and gene expression alterations.

**Results:** The results revealed a profound dysregulation in both the methylome and gene expression landscape of CD14+ monocytes of GCA patients. In particular, monocytes from patients with active disease showed a more pro-inflammatory phenotype compared to controls and patients in remission. As examples, response to interleukin-6 (IL-6) and IL-1 as well as IL-11, that emerged as a new cytokine pathway implicated in GCA, were dysregulated in monocytes from active patients. Furthermore, monocytes from patients in remission with treatment presented an anti-inflammatory phenotype when comparing with controls and patients in remission without treatment, with overexpression of glucocorticoid receptor-target genes and downregulation of genes involved in crucial pathways of the inflammatory process. Finally, the integrative analysis allowed identifying new genes with a potential role in GCA pathogenesis, such as *ITGA7* and *CD63*, as well as genes mediating the molecular response to GC in GCA, including *FKBP5*, *ETS2*, *ZBTB16*,and *ADAMTS2*.

**Conclusions:** Overall, the first analysis of the methylation and transcriptomic profiles of monocytes from GCA patients has provided evidence of genes and pathways that contribute to the pathogenic role of this cell type in GCA as well as to the molecular response to GC treatment.

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