BITS :: Call for Abstracts 2022 - Oral communication

Type	Oral communication
Session	Multi-omics data analysis and integration
Title	Integrative analysis of multiple omics and interactomes to find key mechanisms underlying disease activity in the early phases of Multiple Sclerosis
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Motivation

Multiple Sclerosis (MS) is an autoimmune disease of the Central Nervous System (CNS) that is characterized by high clinical heterogeneity. The pathogenic events of the disease arise from a complex interplay of mechanisms acting at CNS and peripheral immune cells levels. Here, we used a multi-omics approach involving genomics, epigenomics and transcriptomics data together with molecular networks involving coding and non-coding genes, to disentangle the biological basis of MS inflammatory activity by identifying relevant gene networks and pathways implicated in disease activity.

Methods

A total of 270 untreated relapsing remitting MS patients were recruited in two centers: San Raffaele Hospital (Italy) and the Centre Hospitalier Universitaire de Toulouse (France). Patients were classified as EDA (Evidence of Disease Activity) or NEDA (No-EDA) at 2 years of follow-up and underwent multi-omics characterization. Specifically, whole-genome genotyping data were generated through the Illumina OmniExpress beadchip kit, methylation profiles through the Infinium MethylationEPIC Kit, mRNA and miRNA profiles through the Truseq stranded mRNA kit (Illumina) and the SMARTer smRNA-Seq Kit (Takara). For each layer of omic information, comparison between EDA and NEDA patients were performed analyzing Italians and French patients separately. In details, a Genome Wide Association Study (GWAS) was performed with PLINK followed by calculation of the gene-wise statistics according to MAGMA tool; specifically for the genetic layer, an additional cohort of 1365 MS patients (1170 from Italy and 195 from France) was included to increase the statistical power. Differential analyses were performed by using minfi tool for methylation data, and DeSeq2 for mRNA and miRNA data. We decided to integrate the omics results to two type of gene-gene interaction (GGI) data: general, as STRING and iRefIndex, and tissue-specific, as HumanBase. To be able to integrate all the omics involved in the study, GGI were integrated with mirTarBase and RNAinter to extend the network to comprehend ncRNA interaction with DNA, mRNA as well as other ncRNAs. At this point, the identification of gene networks supported by multi-omics evidences was performed by using dmfind (https://github.com/emosca-cnr/dmfind002) and mND (https://github.com/emosca-cnr/mND) packages. The relevant genes identified were grouped into pathways by using MSigDB. Enrichment analysis and pathway cross talk analysis were performed using Ulisse package.

Results

As the patients are divided in two cohorts, we decided to analyze them independently to account for the differences between them. Moreover, by comparing the results obtained for each cohort, we can validate them: the shared features identified by the two analyses should be related to the pathology and not influenced by sources of variability present in each cohort. For each cohort, we mapped the results of EDA-NEDA GWAS and differential methylation/expression analysis onto genome-wide molecular networks. We found brain-specific and lymphocyte-specific networks of genes that carry variants associated with EDA, and interact with “core” (recurring) network regions. The integrative analysis revealed gene networks that are supported by genomics, epigenomics and transcriptomics. Network analysis shed light on key genes and ncRNA involved in multiple connections and/or connectors between diverse pathways. Our network-based multi-omics analysis provides an in-depth knowledge of genes and pathways which appear to be associated with inflammatory activity in MS, including novel candidates that require further study.

Info

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