Molecular heterogeneity of autoimmune patients reveals insight to disease progression and personalized management: the model of celiac disease

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Impartido por:

Valentina Discepolo. MD, PhD, Pediatrician. Assistant Professor on a tenure Track. Department of Translational Medical Sciences, University of Naples Federico II, Naples, Italy.

Valentina Discepolo is a pediatrician and a physician scientist with a major interest in gastrointestinal and immune mediated disorders that has investigated in an academic setting from both a clinical and a pathogenetic prospective. In addition to her research experience, she has a great passion for science communication, as well as for educational and public health-oriented projects.

Presenta:

Joaquín Sanz, PhD.

Ramón y Cajal research fellow. Institute for Bio-computation and Physics of Complex Systems & Dpt. of Theoretical Physics. University of Zaragoza.

Lugar: Avda. San Juan Bosco, 13 – 50009 Zaragoza

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Background. Autoimmune processes are the result of a complex interaction between genetic and environmental factors that lead to inflammatory immune responses, responsible for complex clinical pictures. Several genetic predisposing factors have been shown to be shared across tissue-specific and systemic autoimmunity. Moreover, environmental factors such as viral infections and dysbiosis have been suggested as possible shared triggers for autoimmune diseases.

Coeliac disease (CeD) is a systemic inflammatory disorder with autoimmune features, occurring upon the ingestion of dietary gluten in genetically susceptible individuals and typically characterized by a small intestinal enteropathy with intraepithelial lymphocyte infiltration, crypts hyperplasia and villous atrophy. Since we know the main environmental trigger (gluten) and the HLA predisposing genes (HLA-DQ2 and/or HLA-DQ8), and we can also easily access to the affected tissue (duodenum) through upper gastrointestinal endoscopy, CeD is considered a great model to study intestinal inflammatory and autoimmune processes.

Hypothesis and Study. Despite the common histological picture, the molecular pathways leading to tissue destruction may vary across CeD patients as suggested by immunological, epidemiological and clinical observations. In line with this hypothesis, we analyzed the duodenal transcriptional signature of active CeD individuals to investigate their heterogeneity and identify novel pathways involved in disease development.

Methods. RNA was isolated from duodenal biopsies obtained from 45 non-celiac subjects (CTR) and 48 active CeD patients (ACD) undergoing EGDS and processed for RNA-sequencing, that was performed on a HiSeq Illumina 4000. All patients were enrolled at the University of Chicago and the study protocol was IRB approved. Computational and statistical analysis were performed using R in Collaboration with Joaquin Sanz at your Institute.

Results. In order to identify distinct subgroups of active celiac patients featuring different gene expression signatures, we conducted a clustering analysis. This consisted of three major steps: (1) first, we analyzed the degree of variance across all measured genes and selected those showing significantly higher variance than expected given their average expression levels, only across ACD patients, but not across CTR patients. (2) Then, we conducted a dimensionality reduction on the selected genes. (3) Finally, we identified two clusters of ACD patients showing distinct signatures, as delineated by differential expression followed by functional enrichment analyses. In particular, one group showed an enrichment in HLA class II and antigen presentation pathways, while the other group in B cell response and IL-15 pathways. Importantly, most of the genes involved in cytotoxicity or IFN-gamma inflammatory response was enriched in both groups and defined what we called the transcriptional “common-core”.

Conclusion. Despite a common histopathological picture, transcriptome analysis revealed distinct clusters of ACD patients, mirroring both clinical differences and immunological heterogeneity. Patients' grouping has key implications for future personalized medicine.