BIONAND 2019 CONFERENCE SERIES

Dra. Marta Alarcón Riquelme

Coordinadora de Área de Medicina Genómica, Centro Pfizer/Universidad de Granada/Junta de Andalucía de Genómica e Investigaciones Oncológicas

"Estratificación de las enfermedades autoinmunes sistémicas y su relevancia clínica"

Abstract:

Systemic autoimmune diseases (SADs) are chronic inflammatory conditions with autoimmune aetiology and many common clinical features, difficulting diagnosis and adequate treatment decisions. Finding new treatments or applying the existing ones in a more effective way is especially hard in SADs due to the heterogeneity of molecular mechanisms within the same disease class. Based on this premise, the first step towards establishing a precision medicine strategy for SADs is to reclassify these conditions at the molecular level, which might result in a more homogenous stratification in terms of pathological molecular pathways. SADs have a multi-factorial predisposition, where the interplay between genetic, epigenetic and environmental conditions is essential in the pathogenesis of the diseases. Thus, in order to capture as many aspects as possible the molecular stratification is performed using multiple layers of information (e.g. genome, transcriptome, methylome or metabolome). Among all available molecular levels of information, the most informative in terms of functionality and dimensionality are transcriptome and methylome, reflecting different aspects of regulation and environmental influence, respectively, giving a wide view of the molecular background.
Methods: We performed an unsupervised integrative clustering analysis to classify SADs patients into subtypes based on genome-wide trancriptome and methylome profiling of 800 cases distributed across 7 different clinical entities (rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, primary Sjögren s syndrome, primary antiphospholipid antibody syndrome, mixed connective tissue disease and undifferentiated connective tissue disease) and 200 healthy individuals.
Results: Interestingly, patients with different diagnoses were grouped statistically into new groups in terms of molecular functions. These results were replicated in two independent subsets of patients. The new groups of patients are characterized by a major subdivision, where some clusters show an increased inflammatory response and neutrophil degranulation functions, while others are enriched in lymphocyte proliferation and differentiation signatures. This major signal is subdivided into more specific subgroups defined by functional signatures such as type I interferon signaling, complement activation or neural functionalities among others.
Conclusion: This is the first attempt of integrating and characterizing SADS patients based on molecular profiles. The results show that we are able to identify new groups of patients sharing molecular features that do not reflect the clinical diagnoses. This new molecular classification might suppose a first step through precision medicine in SADS.

References:

Barturen, G., Beretta, L., Cervera, R., Van Vollenhoven, R. & Alarcon-Riquelme, M.E. Moving towards a molecular taxonomy of autoimmune rheumatic diseases. Nat Rev Rheumatol 14, 75-93 (2018).

Banchereau, R. et al. Personalized Immunomonitoring Uncovers Molecular Networks that Stratify Lupus Patients. Cell 165, 1548-1550 (2016).**A first study using longitudinal transcriptome data to stratify SLE patients.

Toro-Dominguez, D. et al. Stratification of Systemic Lupus Erythematosus Patients Into Three Groups of Disease Activity Progression According to Longitudinal Gene Expression. Arthritis Rheumatol 70, 2025-2035 (2018).

Toro-Dominguez, D., Carmona-Saez, P. & Alarcon-Riquelme, M.E. Support for phosphoinositol 3 kinase and mTOR inhibitors as treatment for lupus using in-silico drug-repurposing analysis. Arthritis Res Ther 19, 54 (2017).