EPIGENOMIC ANALYSIS OF RA PATIENTS SHOWS DISTINCT BIOLOGICAL PROCESSES ASSOCIATED WITH ANTI-TNF RESPONSE

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Background: Blocking Tumor Necrosis Factor (TNF) activity is a successful therapeutic approach for approximately 60% of patients with rheumatoid arthritis (RA). To date, however, the biological basis of the lack of efficacy of anti-TNF agents is unknown.

Objectives: The objective of present study was to characterize the biological basis of anti-TNF lack of efficacy in RA using an epigenomic data approach in two steps: first, to assess the differential methylation changes between responders and non-responders and second, to use this differential methylation profile in a systems biology approach to infer differential methylated biological modules according to anti-TNF response.

Methods: A total of n=68 patients diagnosed with RA according to the ACR-EULAR criteria belonging to 16 Hospitals across Spain were recruited. All patients were >18 years old, with more than 6 months of disease evolution and a baseline disease activity of DAS28 > 3.2. Treatment response was defined according to the EULAR criteria at week 12. Good and moderate responders were aggregated into a single responder group. Genomic DNA was collected at baseline and the methylation profile was assessed using the Illumina Infinium EPIC array, which interrogates 850,000 methylation CpG sites across the genome. Differential Methylation analysis, biological pathway association and the systems Biology approach using Protein-Protein Interaction Networks, were conducted using the R statistical language and the Bioconductor libraries.

Results: From 68 anti-TNF treated patients, n=27 (39.7%) were good responders, n=26 (38.2%) moderate responders and n=15 (22.05%) non-responders at week 12 of treatment. Differential methylation analysis identified two distinctive biological profiles associated with the clinical response: responders were associated to interleukin and cytokine production, and non-responders were associated with biological pathways associated to TGF-Beta production and T cell regulation. Using these differentially methylated epigenetic modules, differential methylated hotspots between responders and non-responders were also found. Two epigenetic modules with significant enrichment in inflammatory and interleukin production and immune regulatory processes were validated in an independent patient cohort.

Conclusion: The epigenetic analysis of whole blood from RA patients using a module-based approach shows reproducible biological mechanisms associated with the response to anti-TNF therapy.

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ATTEMPTS TO LINK EXONIC GENIC POLYMORPHISMS TO SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)-ASSOCIATED PROTEIN MODIFIED FUNCTIONALITY: A STRUCTURAL BIOLOGY APPROACH

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Background: Gene association studies and genome wide association studies (GWAS) have played a primary role in depicting genetic contributions to systemic lupus erythematosus (SLE) development, while accommodating the exonic polymorphisms on the protein structure level, when available, enhances our understanding of protein function modification or depletion. Linking human genetics with therapeutic targets requires the biological function of the causal gene variant to be known.

Objectives: To investigate recently identified SLE-associated functional gene polymorphisms, such as PARP1, ITGAM, TNFAIP3, NCF1, PON1, IFIH1, SH2B3 and TYK2 [1-4] by correlation to protein structure and function.

Methods: Three-dimensional (3D) homology modeling and molecular mechanics/dynamics studies were applied for the localization of the polymorphisms under study on the respective proteins. The mutants were constructed using molecular modeling with the program Maestro (Schrodinger, LLC), which was under study on the respective proteins. The mutants were constructed using molecular modeling with the program Maestro (Schrodinger, LLC), which was under study on the respective proteins. The mutants were constructed using molecular modeling with the program Maestro (Schrodinger, LLC), which was under study on the respective proteins. The mutants were constructed using molecular modeling with the program Maestro (Schrodinger, LLC), which was under study on the respective proteins. The mutants were constructed using molecular modeling with the program Maestro (Schrodinger, LLC), which was under study on the respective proteins.

Results: From 68 anti-TNF treated patients, n=27 (39.7%) were good responders, n=26 (38.2%) moderate responders and n=15 (22.05%) non-responders at week 12 of treatment. Differential methylation analysis identified two distinctive biological profiles associated with the clinical response: responders were associated to interleukin and cytokine production, and non-responders were associated with biological pathways associated to TGF-Beta production and T cell regulation. Using these differentially methylated epigenetic modules, differential methylated hotspots between responders and non-responders were also found. Two epigenetic modules with significant enrichment in inflammatory and interleukin production and immune regulatory processes were validated in an independent patient cohort.

Conclusion: The epigenetic analysis of whole blood from RA patients using a module-based approach shows reproducible biological mechanisms associated with the response to anti-TNF therapy.

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