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Gene Expression Meta-Analysis of Potential Shared and Unique Pathways Between Autoimmune Diseases Under anti-TNFα Therapy

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Abstract : The extended tissue damage and severe clinical outcomes of autoimmune diseases, accompanied by the high annual costs to the overall health care system, highlight the need for an efficient therapy. Increasing knowledge over the pathophysiology of specific chronic inflammatory diseases, namely Psoriasis (PsO), Inflammatory Bowel Diseases (IBD) consisting of Crohn's disease (CD) and Ulcerative colitis (UC), and Rheumatoid Arthritis (RA), has provided insights into the underlying mechanisms that lead to the maintenance of the inflammation, such as Tumor Necrosis Factor alpha (TNF-α). Hence, the anti-TNFα biological agents pose as an ideal therapeutic approach. Despite the efficacy of anti-TNFα agents, several clinical trials have shown that 20-40% of patients do not respond to treatment. Nowadays, high-throughput technologies have been recruited in order to elucidate the complex interactions in multifactorial phenotypes, with the most ubiquitous ones referring to transcriptome quantification analyses. In this context, a random effects meta-analysis of available gene expression cDNA microarray datasets was performed between responders and non-responders to anti-TNFα therapy in patients with IBD, PsO, and RA. Publicly available datasets were systematically searched from inception to 10th of November 2020 and selected for further analysis if they assessed the response to anti-TNFα therapy with clinical score indexes from inflamed biopsies. Specifically, 4 IBD (79 responders/72 non-responders), 3 PsO (40 responders/11 non-responders) and 2 RA (16 responders/6 non-responders) datasetswere selected. After the separate pre-processing of each dataset, 4 separate meta-analyses were conducted; three disease-specific and a single combined meta-analysis on the disease-specific results. The MetaVolcano R package (v.1.8.0) was utilized for a random-effects meta-analysis through theRestricted Maximum Likelihood (RELM) method. The top 1% of the most consistently perturbed genes in the included datasets was highlighted through the TopConfects approach while maintaining a 5% False Discovery Rate (FDR). Genes were considered as Differentialy Expressed (DEGs) as those with $P \leq 0.05$, $|\log2(FC)| \geq \log2(1.25)$ and perturbed in at least 75% of the included datasets. Over-representation analysis was performed using Gene Ontology and Reactome Pathways for both up- and down-regulated genes in all 4 performed meta-analyses. Protein-Protein interaction networks were also incorporated in the subsequentanalyses with STRING v11.5 and Cytoscape v3.9. Disease-specific meta-analyses detected multiple distinct pro-inflammatory and immune-related down-regulated genes for each disease, such asNFKBIA, IL36, and IRAK1, respectively. Pathway analyses revealed unique and shared pathways between each disease, such as Neutrophil Degranulation and Signaling by Interleukins. The combined meta-analysis unveiled 436 DEGs, 86 out of which were up- and 350 down-regulated, confirming the aforementioned shared pathways and genes, as well as uncovering genes that participate in anti-inflammatory pathways, namely IL-10 signaling. The identification of key biological pathways and regulatory elements is imperative for the accurate prediction of the patient's response to biological drugs. Meta-analysis of such gene expression data could aid the challenging approach to unravel the complex interactions implicated in the response to anti-TNFα therapy in patients with PsO, IBD, and RA, as well as distinguish gene clusters and pathways that are altered through this heterogeneous phenotype.

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