A Novel Computational Modeling Framework To Analyze Synovial-Tissue Based Drug Targets and Diagnostic Biomarkers in Rheumatoid Arthritis

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Rheumatoid Arthritis (RA) is an inflammatory autoimmune disease that affects 23 million people worldwide. It is a clinically heterogeneous disorder characterized by the attack of inflammatory chemicals on the synovial tissue that lines joints. It is advantageous to develop effective, targeted treatments and identify specific diagnostic biomarkers for RA before extensive joint degradation, bone erosion, and cartilage destruction. Current modes of RA treatments have alleviated and notably halted the progression of RA. Despite this, not many patients reach low disease activity status after treatment, and a significant number of patients fail to respond to medication due to drug non-specificity. While the reasons for these rates remain unknown, the cellular and molecular signatures present in the synovial tissue for RA patients likely play a role in the varied treatment response. Thus, a drug that particularly targets specific genes and networks may have a significant effect in halting the progression of RA. This study evaluates and proposes potential drug targets through in silico mathematical modeling of various pathways of interest in RA. To understand how drugs interact with genes, a mathematical model was built with 30 two-gene and three-gene network interactions and analyzed the effect of 92 different perturbations to rate constants. It was determined that inhibition of the LCK-CD4, VAV1-CD4, and MLT-ROR pathways could potentially serve as drug targets. It also found that increased activity of the DEC2-IL1? and the NF-kB-interleukin pathway and the decreased activity of the TNF-a-REV-ERB pathway could serve as diagnostic biomarkers.

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