[BIOINFO 2025]

Oral Microbiome Signatures Predict Responsiveness to Adalimumab in Patients with Rheumatoid Arthritis

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Predicting response to biologic DMARDs in rheumatoid arthritis (RA) is a clinical challenge; the oral microbiome may offer non-invasive biomarkers. This study aimed to identify oral microbiome features that characterize RA and predict adalimumab responsiveness. We performed shotgun metagenomic sequencing on pre-treatment saliva from a prospective cohort of 35 RA patients starting adalimumab and a cross-sectional cohort of 7 additional RA and 34 osteoarthritis (OA) patients. The prospective cohort was classified as good responders (n=24) or moderate/poor responders (n=11) using EULAR criteria. Our analysis included multi-kingdom diversity, differential abundance (DA), functional profiling, and machine learning. While overall microbial diversity was similar, DA analysis revealed *Haemophilus parainfluenzae* was significantly enriched in good responders. Notably, *H. parainfluenzae* was also enriched in OA patients compared to RA patients, suggesting its depletion is a feature of the RA oral environment. Functional profiling linked this bacterium to specific metabolic pathways, while distinct viral and fungal signatures also characterized the response groups. A Random Forest model showed moderate predictive power. Our findings suggest specific multi-kingdom signatures distinguish adalimumab responders. The consistent association of *H. parainfluenzae* enrichment with a favorable clinical outcome (good response) and a non-RA state (OA) highlights its potential as a robust biomarker for personalizing therapy.