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RHEUMATOID ARTHRITIS

Microbiome reflects status of RA and response to therapy

Microbial components have been implicated in the aetiology of rheumatoid arthritis (RA), but the identity of microbes that associate with this disease is unclear. The results of a new metagenome-wide association study (MGWAS) of human microbiomes revealed multiple links with RA that can be of diagnostic value and predict responses to treatment.

Next-generation sequencing techniques enable rapid analysis of multiple bacterial genomes in the microbiome. In this study, Zhang *et al.* compared microbiomes in faecal, dental plaque and salivary samples. The study included a cohort of DMARD-naïve patients with RA and healthy controls from which faecal samples (94 patients and 97 controls, along with 21 DMARD-treated patients with RA), dental samples (54 patients and 51 controls) and salivary samples (51 patients and 47 controls) were collected. Sample analyses yielded 117,219 (faecal), 371,990 (dental plaque) and 258,055 (salivary) differentially enriched gene markers which were clustered into metagenomic linkage groups (MLGs) of specific bacterial species. Differentially enriched gene markers from the three sites belonged to similar biological pathways (including reduction–oxidation, as well as metabolism and transport of iron, sulphur, zinc and arginine).

MLG analysis revealed dysbiosis in patients with RA. A cluster that included MLGs from *Haemophilus* strains was decreased in patients with RA compared with healthy controls in all three sets of samples, and was negatively correlated with autoimmune antibody titres. In gut samples, a correlation was identified between some MLGs

and titres of IgA, and between one MLG (possibly corresponding to *Lactobacillus salivarius*) and titres of IgG. Notably, *L. salivarius* was abundant in patients with RA, especially in those with high disease activity.

Diagnostic models to differentiate patients with RA from healthy controls were generated using either eight gut MLGs (area under the receiver operating characteristic curve [AUC] 0.940; specificity 0.922; sensitivity 0.838), six dental MLGs (AUC 0.870 specificity 0.860; sensitivity 0.800) or two salivary MLGs (AUC 0.814; specificity 1.000; sensitivity 0.702). Combination of the models from the three sites improved accuracy.

Notably, DMARD therapy changed MLG abundance, particularly in oral samples. MLGs that were reduced in treatment-naïve individuals with RA compared with healthy controls were increased after DMARD treatment, and DMARD-naïve MLG status distinguished patients who showed clinical improvements after treatment from those who did not.

This study shows that the gut and mouth microbiome is altered in patients with RA and can be analysed to predict response to treatment. “We expect the MGWAS will be helpful in promoting patient stratification, predicting drug efficacy and exploring novel therapeutic targets, leading to precise diagnosis and treatment of RA,” explain the authors.

Robert Phillips

Original article Zhang, X. *et al.* The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. *Nat. Med.* doi:10.1038/nm.3914