

Gut microbiota: A potential trigger of rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder characterized by synovitis in multiple joints and systemic comorbidities. Both genetic and environmental agents are thought to be the risk factors for arthritis. Recent studies have suggested that mucosal sites such as oral cavity and gut contribute to arthritis development. Additionally, previous studies showed that RA patients have altered composition of microbiota in fecal samples (called dysbiosis). However, it is unexplored whether dysbiosis in RA patients triggers arthritis. We first examined whether recent-onset Japanese RA patients have altered composition of intestinal microbiota. To this end, we collected fecal samples from 17 untreated recent-onset RA patients and 14 healthy controls to investigate the microbiota by 16S rRNA-based high-through-put sequencing. We clustered the operational taxonomic units (OTUs) in four clusters and found that one of the clusters corresponding to *Prevotella copri* was enriched in 6 RA patients. None of the healthy controls harbored such abundance of *P. copri*. These results are consistent with a previous finding from the United States.

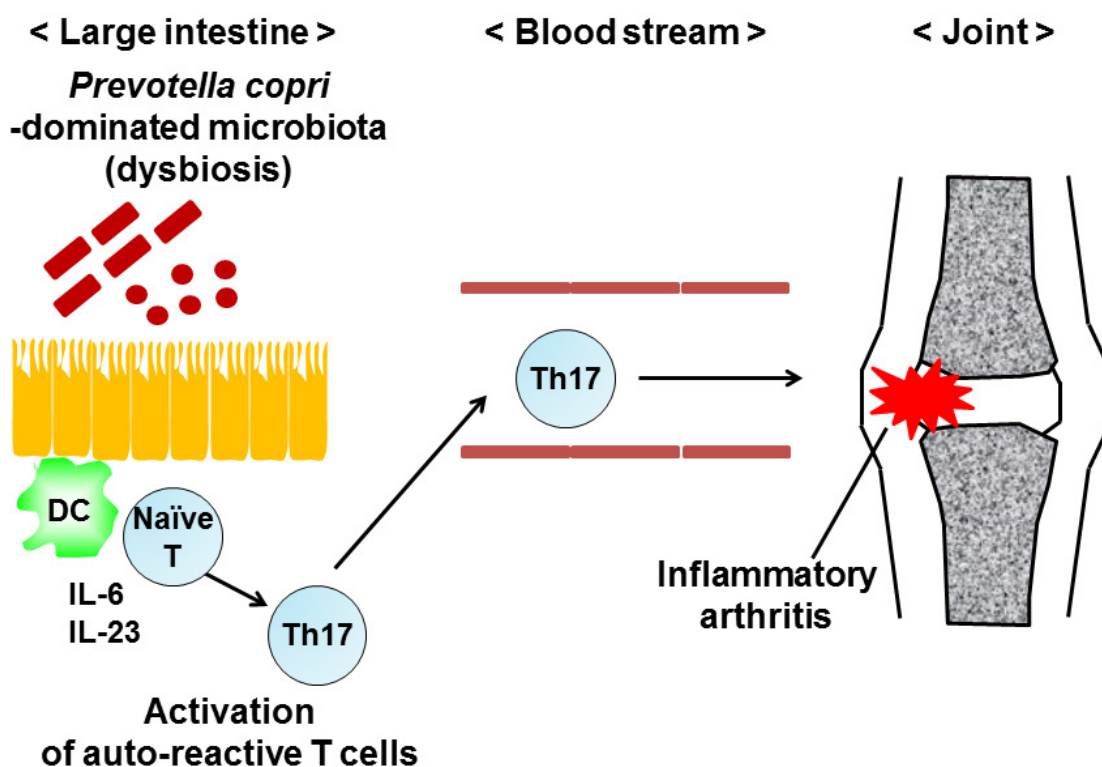


Fig. 1. Schematic representation of activated autoreactive T cells in the large intestine, which possess the ability to induce inflammatory arthritis.

In order to investigate the correlation between altered composition of microbiota and arthritis development, we produced intestinal microbiota-humanized mice. We used SKG mice which develop T cell-mediated autoimmune arthritis. SKG mice evoke Th17 cell-dependent arthritis through fungi-induced activation of

innate immunity. We inoculated human fecal samples from 3 recent-onset RA patients with high abundance of *P. copri* or those from 3 healthy controls into germ free SKG mice. SKG mice harboring *P. copri*-dominated microbiota (RA-SKG mice) elicited severe arthritis after a single injection of zymosan (a fungal β -glucan). Histologic and radiographic observations also revealed RA-SKG mice developed severe synovitis and bone erosion. RA-SKG mice showed increased numbers of Th17 cells, but not Th1 cells in the large intestine and regional lymph nodes. We also analyzed whether lymphocytes of RA-SKG mice react with arthritis-related autoantigen, RPL23A. Lymphocytes in regional lymph nodes and large intestine of these mice showed increased IL-17 responses to RPL23A. *In vitro* analysis revealed that *P. copri* co-cultured with dendritic cells induced high production of IL-6 and IL-23, indicating that *P. copri* has an ability to induce Th17 cells. Next, we investigated whether *P. copri* alone could induce arthritis in SKG mice. Germ free SKG mice monocolonized with *P. copri* showed arthritis with increased numbers of Th17 cells in large intestine and regional lymph nodes. Finally, we analyzed whether SKG T cells activated in the large intestine directly contributes to arthritis development. To this end, CD4⁺ T cells were sorted from the large intestine or spleen of SKG mice and transferred into severe combined immunodeficiency (SCID) mice, which were treated with antibiotics. The SCID mice that had received large intestinal CD4⁺ T cells rapidly induced arthritis. Thus, these results indicate that pathogenic T cells were activated in the large intestine, and might migrate to the regional lymph nodes of the joints to evoke arthritis (Fig. 1).

In conclusion, our findings support the idea that intestinal commensal microbiota, especially *P. copri*-dominated microbiota plays an important role in arthritis development of SKG mice. Further studies are needed to clarify the mechanistic links between *P. copri* and human arthritis development.

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