Gut Microbes as the Major modulators of Rheumatoid Arthritis: - a tale of 2 microbes.

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Rheumatoid arthritis (RA) is preceded by a preclinical phase marked by cellular and humoral autoreactivity as well as microbial dysbiosis, suggesting a mucosal origin and perpetuation of disease. Microbial development is dynamic as it occurs in conjunction with immune programming and is affected by multiple environmental factors. The human gut harbors a diverse community of commensals which are essential for maintaining intestinal homeostasis. Disruption of microbial homeostasis can alter immune response and promote inflammation. Although gut dysbiosis and abundance of certain commensals has been increasingly associated with RA, it remains unclear whether microbial alterations are a cause or consequence of disease. Identifying microbial markers of disease progression and treatment efficacy has been challenging due to heterogeneity of disease and varied therapeutic responses. A key unresolved question is what defines a healthy microbiome for an individual and how to restore it if dysbiosis occurs. Humanized mouse model, in particular, has been critical for understanding the role of opportunistic microbes as markers of disease severity and for exploring the therapeutic potential of endogenous commensals for regulating immune responses to suppress inflammation in the context of genetic susceptibility. Mice expressing RA-susceptible HLA genes in a model of induced arthritis provide support to the notion that microbial alterations precede disease onset, preclinical autoreactivity and augmented senescence. On the other hand, a small intestinal commensal such as *Prevotella histicola*, protects mice from developing arthritis by shifting the microbial and metabolic profile thereby regulating immune response, suggesting that gut commensals and metabolites can serve as valuable tools as biomarkers for disease severity as well as for therapeutic strategies.