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Gut Microbiota and the Anti-Inflammatory Role on Rheumatoid Arthritis

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Introduction:

Gut microbiota is the large community of microorganisms that resides in the gut **(Spanogiannopoulos et al., 2016)**. It is constituted by bacteria, viruses, fungi, and parasites, counting approximately trillions of microorganisms. The number of microbes in the intestinal tract increases from the stomach to the colon, ranging approximately from 10^1–10^4 to 10^{10}–10^{12} microbes per gram of luminal content, respectively (**Sender et al., 2016).** The gastrointestinal tract can harbor up to 70% of the total lymphocyte population, whose phenotype can be modulated by the composition of commensal bacteria **(Sun and Zhang, 2023)**.

The gut microbiota is a highly plastic community which is influenced by numerous factors like diet, gender, environment, eating behavior, and xenobiotic and microbial metabolites (**Sender et al., 2016).** Diet might modulate RA symptoms by influencing the patient's metabolic profile and increasing antioxidant levels, but also by altering the microflora of the intestine. The gut microbiome is incredibly dynamic and can change rapidly to dietary perturbations **(Derrien and Veiga, 2017)**. In addition, the gut microbiome is also involved in the metabolism of some dietary components and has the potential to modify circulating pro- or anti-inflammatory mediators **(Schroeder and Bäckhed, 2016).** For example, trimethylamine-N-oxide, a pro-inflammatory metabolite that derives from choline and carnitine present in red meat, eggs, and dairy products, is produced by Prevotella copri among other bacteria **(Koeth et al., 2013).**

Bacteria that have an almost exclusive saccharolytic metabolism, such as lactobacilli and bifidobacterial, are considered potentially beneficial **(Goel et al., 2022)**. Both gut microbial species produce a variety of tryptophan catabolites which are critical for intestinal homeostasis by decreasing intestinal permeability **(Pei et al.,)**. In addition, some of these catabolites enter the bloodstream and have anti-inflammatory and anti-oxidative effects (**Roager and Licht, 2018).** Various dietary components including miso and yogurt are a source of this beneficial flora. Daily yogurt was shown to reduce biomarkers of chronic inflammation **(Pei et al., 2017)**. Dietary fiber, other complex carbohydrates, and sugar alcohols present in fruits are prebiotics and might also be beneficial by supporting healthy microbiome **(Lyte et al., 2016)**. For instance, microbial degradation of whole-grain complex carbohydrates increases short chain fatty acids (SCFA), which were shown to be beneficial to intestinal immune response (**Knudsen et al., 2015).**

It is worthy to say that the gut microbiota can be considered as an important metabolic "organ" for drugs, with a metabolic capacity at least equal to that of the liver **(Maseda and Ricciotti, 2020).** The critical role of symbiotic microorganisms in healthy development and function of the human immune system is necessary to be considered **(Suchiita et al.,).**

Chronic inflammatory diseases are increasingly recognized as attributable (at least partially) to immune dysregulation resulting from inadequate or adverse exposure to microorganisms **(Fox et al., 2019)**. Clinical findings suggest that the composition of gut microbiota was altered in RA patients before the appearance of typical joint symptoms **(Maeda and Takeda, 2017).** Moreover, this bidirectionality might be influenced by the gut microbiome and increased permeability of the gut barrier, thereby increasing neuroinflammation and accelerating neurodegeneration **(Heneka et al., 2015)**. Of note, the chronic systemic inflammation caused by rheumatic pathologies could cause this increased permeability **(Duque and Fricchione, 2019).**

❖ **Gut dysbiosis in autoimmune diseases**

Several studies confirm that dysbiosis occurs in a variety of autoimmune diseases, including RA **(Malesza et al., 2021)**. Gut dysbiosis—a high number of pathogenic species or a pathological lack of species diversity in the gut—has been associated with aging, metabolic inflammatory diseases (MIDs) These conditions have overlapping etiologies with RA, and the ways in which gut dysbiosis affects risk (via inflammation and gut epithelial permeability) may also apply to RA **(Romero-Figueroa et al., 2023)**

Gut dysbiosis may compromise barrier integrity, which may promote RA pathogenesis by allowing translocation of pathogenic agents out of the gut and into joints **(Blenkinsopp et al., 2024)**. Also, dysfunction of tight junctions is a common feature of autoimmune diseases. It leads to altered intestinal permeability, which is associated with increased transport of antigens from the intestinal lumen and the risk of malabsorption of macro- or micronutrients such as vitamin D (**Mazzucca et al., 2021)**

❖ **<u>Effect of pharmacotherapeutics of RA on microbiota:</u>**

(1) Disease-modifying antirheumatic drugs (DMARDs)

Disease-modifying antirheumatic drugs (DMARDs) modify the microbiome in murine models of RA and RA patients. Interestingly, gut dysbiosis in New-Onser Rheumatoid Arthritis (NORA) individuals can be partially reversed by DMARDs, especially in those RA patients who achieved remission of low disease activity, indicating that gut microbiota is associated with RA disease status **(Zhang et al., 2020)**

(2) Methotrexate

Methotrexate induces a reduction of Bacteroidetes, permitting increases in Firmicutes' abundance. In patients treated orally with MTX, the treatment is associated with the restoration of gut microbiota because it favors the increase of Lactobacillus salivarus, Lachnospiraceae bacterium, and Clostridium asparagiforme and the decrease of some Firmicutes of the family Veillonellaceae of oral microbiota, These findings suggest that MTX exerts its anti-inflammatory effects in part by reducing the gut microbiome's ability to contribute to an inflammatory response **(Zhang et al., 2015)**

It has been described that the intestinal microbiota may explain the lack of response to MTX treatment. Patients' communities enriched for gut bacteria capable of efficiently metabolizing and depleting MTX are associated with worsened clinical outcomes **(Artacho et al., 2021)**

(3) Corticosteroids/ NSAIDs

- **Corticosteroids:** gut microbiota was affected by the duration and the dosage of glucocorticoid usage. A dramatic decrease in gut microbial diversity was observed in the patients after a period of use **(Zhang et al., 2024).**
- **NSAIDs**: they can affect the composition of gut microbiota in animals and in humans. NSAID use can affect the gut microbiota composition and metabolic activity through a direct effect on the microbiota (e.g. by inhibiting/facilitating microbial growth, inducing microbial cell death and/or influencing microbial metabolism) or through an indirect effect by interacting with the host (e.g. by changing the metabolism, gut environment, mucosa integrity, and permeability **(Maseda and Ricciotti, 2020).**

(4) Biological therapy (Anti-TNF therapy as etanercept)

Anti-tumor necrosis factor alpha (Anti-TNF-α) ETN (etanercept) is able to modify microbial communities **(Picchianti-Diamanti et al., 2018)**. Etanercept has been correlated with partial restoration of the disturbed microbiome (restores the beneficial microbiota) in these patients **(Ciccia et al., 2024)**.

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