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Letters to Editor

Postbiotic driven immunomodulation: SCFAs as therapeutic agents in rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic autoimmune condition characterized by persistent synovial inflammation, immune dysregulation, and progressive joint destruction. While current therapies target inflammatory cytokines and immune cells, emerging evidence has underscored the contribution of the gut microbiota and its metabolic byproducts, particularly short-chain fatty acids (SCFAs) in the pathogenesis and regulation of autoimmune diseases, including RA. SCFAs, primarily acetate, propionate, and butyrate, are postbiotic metabolites derived from microbial fermentation of dietary fibers and are increasingly recognized for their potent immunomodulatory properties [1].

Mechanistically, SCFAs influence both innate and adaptive immune responses through several pathways. These include binding to G-protein-coupled receptors (e.g., GPR41 and GPR43), inhibition of histone deacetylases (HDACs), and modulation of gene expression in immune cells. Butyrate has been shown to enhance the differentiation of regulatory T cells (Tregs), which are essential for maintaining peripheral immune tolerance, and to suppress Th17 responses, which are implicated in RA pathogenesis. Propionate, on the other hand, attenuates dendritic cell maturation, reduces pro-inflammatory macrophage polarization, and limits fibroblast-like synoviocyte (FLS) activation, a hallmark of joint inflammation in RA [2,3].

Preclinical studies have provided robust evidence supporting the anti-arthritic effects of SCFAs. In a collagen-induced arthritis (CIA) mouse model, butyrate significantly reduced joint swelling, inflammatory cytokine production, and histopathological damage [4]. Additionally, the role of SCFAs in promoting intestinal epithelial barrier integrity further underscores their systemic immunoregulatory capacity by reducing translocation of gut-derived antigens and endotoxins [5].

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Translational research and early clinical evidence also support the therapeutic relevance of SCFAs in RA. A study by Dürholz et al. demonstrated that RA patients consuming a high-fiber diet for short-term exhibited increased fecal SCFA levels and decreased serum concentrations of pro-inflammatory cytokines including IL-18, IL-33, and MCP-1. Such findings highlight the feasibility of targeting the gut microbiome–immune axis through dietary or postbiotic interventions [6].

Despite these promising developments, several challenges remain. The optimal dosage, route of administration, and combination of SCFAs necessary to achieve sustained therapeutic effects in RA patients are not yet fully defined. Moreover, individual variations in gut microbiota composition may influence SCFA production and responsiveness, necessitating personalized approaches. Novel delivery systems, including SCFA prodrugs and microbiota-derived vesicles, are currently under investigation to enhance bioavailability and site-specific effects [7].

In conclusion, SCFAs represent a promising class of postbiotic agents capable of modulating immune responses in RA. Their multifaceted effects on immune cells, coupled with favorable safety profiles and the potential for dietary enhancement, warrant further clinical exploration. Integrating SCFAs into RA management may open a new frontier in immunometabolic therapy, bridging gut microbial function with systemic immune regulation.

Authors' contributions

Study concept, design, data collection, drafting, and revision: MK, SK. All authors read and approved the final version of article.

Conflict of interest

No potential conflict of interest was reported by the authors.

Ethical declarations

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