An investigation into the theories and mechanisms that have been proposed in the research literature for the role of gut-derived butyrate in the modulation of the immune response in Multiple Sclerosis

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Abstract

Objectives

Multiple Sclerosis is a T cell mediated autoimmune disease that is characterised by chronic inflammation and de-myelination in the CNS. Environmental factors are thought to play a significant role in the pathogenesis of the disease. It has been observed that the gut microbiome of patients with MS may have lower levels of fermentative bacteria and reduced levels of gut derived butyrate. Increasing evidence suggests that butyrate modulates the adaptive immune response in the lymphoid tissue which is mostly found around the intestine. Immunological imbalances that arise here can establish an inflammatory milieu that predisposes towards inflammation and autoimmune disease with effects also observed in extra-intestinal tissues such as the CNS. The main **research objectives** of this study were to:

1. To establish the profile of the disrupted immune response in MS in humans in terms of imbalances in immune cells and cytokines
2. To establish the immune-modulatory mechanisms of gut derived butyrate relevant to imbalances in immune cells and cytokines determined in 1.
3. To examine approaches that may restore butyrate in the gut, and evaluate the benefit in terms of improved immune profile and MS symptomology.

Methodology

Systematic searches of the literature were conducted and documented, following a reproducible methodology. The searches were conducted in three tranches using specific search terms to investigate the research objectives. In this process 599 papers were superficially reviewed, 91 were accepted for evaluation and form the basis of the following results and analysis.

Results (in relation to the research objectives 1-3):

1. Observational studies show that the reduction of Tregs, or loss of their immunosuppressive functionality plays an important role in MS. IL-17

producing Th17 cells are specifically implicated in promoting progression of the disease. The ratio of Tregs and Th17 is a critical determinant in the progression of the disease.

2. Butyrate is shown to induce Tregs directly and via dendritic cells. The principal mechanism is by inhibition of histone deacetylases that moderate expression of transcription factors that are central to immune homeostasis in MS, including STAT3, Foxp3, and RORγt. Butyrate inhibits maturation of dendritic cells, attenuates T cell activation and proliferation, and directly influences the expression of Tregs and Th17 functional phenotypes. The mechanisms suggests that butyrate could ameliorate the disrupted immune imbalance observed in MS
3. Interventions that increase gut-derived butyrate show improvements in disease severity in both human and animal models of MS or related inflammatory disease.

Conclusion

Longitudinal studies of MS patients that monitor immunological parameters, disease status and the status of the gut microbiome with particular reference to the fermentative mass and butyrate production, are required to establish a more dynamic view of the immune system and the interaction with the gut microbiome. The implications of these findings should be evaluated with results that are emerging from major projects to map the MS microbiome.

However there is good corroborating evidence for the beneficial effect of interventions that increase levels of butyrate in the intestine. These approaches may be effective in extending periods of remission and slowing disease progession, but further studies are required to validate existing findings.

There has been progress in the development of analysis tools for analysing the microbiome that facilitates the identification of bacterial strains and bacterial genomes. Further work is required to identify microbial markers for MS that can be predictive or diagnostic. The development of easier methods for assessing levels of butyrate in the gut (by urine test or pin prick test) would also help to facilitate the development of a personalised intervention approach.