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Myeloid derived suppressor cells-therapy attenuates experimental autoimmune encephalomyelitis and modulates gut microbiota composition

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Abstract
The role of gut microbiota composition in efficacy of various immune-based therapies is increasingly recognized. Thus, the aim of our study was to investigate if the efficacy of myeloid-derived suppressor cells (MDSC)-Prostaglandin E2 (PGE2) therapy for multiple sclerosis (MS) correlates with gut microbiota composition and function. MDSC generated from bone marrow cells in the presence of PGE2 were applied to spinal cord homogenate/CFA-induced experimental autoimmune encephalomyelitis (EAE) in Dark Agouti (DA) rats, an animal model of MS. MDSC-PGE2 therapy resulted in a significant attenuation of EAE symptoms over 30 days of disease monitoring. These results correlated with lower percentage of proinflammatory interferon-gamma and interleukin-17 producing cells and higher percentage of anti-inflammatory IL-4 producing cells in spinal cord and spleen. Gut microbial composition were studied using amplicon(16S rRNA)-based metagenomic analyses of fecal samples collected prior to the induction of EAE and MDSC-PGE2 therapy application, and at the peak of the disease. The induction of EAE resulted in a decrease of microbiota diversity, whereas the MDSC-PGE2 therapy preserved the diversity in EAE-induced animals. The induction of EAE in control group associated with a higher relative abundance of *Peptococcaceae,* but the lower levels of *Veillonellaceae* and different groups of *Prevotellaceae*, known to produce immunosuppressive short chain fatty acid (SCFA), and *Lactobacillus reuteri*, known for its anti-inflammatory function. In contrast, there were no changes in levels of these immunoregulatory taxa in EAE-animals treated with MDSC-PGE2 therapy. Also, SCFA producing *Ruminococcaceae,* and *Coriobacteriaceae,* known to metabolize phytoestrogens to immunosuppressive metabolites were more abundant in EAE-animals treated with MDSC-PGE2 therapy. Predicted metabolic profiling obtained by PICRUSt2 revealed that pathways involved in biosynthesis of polyamines, metabolites known to contribute to homeostasis of gastrointestinal mucosa, were enriched in MDSC-PGE2 treated animals. Considering these results, the modification of gut microbiota composition and function could further increase efficacy of MDSC-PGE-2 based therapy of autoimmune diseases.

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