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Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

Transcriptional rewiring in human dendritic cells by the gut microbial metabolite butyrate is associated with propagation of a tissue-sustaining type 2-like immune response

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Depletion of short-chain fatty acid (SCFA)-producing bacterial species in the gut microbiota is associated with poor health and higher disease prevalence in multiple non-communicable diseases, such as obesity, type 2 diabetes, and asthma. Butyrate is one of the major SCFAs in the human gut and has anti-tumoral and anti-inflammatory effects, but little is known about the molecular mechanism governing the anti-inflammatory effects of butyrate on primary immune cells.

Using human monocyte-derived dendritic cells (moDCs) activated with LPS and IFN-γ (strong inducers of a type 1 immune response), we performed an investigation of butyrate's effects on 1) early intracellular signaling using global shotgun phospho-proteomics, 2) transcriptional regulation using RNA-sequencing, and 3) production of cytokines, chemokines and co-stimulatory molecules by activated moDCs using flow cytometry and high-sensitivity immunoassays.

In moDCs, butyrate redirected the development of a pro-inflammatory type 1 immune response in moDCs to a tissue-sustaining type 2-like phenotype. Integrative data analysis showed that butyrate had profound effects on the early transcriptional responses, which were in concordance with the phenotype that subsequently developed in butyrate-treated moDCs. These moDCs were characterized by IL-18 production, inhibition of expression of pro-inflammatory cytokines such as IL-12p70 and IL-23, and upregulation of expression of prostaglandin E_2 synthase and efferocytotic genes, which together contribute to a tissue-sustaining and non-inflammatory type 2-like phenotype. Together with data on butyrate-induced changes in genome-wide chromatin states, the proposed mechanism for butyrate's effective diversion of the LPS/IFN-γ-induced type 1 response in moDCs will be presented. In conclusion, the potent anti-inflammatory effects of butyrate to sustain tissue integrity in the gut may contribute to the association of butyrate with homeostatic gut conditions.