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Short-Chain fatty acid (SCFA) histone deacetylase inhibitors produced by gut microbiota regulate selected microRNAs to modulate local and systemic antibody responses.

Sanchez, H.N.¹, Shen, T.¹, Taylor, J.R.¹, Munoz, K.¹, El Benni, R.¹, Zan, H.¹ and Casali, P.¹

¹Department of Microbiology and Immunology, School of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, Texas 78229.

Epigenetic marks and factors, such as histone modifications and miRNAs, interact with genetic programs to regulate intrinsic B cell functions and inform antibody responses. As shown by our transcriptome and miRNome analyses, histone deacetylase inhibitors (HDIs) selectively downregulate AID, which is critical for class switch DNA recombination (CSR) and somatic hypermutation (SHM), and Blimp-1, the master transcription factor for B cells differentiation to plasma cells. They do so, by selectively upregulating miRNAs that target *Aicda* and *Prdm1* mRNAs. As we have also shown, HDI-mediated impairment of CSR, SHM and plasma cell differentiation blunted T-dependent and T-independent antibody responses in wild type mice and autoantibody responses in lupus-prone mice. Potent HDI activity is displayed by butyrate and propionate, two abundant SCFA molecules generated by gut microbiota through fermentation of dietary fibers. We found that these SCFAs synergistically downregulate AID and Blimp-1 expression through selective miRNA upregulation. Feeding a no-fiber diet, or decreasing the load of SCFA-producing microbiota by treating mice with antibiotics reduced gut and serum SCFAs and resulted in increased IgA and IgG1 titers in feces and serum, and IgA⁺, IgG1⁺ B cells and plasma cells in Peyer's patches, mesenteric lymph nodes and spleen. This outcome was reversed by administration of butyrate and propionate, which also synergistically inhibited CSR to IgG and IgA in purified human and mouse B cells in a dose-dependent fashion. Thus, endogenous HDIs integrate cues from metabolites by gut microbiota and relay them to selective downstream effectors, e.g. miRNAs, thereby modulating B cell differentiation and antibody/autoantibody responses.

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