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Short Chain Fatty Acids Modulate Mast Cell Activation

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Humans have evolved in an environmental and social context that enabled reliable transmissiosn and dispersal of symbionts, accompanied by appropriate nutritional support. However, recent changes in lifestyles, diet and social interactions have altered these metacommunity processes, disrupted the human microbiome and, as a consequence, increased risk of immune-mediated diseases such as allergy and asthma (1, 2). The mechanisms that mediate host-microbe communication are highly sophisticated and are being intensely investigated. One microbial-dietary interaction that has important immunoregulatory consequences for the host is the fermentation of dietary fibers by commensal microbes in the gut, resulting in the generation of short-chain fatty acids (SCFAs), which include acetate, propionate and butyrate (3, 4). SCFAshave been shown to increase Treg numbers and effectiveness, reduce effector T cell activity, promote B cell IgA production, support maturation and maintenance of tolerogenic dendritic cells, influence bone marrow haematopoiesis, improve epithelial barrier function and modulateinnate lymphoid cellactivation (5). SCFAs can mediate their effects via multiple mechanisms that include binding to metabolite-sensing G-protein coupled receptors (GPCRs), such as GPR41, GPR43 and GPR109A, or by inhibiting the activity of chromatin modifying enzymes (such as histone deacetylases (HDACs)) thereby regulating gene transcription.

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However, the effects of these metabolites on the activation of key effector cells in allergy and asthma, specifically mast cells, has been poorly characterised. In this issue, Folkerts and colleagues investigate the effects and underlying mechanisms for SCFAs modulation of mast cell activation (6). Firstly, they demonstrated that butyrate inhibited IgE- and allergen-induced airway contraction using precision cut lung slices (PCLS) from the lower airways of guinea pigs, which was associated with reduced histamine release. In addition, butyrate and propionate, but not acetate, inhibited IgE- and non-IgE-mediated mast cell activation using murine primary bone-marrow-derived mast cells and human peripheral blood mononuclear cell-derived mast cells (Figure 1). Using mast cell from GPCR knock-out animals, they showed that inhibition of mast cell activity was independent of GPR41 and GPR43. Nuclear peroxisome-activated receptors (PPARs) were also not required for the observed effects. However, butyrate (and to a lesser extent propionate) attenuated HDAC activity in both murine and human mast cells, suggesting that SCFAs may regulate mast cell degranulation via epigenetic modifications. Indeed, a detailed evaluation of the mast cell transcriptome following exposure to butyrate described altered expression of genes associated with mast cell activation, inflammatory responses and cytokine signalling. The authors also demonstrated that butyrate exposure substantially impacts global mast cell histone acetylation patterns, using ChIP-Seq. Importantly, the authors identified butyrate-induced deacetylation at the transcription start sites of genes critical for FcεRI-mediated mast cell activation, such as Bruton's tyrosine kinase (BTK), spleen tyrosine kinase (SYK) and Linker for Activation of T cells (LAT).

The findings of the present study that identify butyrate and propionate, but not acetate, as modulators of mast cell activity correlates well with a recent study that associated high faecal levels of butyrate and propionate, but not acetate, with reduced risk of allergies and asthma in children (7). Due to their location in the gut and vascularized tissues, mast cells can be exposed to high concentrations of SCFAs coming from within the gastrointestinal tract.In addition, the present study suggests that SCFAs may modulate immune activity in a cell-type specific manner. GPCRs have previously been shown to be required for certain SCFAs effects on dendritic cells and lymphocytes (8), but these receptors do not seem to be required for inhibition of mast cell degranulation.Rather, epigenetic regulation via HDAC inhibition seems to be required for control of mast cell activity, which may have important consequences during *in utero* development.

In summary, this study adds to a growing body of literature that supports the immunomodulatory role of SCFAs in maintaining a tolerogenic mucosal environment and protecting against allergic disorders. Overall, these findings highlight the potential for using targeted manipulations of the gut microbiome and its metabolic functions in promoting immune health.However, the optimal prevention or treatment strategies involving SCFAs in humans have yet to be defined, but could include administration of fibers, synbiotics or the SCFAs themselves. In addition, the inclusionof SCFAs within immunotherapy protocols needs to be further explored in human clinical studies.

Conflict of interest statement: Dr. O'Mahony reports personal fees from Alimentary Health, grants from GSK, outside the submitted work.

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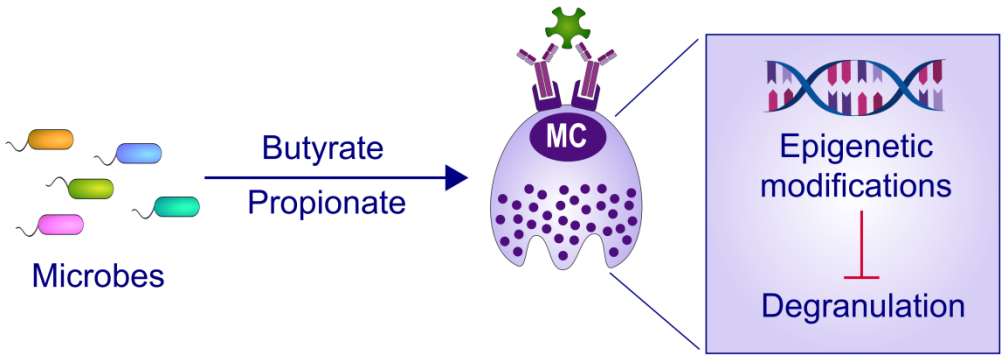

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