

Short-chain fatty acids: linking diet, the microbiome and immunity

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1 **Supplementary Table 1: Butyrate and the immune system**

Clinical application	Evidence	
Inflammatory bowel disease	<i>Butyrate</i>	Reduced levels of butyrate in stool of IBD patients ¹ and reduced butyrate levels associated with Crohn's disease complication rates ² .
	<i>Butyrogenic bacteria</i>	Reduced levels of butyrate-producing bacteria in IBD ³ , including <i>Faecalibacterium prausnitzii</i> with lower levels associated with increased risk of post operative recurrence of Crohn's disease. Reduction in cross feeding bacteria, such as <i>Bifidobacterium longum</i> , that support butyrate producers in IBD ⁴ .
	<i>Animal models</i>	Reduced levels of butyrate exacerbate inflammation in mouse models of colitis and butyrate produced by <i>F. prausnitzii</i> ameliorates colitis ⁵ . A polymeric nanoscale micelle locally released butyrate reduces colitis severity ⁶ .
	<i>Human studies</i>	Butyrate enemas reduce disease activity index and ameliorate symptoms in UC ⁷ , although a subsequent indicates only minor symptom relief in UC ⁸ . Total SCFA enema only effective in reducing symptoms in subset of UC patients ⁷ .
Environmental enteropathy	<i>Butyrate</i>	Lower levels of 2-hydroxyisobutyrate in stool of undernourished children with enteropathy ⁹ .
	<i>Butyrogenic bacteria</i>	Stunted children show lower levels of butyrate producing bacteria in the intestine, in particular <i>Clostridia</i> ¹⁰ .
	<i>Human studies</i>	Combination of fructo-oligosaccharide as a source of fibre for SCFA generation and <i>Lactobacillus plantarum</i> prevents sepsis and death of infants in rural India ¹¹ .
Infections	<i>Animal models</i>	Butyrate prevents dissemination of murine intestinal <i>Citrobacter rodentium</i> infection ¹² .

	<i>Human studies</i>	<i>Bifidobacteria</i> protects against enteropathogenic <i>E.coli</i> ¹³ . <i>Bifidobacteria</i> and <i>Lactobacillus</i> supplements to mothers of premature low birth weight infants prevents necrotizing enterocolitis ¹⁴ . Symbiotic preparation of <i>Lactobacillus plantarum</i> and fructo-oligosaccharide (source of fibre for SCFA-producing bacteria) prevents sepsis and death in infants ¹¹ .
Multiple sclerosis	<i>Butyrate</i>	Butyrate levels in stool of MS patients reduced (reviewed in 15)
	<i>Butyrogenic bacteria</i>	Reduction of butyrogenic bacteria in stool of MS patients (reviewed in 15)
	<i>Animal models</i>	Oral administration of butyrate ameliorated disease in cuprizone-induced MS models and in experimental autoimmune encephalomyelitis ¹⁶ .
Food allergies	<i>Butyrate</i>	Early-life reduction in faecal butyrate levels are associated with food allergy later in life (reviewed in 17)
	<i>Animal models</i>	High fibre diet in mice protects against food allergy and increased levels of intestinal butyrate and acetate, alongside increased retinoic acid activity in CD103 ⁺ dendritic cells ¹⁸ .
	<i>Human studies</i>	Supplementing infant formula with <i>Lactobacillus rhamnosus</i> GG expands butyrogenic bacteria, boosting tolerance to cow's milk allergy in infants, and protecting against asthma, eczema, urticaria and rhinoconjunctivitis in children with cow's milk allergy ¹⁹ .
Allergic airway disease, asthma and lung infections	<i>SCFAs</i>	Reduced levels of SCFAs in stool of allergic children, compared to non-allergic ²⁰ .
	<i>Animal models</i>	Intestinal-derived propionate protects against allergic airway disease in mice ²¹ and influenza infection in mice ²² .
Atopic eczema	<i>Butyrate</i>	Butyrate levels reduced in stool of infant eczema patients preceding onset of eczema ²³ .
	<i>Butyrogenic bacteria</i>	Eczema severity in infants inversely correlated with intestinal butyrate-producing bacteria ²⁴ .

	<i>Animal models</i>	Butyrate applied topically or injected subcutaneously reduced contact hypersensitivity reaction in hapten-sensitised mice ²⁵ .
Type 1 Diabetes	<i>Butyrate</i>	Key features of disease in NOD mice correlate with low concentrations of butyrate (and acetate) ²⁶ .
	<i>Butyrogenic bacteria</i>	Reduced amounts of butyrate-producing bacteria in type 1 diabetes compared to controls ²⁷ .
	<i>Animals models</i>	Diets releasing high levels of butyrate and acetate enhance protection from diabetes in NOD mice ²⁶ . Butyrate alleviates antibiotic-driven type 1 diabetes in female offspring of NOD mice ²⁸ .
Bacterial Vaginosis	<i>SCFAs</i>	Increased levels of butyrate, propionate and acetate in the vagina of BV patients ²⁹ . Vaginal SCFAs in BV associated with inflammation and loss of barrier integrity ³⁰ .
	<i>Butyrogenic bacteria</i>	Increased SCFA -producing anaerobic bacteria including <i>Gardnerella vaginalis</i> in the vagina in BV ³¹ .
Uterus and pregnancy	<i>Animals models</i>	Dietary administration of butyrate to pregnant rats significantly improved litter size and embryo implantation ³² . Female mice on a high fibre diet during pregnancy and lactation increased plasma levels, alongside increased thymic and peripheral T regs in their offspring ³³ .
SARS-CoV-2	<i>Butyrate</i>	Reduced faecal levels of SCFAs in SARS-CoV-2-infected patients with severe illness ³⁴ .
	<i>Butyrogenic bacteria</i>	Depletion of butyrogenic bacteria, such as <i>Faecalibacterium prausnitzii</i> in SARS-CoV-2-infected patients ^{35,36} .

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