Cell

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Review

# From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites

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http://dx.doi.org/10.1016/j.cell.2016.05.041

**A compelling set of links between the composition of the gut microbiota, the host diet, and host physiology has emerged. Do these links reflect cause-and-effect relationships, and what might be their mechanistic basis? A growing body of work implicates microbially produced metabolites as crucial executors of diet-based microbial influence on the host. Here, we will review data supporting the diverse functional roles carried out by a major class of bacterial metabolites, the short-chain fatty acids (SCFAs). SCFAs can directly activate G-coupled-receptors, inhibit histone deacetylases, and serve as energy substrates. They thus affect various physiological processes and may contribute to health and disease.**

## Introduction

The human microbiota is the collection of microbes that live on and in our body, with the largest and most diverse cluster of microorganisms inhabiting the gut. The gut microbiota has co-evolved with the host, which provides the microbes with a stable environment while the microbes provide the host with a broad range of functions such as digestion of complex dietary macronutrients, production of nutrients and vitamins, defense against pathogens, and maintenance of the immune system. Emerging data have demonstrated that an aberrant gut microbiota composition is associated with several diseases, including metabolic disorders and inflammatory bowel disorder (IBD). One of the mechanisms in which microbiota affects human health and disease is its capacity to produce either harmful metabolites associated with development of disease or beneficial metabolites that protect against disease. Diet drives gut microbiota composition and metabolism, making microbes a link between diet and different physiological states via their capacity to generate microbial metabolites depending on dietary intake. Some studies representing evidence of the interplay between diet, microbial composition, and physiology are described in the next paragraph, and the Review will then focus on a particularly versatile class of microbial metabolite short-chain fatty acids (SCFAs) that are derived from microbial fermentation of dietary fibers and are likely to have broad impacts on various aspects of host physiology.

Human populations with a diet enriched in complex carbohydrates, such as the Hadza hunter gatherers from Tanzania, have increased diversity of the gut microbiota (Schnorr et al., 2014). In contrast, long-term intake of high-fat and high-sucrose diet can lead to the extinction of several taxa of the gut microbiota (Sonnenburg et al., 2016). Barley kernel-based bread consumption improved glucose tolerance in healthy individuals with normal body mass index (BMI) in association with enrichment of *Prevotella copri* and increased capacity to ferment complex polysaccharides (Kovatcheva-Datchary et al., 2015). Improved postprandial glucose response and enrichment of butyrate-producing bacteria were found after 3 months intake of a mixture of inulin and oligofructose in obese women (Dewulf et al., 2013), and in mice that are obese due to either genetic manipulation or diet, supplementation with inulin-type fructans (fructo-oligosaccharides [FOS]) induced a remarkable increase of the number of *Bifidobacterium spp*, which is inversely correlated with adiposity and glucose intolerance (Cani et al., 2007).

## Microbial Fermentation Products: Short-Chain Fatty Acids

Dietary fibers, but also proteins and peptides, which escape digestion by host enzymes in the upper gut, are metabolized by the microbiota in the cecum and colon (Macfarlane and Macfarlane, 2012). The major products from the microbial fermentative activity in the gut are SCFAs—in particular, acetate, propionate, and butyrate (Cummings et al., 1987). However, when fermentable fibers are in short supply, microbes switch to energetically less favorable sources for growth such as amino acids from dietary or endogenous proteins, or dietary fats (Cummings and Macfarlane, 1991; Wall et al., 2009), resulting in reduced fermentative activity of the microbiota and SCFAs as minor end products (Russell et al., 2011). Protein fermentation can contribute to the SCFA pool but mostly gives rise to branched-chain fatty acids such as isobutyrate, 2-methylbutyrate, and isovalerate, exclusively originating from branched-chain amino acids valine, isoleucine, and leucine (Smith and Macfarlane, 1997), which are implicated in insulin resistance (Newgard et al., 2009). Further supplementation of diet rich in protein or fat with dietary fiber

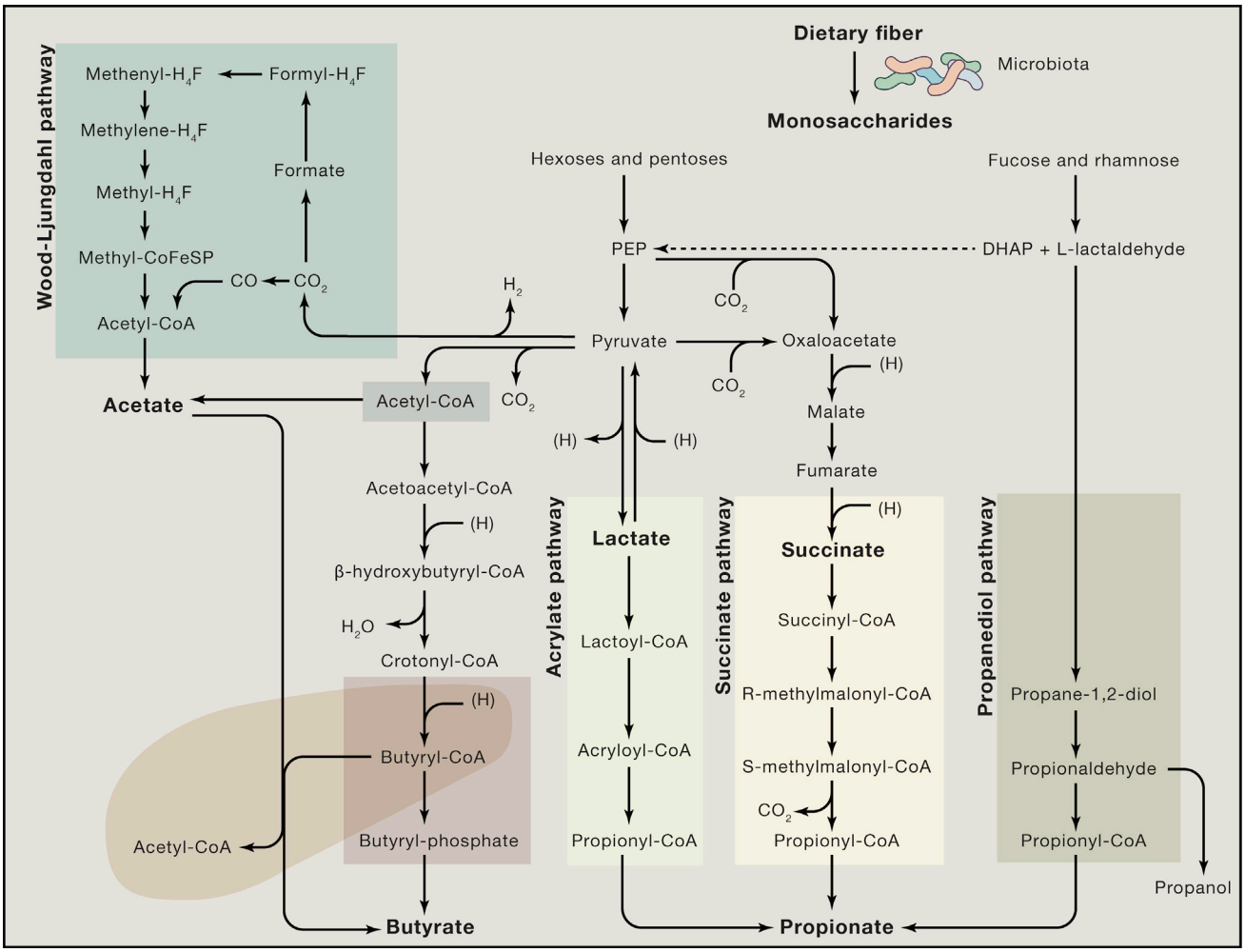


**Figure 1. Known Pathways for Biosynthesis of SCFAs from Carbohydrate Fermentation and Bacterial Cross-Feeding**

The microbial conversion of dietary fiber in the gut results in synthesis of the three major SCFAs, acetate, propionate, and butyrate. Acetate is produced from pyruvate via acetyl-CoA and also via the Wood-Ljungdahl pathway. Butyrate is synthesized from two molecules of acetyl-CoA, yielding acetoacetyl-CoA, which is further converted to butyryl-CoA via β-hydroxybutyryl-CoA and crotonyl-CoA. Propionate can be formed from PEP through the succinate pathway or the acrylate pathway, in which lactate is reduced to propionate. Microbes can also produce propionate through the propanediol pathway from deoxyhexose sugars, such as fucose and rhamnose. PEP, phosphoenolpyruvate; DHAP, dihydroxyacetonephosphate.

restores the levels of beneficial microbes, lowers the levels of toxic microbial metabolites, and increases SCFAs (Sanchez et al., 2009).

### *SCFA Biosynthesis, Absorption, and Distribution*

The microbial conversions of dietary fiber to monosaccharides in the gut involve a number of principal events (reactions) mediated by the enzymatic repertoire of specific members of the gut microbiota (Figure 1 and Table 1). Major end products from these fermentations are the SCFAs. One of the major SCFAs, acetate, can be produced from pyruvate by many gut bacteria either via acetyl-CoA or via the Wood-Ljungdahl pathway in which acetate is synthesized via two branches: (1) the $C_1$-body branch (also known as Eastern branch) via reduction of $CO_2$ to formate and (2) the carbon monoxide branch (the Western branch) via reduction of $CO_2$ to CO, which is further combined with a methyl group to produce acetyl-CoA (Ragsdale and Pierce, 2008). Another major SCFA, propionate, is produced from succinate conversion to methylmalonyl-CoA via the succinate pathway. Propionate can also be synthesized from acrylate with lactate as a precursor through the acrylate pathway (Hetzel et al., 2003) and via the propanediol pathway, in which deoxyhexose sugars (such as fucose and rhamnose) are substrates (Scott et al., 2006). The third major SCFA, butyrate is formed from the condensation of two molecules of acetyl-CoA and subsequent reduction to butyryl-CoA, which can be converted to butyrate via the so-called classical pathway, by phosphotransbutyrylase and butyrate kinase (Louis et al., 2004). Butyryl-CoA can also be transformed to butyrate by the butyryl-CoA:acetate CoA-transferase route (Duncan et al., 2002). Some microbes in the gut can use both lactate and acetate to synthesize butyrate (Table 1), which prevents