 DOI 10.1099/mic.0.078105-0

Review

From food to cell: nutrient exploitation strategies of enteropathogens

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Received 12 February 2014
Accepted 31 March 2014

Upon entering the human gastrointestinal tract, foodborne bacterial enteropathogens encounter, among numerous other stress conditions, nutrient competition with the host organism and the commensal microbiota. The main carbon, nitrogen and energy sources exploited by pathogens during proliferation in, and colonization of, the gut have, however, not been identified completely. In recent years, a huge body of literature has provided evidence that most enteropathogens are equipped with a large set of specific metabolic pathways to overcome nutritional limitations *in vivo*, thus increasing bacterial fitness during infection. These adaptations include the degradation of *myo*-inositol, ethanolamine cleaved from phospholipids, fucose derived from mucosal glycoconjugates, 1,2-propanediol as the fermentation product of fucose or rhamnose and several other metabolites not accessible for commensal bacteria or present in competition-free microenvironments. Interestingly, the data reviewed here point to common metabolic strategies of enteric pathogens allowing the exploitation of nutrient sources that not only are present in the gut lumen, the mucosa or epithelial cells, but also are abundant in food. An increased knowledge of the metabolic strategies developed by enteropathogens is therefore a key factor to better control foodborne diseases.

Introduction

Animals are generally considered nutrient-rich resources for micro-organisms and it is assumed that the evolution of pathogenic bacteria was at least in part driven by the opportunity to profit from increased substrate availability in host organisms (Rohmer *et al.*, 2011). Metabolic activity is a requirement for enteric pathogens to express their full virulence as they need energy as well as carbon and nitrogen sources to proliferate within the gut, to colonize the epithelial barrier, to produce virulence factors, to withstand the host's immune response and finally to transmit themselves to other hosts or the environment. Although the digestion activity of the intestinal microbiota and the enzymes of the host provide sufficient substrates for the indigenous gut microbes, the high nutrient competition between the commensal microbiota and enteropathogens requires the latter to occupy their own metabolic niches to survive and proliferate within the gut. As they use metabolic traits absent in avirulent bacteria, pathogens now appear to be adapted specifically to their varying environments during infection in terms of metabolism – a fact that also points to a shortage of easily available nutrients in those niches. The role of metabolism is therefore increasingly recognized as a priority equivalent to studying pathogenicity, and metabolic factors required for successful infection are considered virulence factors (Abu Kwaik & Bumann, 2013; Fuchs *et al.*, 2012a). Consequently, the identification of key enzymes such as PycA essential for metabolic functions during infection might open the way to novel therapeutic compounds (Schar *et al.*, 2010).

The complex interdependencies between the gut microbiota, host and pathogens remain to be elucidated in more detail. Given the strong competition for nutrients by the resident microbiota of the gut, this host compartment provides a particular challenge for pathogens. In turn, the availability and composition of nutrients are well known to trigger the regulation of virulence factors, e.g. by carbon catabolite repression (Fuchs *et al.*, 2012a; Le Bouguénec & Schouler, 2011; Poncet *et al.*, 2009). Modulations of the surrounding metabolome might also activate virulence factors via the stringent response through (p)ppGpp (Dalebroux *et al.*, 2010). It is therefore tempting to speculate that the specific metabolic adaptations of enteropathogens during infection might have been shaped by the dynamic interaction with the gut microbiota and its metabolome.

Major efforts have been made during recent years to better understand the metabolism of enteric pathogens such as

Abbreviations: EHEC, enterohaemorrhagic *Escherichia coli*; EPEC, enteropathogenic *Escherichia coli*; ETEC, enterotoxigenic *Escherichia coli*; GPC, glycerophosphocholine; HMO, human milk oligosaccharide; LEE, locus of enterocyte effacement; PTS, phosphotransferase system; SCFA, short-chain fatty acid; SPI, *Salmonella* pathogenicity island; TCS, two-component system.

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Salmonella enterica and *Listeria monocytogenes*, with a focus on their intracellular replication or systemic infection (Becker *et al.*, 2006; Eisenreich *et al.*, 2010; Fuchs *et al.*, 2012a, b; Schauer *et al.*, 2010; Steeb *et al.*, 2013). However, an overview of the metabolic strategies of pathogens during proliferation in, and colonization of, the gut is still missing. Here, we review the major nutrient requirements of foodborne enteropathogens during their life cycle with a focus on the complex environment of the gut. Examples of functional links between metabolic adaptations and bacterial virulence are also emphasized. The bacteria considered belong to the genera *Bacillus*, *Salmonella*, *Shigella*, *Campylobacter*, *Listeria*, *Clostridium*, *Enterococcus*, *Escherichia*, *Yersinia* and *Vibrio*, all of them causing gastroenteritis or related diseases. The title of this review suggests that metabolic adaptations useful in the gut also provide growth advantages prior to and during infection. To support the 'from food to cell' hypothesis, we provide evidence that some of the substrate degradation properties delineated below are useful not only to cope with nutrient limitations within the gut or, in the case of the facultative intracellular pathogens *L. monocytogenes* and *Salmonella enterica*, within epithelial cells, but also during proliferation in food.

Gut microbiota

About 1000 bacterial species inhabit the human intestine and an individual can harbour at least 160 species with up to 10^{14} prokaryotic cells (Qin *et al.*, 2010). It is estimated that 50–65 g of hexose sugars are required to substitute the 15–20 g dry weight of bacteria excreted per day and individual (McNeil, 1984). The composition and diversity of the gut microbiota are variable, and reflect the maturation phases of the host as well as its diet (Dominguez-Bello *et al.*, 2010). Metagenomic studies of the microbiome identified *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Fusobacteria*, *Lentisphaerae*, *Proteobacteria, Verrucomicrobia* and *Deinococcus–Thermus* as the most common phyla in the gut microbiota, with a prevalence of the first two phyla (Maccaferri *et al.*, 2011; Qin *et al.*, 2010). The proximal small intestine is only weakly colonized, and is characterized by the host digestion of carbohydrates, fat and proteins, and the absorption of monosaccharides (Martins dos Santos *et al.*, 2010), whereas the distal regions of the gut are densely colonized. They are characterized by a low oxygen tension (Contag *et al.*, 1995), with the exception of the mucosa as the only zone of relative oxygenation due to diffusion from the capillary network at the tips of villi (Marteyn *et al.*, 2010). The anoxic environment supports the colonization by anaerobic bacteria, and their enzymic reservoir benefits the host with nutrients and energy by degrading otherwise indigestible polysaccharides (Backhed *et al.*, 2005; Hooper *et al.*, 2002; Savage, 1977).

The microbiota is also known to affect the development of the immune system, which in turn shapes the composition of the gut bacteria (Nicholson *et al.*, 2012). The interaction between the host and its commensals is characterized by mutual benefits: whilst the host provides a warm and nutrient-rich environment, the highly adaptive metabolic activity of the commensals optimizes the nutrient and energy extraction from food (Maynard *et al.*, 2012). Last, but not least, the intestinal microbiota is assumed to deplete most nutrients as one of several strategies that provide colonization resistance against bacterial pathogens. This theory is known as Freter's nutrient niche hypothesis (Freter *et al.*, 1983). For instance, commensal bacteria such as *Escherichia coli* strain Nissle 1917 may outcompete and reduce *Salmonella enterica* sv. Typhimurium colonization due to their iron uptake capacities (Deriu *et al.*, 2013). Another example is the occupation of two distinct nutritional niches by *E. coli* strains HS and Nissle 1917 which together consume five sugars that are also important for the colonization of streptomycin-treated mice by pathogenic *E. coli* (Maltby *et al.*, 2013). A counterpoint to the phenomenon of colonization resistance was the finding that the metabolism of bile salts by the microbiota stimulates the germination of *Clostridium difficile* spores (Giel *et al.*, 2010).

Gut metabolome

The composition of the metabolites in the intestine is a consequence of the diet, on the one hand, and the enzymic activities of both the host and the microbiota, on the other hand. Following food ingestion, both the commensal microbiota and the host exploit food nutrients as efficiently as possible, based partially on metabolic complementarities between the two partners. Studies analysing intact human biopsies or the colonic metabolome of mice identified amino acids, amino sugars (glucosamine, galactosamine, *N*-acetylglucosamine), sialic acids such as *N*-acetylneuraminic acid, dipeptides, carboxylic acids, pyrimidines, membrane component metabolites, urea, creatine, glucose, inositols and triglycerides to be common in the gastrointestinal tract (Matsumoto *et al.*, 2012; Wang *et al.*, 2007). As expected, their concentrations vary with the intestinal location. For example, the duodenum and jejunum are rich in choline, glutathione, glycerophosphocholine (GPC), lipids and glycoproteins, but relatively poor with respect to acetate, glutamate, inositols and phosphorylethanolamine. The ileum is rich in amino acids, ethanolamine and glycoproteins, but poor in GPC. The transverse colonic mucosa contains higher levels of acetate, glutamate, inositols and lactate. Interestingly, a transcriptome profile during infection indicates that bacteria encounter amino acid starvation at the mucosa wall (Harvey *et al.*, 2011).

In addition to protein-rich food, humans and animals commonly consume plant polysaccharides such as cellulose, hemicellulose, mannan, pectin or raffinose that escape absorption in the small intestine. The commensal microbiota in the distal gastrointestinal tract is able to degrade these otherwise poorly utilized macromolecules that are rich in xylose, glucose, galacturonic acid, galactose, fructose, mannose and arabinose (Hooper *et al.*, 2002). The main chemical classes of gut metabolites contributed by the

microbiota activity are bile acids, cholines, benzol and phenol derivatives, indoles, vitamins, polyamines, lipids and short-chain fatty acids (SCFAs) (Cummings & Macfarlane, 1991; Nicholson *et al.*, 2012). The predominant SCFAs acetate, (2-methyl-)propionate and (iso-) butyrate are derived from pyruvate fermentation by anaerobic bacteria in the distal intestinal lumen, thus providing additional carbon and energy. The SCFAs are then mainly absorbed by the host (Hooper *et al.*, 2002). Under a diet rich in plant polysaccharides and low in sugar or fat, the concentration of SCFAs might exceed the absorption rate (De Filippo *et al.*, 2010). The presence of SCFAs, which are assumed to inhibit bacterial growth by decreasing the luminal pH (Cummings *et al.*, 1987), closely links metabolism to virulence: *Salmonella enterica* shows limited invasion of epithelial cells in the intestine due to the specific downregulation of *Salmonella* pathogenicity island 1 (SPI1) genes upon exposure to butyric acid (Gantois *et al.*, 2006), mainly synthesized by *Firmicutes* (Martins dos Santos *et al.*, 2010).

The gut microbiota also provides a broad enzymic capacity to cleave host glycans or glycoconjugates such as highly glycosylated mucin or glycosphingolipids from epithelial cells. A metagenomic study comparing 18 microbiomes identified 156 families of carbohydrate-active enzymes, including glycoside hydrolases, glycosyltransferases, polysaccharide lyases and carbohydrate-esterase families (Turnbaugh *et al.*, 2009), and the microbiome represents at least 81 different glycoside hydrolase families that are absent in the human 'glycobiome' (Gill *et al.*, 2006). These data indicate the enormous capability of the gut microbiota to metabolize various carbon sources derived from ingested food or host glycoconjugates especially present on the surface of epithelial cells. An outstanding example for this metabolic capacity is *Bacteroides thetaiotaomicron*, a common, Gram-negative member of the intestinal microbiota in humans and mice that expresses more glycosylhydrolases than any other prokaryote sequenced so far, and it is concluded that nearly all glycosidic bonds found in nature can be cleaved by this gut bacterium (Wexler, 2007).

Disturbances of the gut metabolome: diet, inflammation and antibiotic treatment

The interdependencies between the host and the microbiota are complex, and their metabolic equilibrium can be disrupted by external factors. As revealed by a metagenomic approach, food profoundly affects the composition of the microbiota that is able to respond to a change in the diet within 1 day (Turnbaugh *et al.*, 2009). A comparative study with children from Europe, with a diet rich in animal proteins, sugar and starch, and from rural Africa, with a fibre-rich, predominantly vegetarian diet, revealed an impact of dietary habits on the gut microbiota. *Enterobacteriaceae* such as *Shigella* and *Escherichia* in the African children were under-represented, possibly due to the abundance of SCFA-producing bacteria in their intestines (De Filippo *et al.*, 2010). Different illnesses, such as inflammatory bowel disease, are associated with imbalances of the microbiota, called dysbiosis, which is characterized by a reduction in taxonomic diversity and species membership (Pham & Lawley, 2014; Winter & Baumler, 2014), and, consequently, by a change of the metabolic functions present in the gut lumen. Dysbiosis is also due to host-mediated inflammation upon infection and has been demonstrated to disrupt the colonization resistance, resulting in a decrease of inhibitory substances, including SCFAs, and an increase of nutrient availability within the gut (Lupp *et al.*, 2007; Stecher *et al.*, 2007; Stecher & Hardt, 2008). Examples for the latter are the local release of high-energy nutrients like galactose-containing glyco-conjugates as an element of the mucosal defence (McGuckin *et al.*, 2011; Stecher *et al.*, 2008) and the formation of tetrathionate, an alternative electron acceptor for respiration under anaerobic conditions, which allows *Salmonella enterica* sv. Typhimurium to use sugars more efficiently and thus to overgrow the microbiota (see below). *E. coli* strains that harbour nitrate reductases also benefit from intestinal inflammation as they can use nitrate as an electron acceptor to obtain a growth advantage over the majority of the microbiota (Winter *et al.*, 2013). Nitrate is present in the intestine at physiologically relevant concentrations (Jones *et al.*, 2007) and, like tetrathionate, it is produced upon infection, inducing the expression of nitric oxide synthetases, which generate nitric oxide. Nitric oxide can react with superoxide radicals produced during inflammation to yield peroxynitrite, which is rapidly converted to nitrate (Spees *et al.*, 2013). *Enterococcus faecalis*, *Bacillus cereus*, *Clostridium perfringens*, *Salmonella enterica*, *Shigella* spp. and pathogenic *E. coli* possess nitrate reductases which might help these enteric pathogens to overcome colonization resistance. Thus, by triggering mucosal inflammation, these and further, yet unknown properties enable pathogens to successfully colonize the host's intestine under otherwise adverse conditions. Inappropriate antibiotic exposure is another reason for dysbiosis that might lead to massive growth of enteric pathogens in the gut due to greater resistance to host defences and better utilization of the gut nutrient environment (Keeney & Finlay, 2011). For example, the antibiotic-associated pathogens *Salmonella enterica* sv. Typhimurium and *Clostridium difficile* profit from an increase of mucosal carbohydrates that are not further consumed by *Bacteroidetes* (Ng *et al.*, 2013).

A frugal or an opulent meal? Nitrogen, carbon and energy sources used by enteropathogens

Despite its richness in metabolites, the gut is considered a competitive rather than a nutrient-rich environment for pathogens. All metabolic niches are already occupied by the commensal microbiota and high-energy nutrients are missing (Derrien *et al.*, 2004; Hansson, 2012). The metabolism of pathogens *in vivo* has been largely unknown. A deeper understanding of this topic has been hampered by (i) the assumption that metabolism only contributes slightly to growth advantages *in vivo*, (ii) the absence of

appropriate animal experiments and (iii) the finding that bacterial metabolism is robust in a sense that one pathway might easily be substituted by another. Transcriptomic studies and predictions from *in vitro* and bioinformatic studies, however, have now helped to overcome this lack of knowledge. Seminal progress in this field was made by establishing an infection model with streptomycin-treated mice that, in contrast to untreated mice, resembles many aspects of human enteritis, including mucosal inflammation, upon *Salmonella enterica* sv. Typhimurium infection (Barthel *et al.*, 2003; Kaiser *et al.*, 2012). This model takes advantage of the effects of dysbiosis described above. Gram-positive microbes are either unaffected by streptomycin treatment or at most reduced in numbers for only 1 day, whereas Gram-negative bacteria are completely eliminated but reappear after 1–2 days, except *E. coli* (Miller & Bohnhoff, 1963). Therefore, the increased susceptibility of mice for *Salmonella enterica* sv. Typhimurium infections in this model is probably due to the depletion of the commensal microbiota.

It is noted in the following text if mice were treated with streptomycin or used as monoassociated animals. In all other cases, e.g. in earlier studies, untreated mice were used by the authors. It should also be emphasized here that animals, in addition to many other aspects, differ from humans in terms of diet and microbiota, and that data obtained by infection models exploited in research cannot be transferred directly to humans.

Nitrogen sources

The presence of amino acids, dipeptides and oligopeptides derived from the diet or the mucosa suggests an abundancy of nitrogen sources in the intestine and colon (Matsumoto *et al.*, 2012; Zheng *et al.*, 2011). They either are utilized directly for protein synthesis or serve as carbon and nitrogen sources following enzymic conversion. However, it is largely unknown whether or not enteric pathogens can profit from this nitrogen pool without being outcompeted by the commensal microbiota. It is well known that glutamate and glutamine are the primary nitrogen donors for all cellular metabolites in *Salmonella enterica*, *L. monocytogenes* and other enteric bacteria (Joseph *et al.*, 2006; Klose & Mekalanos, 1997). *L. monocytogenes* strains lacking oligopeptide transporters are attenuated *in vivo*, pointing to the need for amino acid uptake and utilization (Borezee *et al.*, 2000; Schauer *et al.*, 2010). Due to incomplete glycolytic, Entner–Doudoroff and pentose phosphate pathways, *Campylobacter jejuni* predominantly uses amino acids as the carbon and energy source instead of common sugars during infection (Parkhill *et al.*, 2000). L-Serine, for example, is converted to pyruvate and ammonia, and a lack of this catabolic function results in a growth defect *in vivo* (Velayudhan *et al.*, 2004).

Urea is generated by host tissues and passed into the gut where it is hydrolysed to ammonia by ureases of the intestinal microbiota, which thus contribute to nitrogen recycling in the intestine (Forsythe & Parker, 1985). Some of the enteropathogens discussed here, i.e. *Bacillus cereus*, *Clostridium perfringens*, *Yersinia enterocolitica*, *Vibrio parahaemolyticus* and enterohaemorrhagic *E. coli* (EHEC), harbour genes encoding ureolytic activities (Table 1). So far, urease has only been demonstrated to play a role in gut colonization by Shiga toxin-producing *E. coli* (Steyert & Kaper, 2012) and it remains to be investigated to what extent ureases contribute to improved nitrogen availability of other enteric pathogens.

Hydrogen

Molecular hydrogen is produced as a fermentation byproduct of the microbiota in the large intestine of animals, where it is removed by mesophilic methanogenic archaea (Stams, 1994). Its production can be correlated with the digestibility of the carbohydrates consumed (Maier, 2005). Interestingly, most enteropathogenic bacteria, including *Campylobacter jejuni*, *E. coli*, *Y. enterocolitica*, *Shigella flexneri* and *Salmonella enterica*, are able to use hydrogen as an energy source through respiratory hydrogenases (Table 1). *Salmonella enterica* encodes three putative membrane-associated hydrogenases, all of which are coupled to a hydrogen-oxidizing respiratory pathway which allows energy production. The *Salmonella* hydrogenases contribute to virulence in a typhoid fever mouse model as demonstrated by the strongly enhanced survival rate of mice infected with (multiple) hydrogenase deletion mutants of *Salmonella enterica* sv. Typhimurium (Maier *et al.*, 2004). Consequently, antibiotic treatment of the mice as well as gut precolonization with a hydrogen-consuming strain depleted the initial growth advantages of *Salmonella enterica* using hydrogen in the gut (Maier *et al.*, 2013). Molecular hydrogen produced by the gut microbiota was also demonstrated to support *Salmonella enterica* sv. Typhimurium growth with the alternative carbon source glucarate, an oxidized product of glucose, which contributes to proliferation of this pathogen *in vivo* (Lamichhane-Khadka *et al.*, 2013).

Carbon and energy sources

Sugars are the most favourable energy and carbon sources for bacteria. As *E. coli* is a typical member of the gut microbiota, it is of interest whether or not pathogenic *E. coli* strains differ from commensal strains with respect to carbon and energy sources. Commensal *E. coli* are assumed to use a variety of mucus-derived metabolites, such as arabinose, fucose, sialic acid, *N*-acetylglucosamine, gluconate and *N*-acetylneuraminic acid, during replication in the gut of mice treated with streptomycin (Chang *et al.*, 2004; Fabich *et al.*, 2008). In the same studies, an attenuation of *E. coli* strains defective in the Entner–Doudoroff pathway or glycolysis in the mouse intestine was observed, whereas the glycerol, galactitol, lactose, mannitol or aspartate utilization pathways as well as the TCA cycle, the pentose phosphate pathway or gluconeogenesis were shown to be

Table 1. Specific metabolic properties of enteropathogens

Bacteria	Substrate or cofactors (relevant genes for degradation or synthesis)												
	Ethanolamine (*eutABC*)	Propanediol (*pdu*)	Cobalamin synthesis (*cob*/*cbi*)	Tetrathionate reductase (*ttrABC, ttrSR*)	Sialic acid (*nanRATEK*)[1]*	*myo*-Inositol (*iolR, iolABCDE*)	Fucose (*fucI, fucA, fucK, fucO*)	Melibiose (*melA, melB*)	Rhamnose (*rhaABCD*)	Xylose (*xylABEFGH, xylR*)	Glycerol†	Hydrogenase (*hya, hyf, hyc, hyp, hybC, hydB*)	Urease (*ureABCDEFG*)
Gram-positive													
Enterococcus faecalis	**+**	–	–	–	–	+	–	–	+	+[2]	–[3]	–	–
Bacillus cereus	–	–	–	–	–	+	(+) (*fucK, fucI* present)	–	–	+[2]	–[3]	–	+ (strain dependent)
Listeria monocytogenes	**+**	**+**	**+**	–	–	+	+	–	+	–	+[3]	–	–
Clostridium perfringens	+	+	+	–	+	+	+[4]	+	+	–	+[3]	+	+ (neighbouring toxin genes on plasmid)[5]
Clostridium difficile	+	–	+	–	**+**	–	–	–	+	+[2]	–[3]	+	–
Gram-negative													
Salmonella enterica	**+**	**+**	**+**	+[6]	**+**	+[7]	**+**	**+**	+	+	+[3]	**+**	–
Shigella flexneri	+	–	(+) (*cobUST* present)	–[6]	+	–	+	+	+	+	–[3]	+	–
Shigella dysenteriae	+	–	(+) (*cobUST* present)	–[6]	+	–	+	+	+	+	–[3]	+	–
Shigella boydii	+	–	(+) (*cobUST* present)	–[6]	+	–	+	+	+	+	–[3]	+	–
Shigella sonnei	+	+	(+) (*cobUST* present)	–[6]	+	–	+	+	+	+	+[3]	+	–
Yersinia enterocolitica	–	+	+	+	+	+[7]	–	–	– (strain dependent)	+	+[3]	+	+
Campylobacter jejuni	–	–	–	–	+	–	**+**	–	–	–	–[3]	+	–
Vibrio cholerae	–	–	(+) (*cobUST* present)	–[6]	+	–	–	–	–	–	–[3]	+	–
Vibrio parahaemolyticus	–	–	(+) (*cobUST* present)	+[6]	+	–	–	–	+	–	–[3]	–	+
Escherichia coli [enteropathogenic (EPEC), enterotoxigenic (ETEC), uropathogenic (UPEC), enterohaemorrhagic (EHEC)]	**+**	–/**+** (present in ETEC, EPEC)	(+) (*cobUST* present)	–	+	–	**+**	+	+	+	–[3]	+	+ (EHEC)

nanA, *N*-acetylneuraminic lyase; *nanE*, *N*-acetylmannosamine 6-phosphate epimerase; *nanK*, *N*-acetylmannosamine kinase.
+, Genes present; –, genes absent; bold, *in vivo* relevance has been demonstrated (see text for details).
*References: 1, Almagro-Moreno & Boyd (2009a); 2, Gu *et al.* (2010); 3, Zhang *et al.* (2009); 4, Zúñiga *et al.* (2005); 5, Dupuy *et al.* (1997); 6, Barrett & Clark (1987); 7, Kröger & Fuchs (2009).
†Cobalamin-dependent glycerol dehydratase; anaerobic degradation of glycerol (Lawrence & Roth, 1996).

dispensable. In contrast, pathogenic *E. coli* strain O157 : H7 does not use gluconate and *N*-acetylneuraminic acid, but does use galactose, hexonurates, mannose and ribose. Mutants of *E. coli* O157 : H7 defective in the utilization of fucose, but not of *N*-acetylgalactosamine, showed a weaker colonization of adult cattle treated with streptomycin (Snider *et al.*, 2009).

During proliferation within the gut, *L. monocytogenes* specifically profits from the uptake of sugars and their alcohols, including mannitol, mannose, galactitol and fructose, as indicated by the increased transcription of the respective phosphoenolpyruvate-dependent phosphotransferase system (PTS) (Toledo-Arana *et al.*, 2009). The same study identified the upregulation of genes encoding dihydroxyacetone kinases involved in glycerol utilization, which is already known to play an important role during intracellular replication of this pathogen (Eylert *et al.*, 2008; Joseph *et al.*, 2006). Upon entering epithelial cells, *L. monocytogenes* also upregulates mannose- and fructose-specific PTSs (Chatterjee *et al.*, 2006; Joseph *et al.*, 2006). The main virulence regulator of *L. monocytogenes*, PrfA, is downregulated in the presence of efficiently utilized sugars such as glucose, indicating that these carbon sources are limited when this facultative intracellular pathogen starts to invade epithelial cells (Behari & Youngman, 1998). In EHEC, glycolytic conditions similarly inhibit the expression of *ler* and thus of all other LEE (locus of enterocyte effacement) genes (Njoroge *et al.*, 2012).

As indicated by transcriptomic studies using the enteritis infection model, the uptake of ribose, arginine and glycerol is important for the proliferation of *Salmonella enterica* in the caecal lumen of chicken or mice (Harvey *et al.*, 2011; Rollenhagen & Bumann, 2006). The same studies suggest that *Salmonella* spp. use nutrients such as propionate, melibiose, trehalose and L-ascorbate during replication in the intestine. Loss of the ability to degrade propionate, e.g. the lack of *mhp* genes in *Shigella* spp. and in enterovasive *E. coli*, has been interpreted as an adaptation to the intracellular life cycle of these pathogens, especially because the degradation product 2-methylcitrate inhibits gluconeogenesis critical for *E. coli* virulence (Alteri *et al.*, 2009; Rohmer *et al.*, 2011). D-Xylose is derived from xylan and xyloglucan, the major hemicellulose component of plant cell walls, and can be utilized via D-xylulose by most of the enteropathogens discussed here with the exception of *Clostridium perfringens* and *L. monocytogenes* (Table 1).

Thus, pathogens benefit from the simultaneous exploitation of several sugars that are probably not utilized by the commensal intestinal microbiota. An exception is *Bacteroides thetaiotaomicron* that consumes a similar set of carbohydrates, among them the four main components of mucin, i.e. galactose, *N*-acetylglucosamine, *N*-acetylgalactosamine and fucose (Salyers & Pajeau, 1989), instead of polysaccharides accidentally absent in the diet (Sonnenburg *et al.*, 2005). The role of the mucus for the metabolism of enteric pathogens remains to be further elucidated.

Mucus-derived nutrients and the proliferation of commensal and pathogenic bacteria

In addition to the lumen, other relevant gut compartments encountered by pathogenic bacteria are the mucus-associated space and the mucus. The mucus layer protects the underlying cells against mechanical damage, assists food particle absorption, separates epithelial cells and bacteria of the gut lumen, and, last but not least, constitutes a barrier for pathogens (Corazziari, 2009). The water-rich mucus consists of mucins composed of oligosaccharides (glycans) attached to a protein backbone. The outer mucus layer of the stomach and colon is, in contrast to the inner mucus layer, penetrated by commensal bacteria (Johansson *et al.*, 2008). More than 100 different mucin oligosaccharides have been identified, with a remarkable variation of glycosylation within the various mucin populations of the intestinal regions (Robbe *et al.*, 2004). Mucin carbohydrate side-chains mainly contain galactose, hexosamines such as *N*-acetylglucosamine, and fucose (Cummings & Macfarlane, 1991). At the mucosal wall, sugars such as mannose, galactose, fucose and glucose are available as components of mucin glycoconjugates (Juge, 2012). Fucose is known to be degraded by commensal bacteria including *Bifidobacteria* and *Bacteroidetes* (Gill *et al.*, 2006; Hooper *et al.*, 1999). *Bacteroides thetaiotaomicron* is even able to induce the production of fucosylated glycoconjugates in the distal intestine – an ability that requires a certain population density of the bacterium (Becker & Lowe, 2003; Bry *et al.*, 1996). The spatio-temporal dynamic of epithelial fucosylation confers a growth advantage to *Bacteroides thetaiotaomicron* and provides favourable or unfavourable colonization conditions for other commensals as well as pathogens, thus modifying the composition of the gut microbiota (Hooper *et al.*, 2002).

Exploiting microbiota-released sugars of the epithelial glycocalyx appeared as a successful strategy of enteropathogens to overcome nutrient limitations when proliferating within or passing through this barrier to the surface of the epithelial cells (Gill *et al.*, 2006; Ng *et al.*, 2013; Stahl *et al.*, 2011). Obvious advantages of glycan utilization are that glycans are replenished continuously, and readily fermented as carbon and energy source (Salyers & Pajeau, 1989). A chemotactic gradient of D-galactose, but not L-fucose, was found to lead *Salmonella* from the lumen to the mucosal surface (Stecher *et al.*, 2008). It can be assumed that other gastrointestinal pathogens are attracted by similar chemotactic gradients towards the cell surface. Moreover, mutations in flagellar assembly and chemotaxis impaired the fitness of *Salmonella enterica* sv. Typhimurium in the inflamed, but not the healthy, intestine of specific pathogen-free mice (Stecher *et al.*, 2008). This phenomenon is likely caused by a *Salmonella enterica* sv. Typhimurium-induced inflammation which results in the enhanced secretion of mucus by epithelial cells, thus providing further nutrients for *Salmonella enterica* sv. Typhimurium (McGuckin *et al.*, 2011). Consequently, this pathogen grows well in caecal

mucus, but not in caecal luminal contents of streptomycin-treated mice (McCormick *et al.*, 1988).

L-Fucose, L-rhamnose and sialic acid

L-Fucose and L-rhamnose are components of the carbohydrate moiety of the mucosal glycoconjugates. Additionally, they can be frequently found in plant cell wall polysaccharides and in bacterial exopolysaccharides (Sampson & Bobik, 2008). α-Linked L-fucose represents 4–14 % of the total oligosaccharide content of mucin and is one of the terminal sugars of the oligosaccharide chains attached to the protein backbone of mucins (Muraoka & Zhang, 2011). Both sugars are derived from ingested food or from shedding and turnover of epithelial cells, and at least fucose is abundant in the intestine (Robbe *et al.*, 2004). L-Fucose is also present in human milk oligosaccharides (below) and the monosaccharide rhamnose is a building block of pectin. Sialic (or neuraminic) acid is the only component apart from L-fucose that is uniquely associated with mucin (Salyers & Pajeau, 1989).

Factors involved in fucose degradation

In *E. coli*, L-rhamnose induces the *rha* system, which results in the degradation of L-rhamnose to L-lactaldehyde. The *rha* system consists of the enzymes RhaD (rhamnulose 1-phosphate aldolase), RhaA (L-rhamnose isomerase), RhaB (L-rhamnulose kinase) and RhaC (regulatory protein for *rhaDAB*) (Power, 1967). Expression of 1,2-propanediol oxidoreductase (FucO) is induced when *E. coli* grows anaerobically on L-rhamnose, converting L-lactaldehyde to 1,2-propanediol (Chen *et al.*, 1987). 1,2-Propanediol is excreted by *E. coli* (Cocks *et al.*, 1974) and can then be further utilized by specialized enteropathogens (Fig. 1, Table 1).

The fucose utilization operon of *Bacteroides thetaiotaomicron* comprises the genes encoding L-fucose isomerase (*fucI*), L-fuculose 1-phosphate aldolase (*fucA*), L-fuculose kinase (*fucK*) and lactaldehyde reductase (*fucO*) (Hooper *et al.*, 1999). L-Fucose permease (*fucP*) is expressed constitutively and not located within the fucose utilization operon (Hooper *et al.*, 2002). The expression of the fucose utilization operon is regulated by the gene product of *fucR* located upstream of *fucI*. FucR is removed from its target DNA by the presence of L-fucose, thus enabling gene expression (Hooper & Gordon, 2001). FucR not only regulates the expression of the fucose utilization genes, but also is involved in the induction of host enterocytic Fuc-1,2-α-Gal-*β*-containing glycan production in the case of fucose deficiency (Hooper *et al.*, 2002).

L-Rhamnose and L-fucose utilization by enteric pathogens

Although the capability to degrade L-rhamnose is present in the genomes of many enteropathogens (Table 1), a role of this metabolic pathway *in vivo* remains to be elucidated. Recently, a novel transcription factor was identified in *L. monocytogenes* strains associated with foodborne infections and it could be demonstrated that this *prfA*-like regulator contributes to L-rhamnose utilization (Salazar *et al.*, 2013).

The ability of some enteropathogens to degrade fucose has been demonstrated experimentally (Badia *et al.*, 1985; Obradors *et al.*, 1988) or predicted due to genome analyses. As mentioned above, *Campylobacter jejuni* is unable to use common carbohydrates as a carbon or energy source, although all genes required for gluconeogenesis as well as an intact TCA cycle are present in the genome (Parkhill *et al.*, 2000). However, fucose derived from fucosylated glycoconjugates on the surface of epithelial cells was discovered recently to serve as a carbon and energy source of *Campylobacter jejuni*, and strains lacking the capability to use fucose are attenuated *in vivo* (Stahl *et al.*, 2011). In addition to mucin, organic acid intermediates of the TCA cycle as well as some amino acids, L-fucose was identified as a chemoattractant for *Campylobacter jejuni* (Hugdahl *et al.*, 1988). *Campylobacter jejuni* binds to 1,2-α-fucosylated glycans *in vitro* and adherence to intestinal cells is diminished by free fucose (Muraoka & Zhang, 2011). Similar to *Bacteroides thetaiotaomicron*, the anaerobic utilization of fucose by *Campylobacter jejuni* results in pyruvate production (Stahl *et al.*, 2012). The exact mechanisms of the L-fucose degradation pathway in *Campylobacter jejuni* remain to be elucidated, since only a fucose permease as well as an aldolase homologue of *E. coli*, which converts lactaldehyde to lactate under aerobic conditions, were identified to be involved in fucose degradation by *Campylobacter jejuni* (Stahl *et al.*, 2011).

The genomes of *Salmonella enterica*, pathogenic *E. coli* strains and *Clostridium perfringens* are also equipped with the *fuc* genes, whereas most *Vibrio cholerae* strains and the pathogenic *Yersinia* spp. probably lack the capability to degrade fucose (Table 1). Deletion of genes involved in fucose utilization by *Salmonella enterica* reduces its competitiveness *in vivo* (Ng *et al.*, 2013). *E. coli* accumulating fucose 1-phosphate show stimulation of ribose utilization, indicating the cross-regulation of unrelated carbon sources under nutritional depletion (Alteri & Mobley, 2012). *L. monocytogenes* and *Bacillus cereus* encode a fucose isomerase, but further genes of these Gram-positive enteropathogens involved in fucose utilization have not been annotated. However, the *Bacillus cereus* genes flanking *fucI* as well as their homologues in the genome of *L. monocytogenes* encode enzymes with putative functions in sugar metabolism or regulation and transport.

Fucose-specific glycosylhydrolases (fucosidases) as homologues of the 1,3/4-α-fucosidase from *Bifidobacterium longum* can be found in *Clostridium perfringens*, but not in *L. monocytogenes. Bacillus cereus* secretes an α-L-fucosidase (Miura *et al.*, 2005). For Gram-negative enteropathogens, a protein sequence of an α-L-fucosidase of *Bacteroides thetaiotaomicron* (GenBank accession number NP_811105)

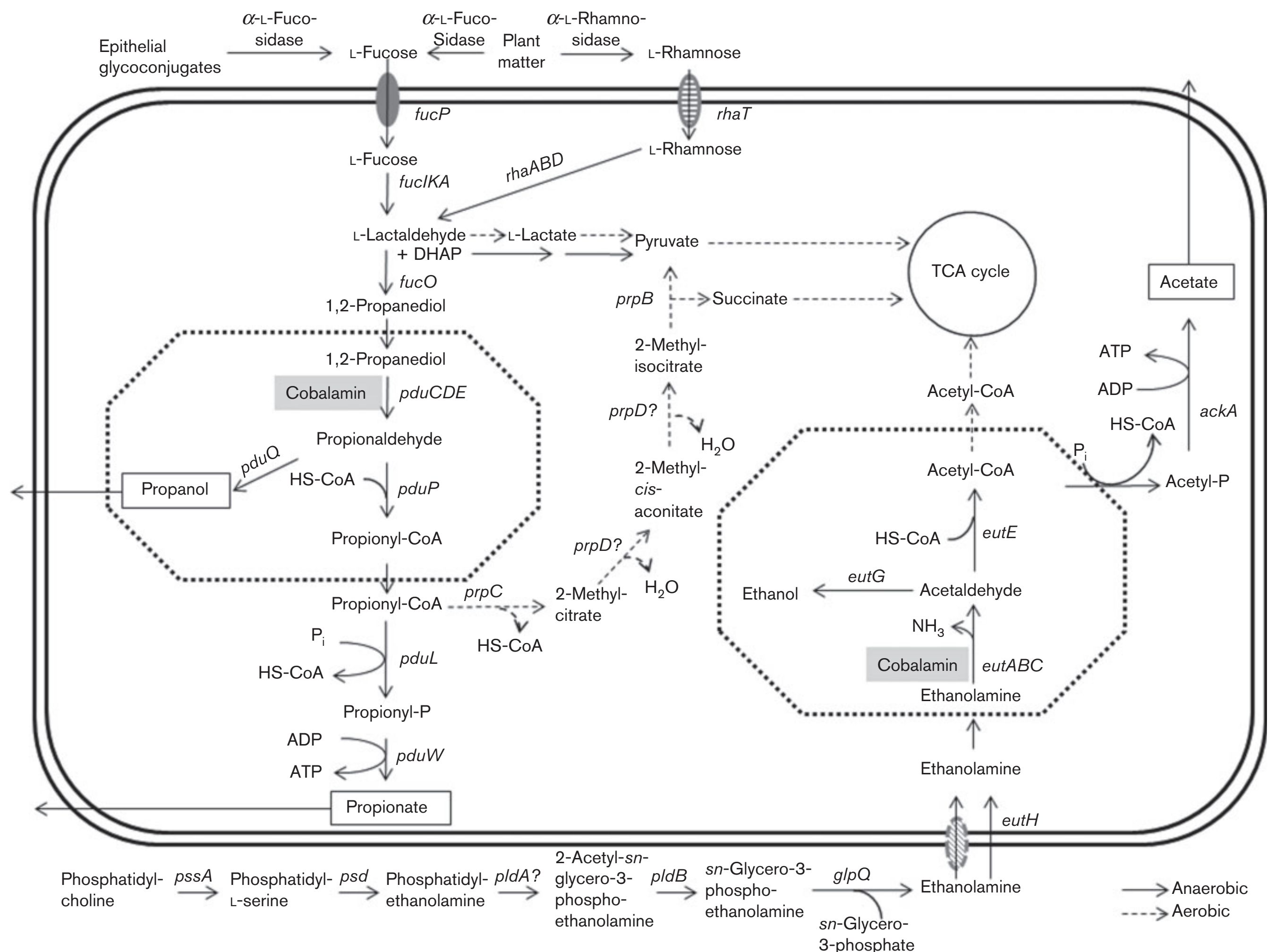

Fig. 1. Degradation pathways of ethanolamine and 1,2-propanediol in *Salmonella enterica* sv. Typhimurium. Phospholipids and mucosal glycoconjugates are degraded to ethanolamine and 1,2-propanediol by a cascade of enzymes produced by *Salmonella enterica* sv. Typhimurium or members of the gut microbiota. The genes involved in these degradation pathways are indicated. Genes *pduCDE* and *eutABC* require cobalamin as a cofactor. Microcompartments are depicted by dotted lines. DHAP, Dihydroxyacetone phosphate; CoA, coenzyme A; P, phosphate.

was used here for database query, but no homologues of this sequence were found in *Salmonella*, *Yersinia* or *Vibrio*. This finding suggests that these bacteria benefit from the fucose-releasing activity of commensal bacteria such as *Bacteroides thetaiotaomicron*.

The cleavage of fucose by *Bacteroides thetaiotaomicron* modulates the pathogenicity of EHEC. Using an infant rabbit infection model, it was demonstrated recently that a novel two-component-system (TCS) of this pathogen, FusKR, senses fucose. The genes encoding this TCS are located within the EHEC pathogenicity island LEE; FusK sensing results not only in the activation of the fucose utilization pathway, but also in enhanced transcription of several LEE genes involved in attaching and effacing lesions on enterocytes (Pacheco *et al.*, 2012).

L-Fucose in milk and impact on newborn gut microbiota

Human milk oligosaccharides (HMOs) are composed of the five monosaccharides D-glucose, D-galactose, *N*-acetylglucosamine, *N*-acetylneuraminic acid and L-fucose. These building blocks contribute to the formation of >130 different HMOs identified so far (Bode, 2006). Fucosylation occurs frequently on the non-reducing termini of the HMOs. Due to their complex structures containing α- and *β*-linkages, HMOs are hydrolysed poorly by typical enterobacteria and are additionally resistant against low pH in the stomach. The high density of bifidobacteria in the intestines of breast-fed infants indicates the ability of these bacteria to hydrolyse the HMOs by removal of the 1,2-α-, 1,3-α- and 1,4-α-fucosyl residues (Sela *et al.*, 2008). Three fucosidases with this function have been characterized in

Bifidobacterium bifidum (Ashida *et al.*, 2009; Katayama *et al.*, 2004). The breakdown of HMOs to SCFAs lowers the gut pH and thus diminishes the growth of harmful bacteria. Another health-beneficial feature of HMOs is the structural similarity of the non-reducing ends of HMOs and the non-reducing ends of glycoconjugates which are often used by pathogenic bacteria and viruses to recognize cell surface receptors and to bind to or invade target cells (Bode, 2006; Kobata, 2010). For example, *Campylobacter jejuni* binds to the fucosylated H-2 antigen expressed on the surface of gut epithelial cells. Interestingly, this attachment is inhibited specifically by fucosylated oligosaccharides present in HMOs (Ruiz-Palacios *et al.*, 2003).

Sialic acid

Sialic acid encompasses a variety of nine-carbon amino sugars that are found mainly in glycoconjugates of eukaryotic cells, and contribute to cell–cell interactions and cell–molecule recognition (Varki, 1993). Several bacterial pathogens, among them *Campylobacter jejuni* and EHEC, sialylate their outer membrane surface to hide themselves from the host immune response (Severi *et al.*, 2007). However, it has been demonstrated that *E. coli*, *Clostridium perfringens* and *Bacteroides fragilis* are able to utilize sialic acid as a carbon, energy and nitrogen source via the factors encoded by the *nanRATEK* operon. A bioinformatic approach identified the genes required for this catabolism additionally in *Salmonella enterica*, *Shigella* spp., *V. cholerae*, *V. parahaemolyticus*, *Y. enterocolitica* and *Clostridium difficile* (Almagro-Moreno & Boyd, 2009b), but not in *Enterococcus faecalis*, *Bacillus cereus* or *L. monocytogenes*. As sialic acid is found primarily in glycoconjugates, it might be hypothesized that its utilization helps gut pathogens to colonize the colon, to occupy a nutrient-rich and competitor-free niche, and/or to penetrate the mucus towards the epithelial cells (Chang *et al.*, 2004). Indeed, it was demonstrated that the presence of SPI1 positively effects the induction of the *nanRATEK* utilization genes of *Salmonella enterica* (Golding *et al.*, 2007), although a sialic acid transporter mutant did not reduce virulence significantly (Steeb *et al.*, 2013). However, a lack of sialic acids due to the colonization of gnotobiotic mice with a sialidase-deficient mutant of *Bacteroides thetaiotaomicron* impaired the expansion of *Salmonella enterica* and *Clostridium difficile* (Ng *et al.*, 2013).

Ethanolamine and 1,2-propanediol

The foodborne pathogens *Clostridium perfringens*, *Salmonella enterica* and *L. monocytogenes* are the only bacteria from Table 1 that are able to degrade ethanolamine as well as 1,2-propanediol (Korbel *et al.*, 2005) derived from phospholipids or fucose. All other enteric pathogens lack one or both of these degradation pathways, which are also missing in the commensal *Bacteroides thetaiotaomicron*. The utilization of ethanolamine and 1,2-propanediol under anoxic conditions has been studied in most detail for *Salmonella enterica* (Roth *et al.*, 1996). These pathways, which are summarized in Fig. 1, need exogenous tetrathionate as an alternative electron acceptor (Price-Carter *et al.*, 2001) and the cofactor cobalamin that can be synthesized by the three pathogens (see below for details) (Price-Carter *et al.*, 2001; Roth *et al.*, 1996). Enteropathogens that lack the complete cobalamin synthesis apparatus either contain the BtuFCD importer or use precursors for the final production of this cofactor (Table 1).

The organization of the genes responsible for the degradation of 1,2-propanediol and ethanolamine in *Salmonella enterica*, *L. monocytogenes* and *Clostridium perfringens* is depicted in Fig. 2. In *Salmonella enterica*, the two gene sets plus the genetic determinants required for cobalamin synthesis (*cob*/*cbi*) cover ~1 % of the genome and are found on two separated chromosomal fragments. In *L. monocytogenes*, these genes are organized consecutively in one chromosomal region, but they are scattered over the chromosome of *Clostridium perfringens*.

Recent publications provide indirect and direct experimental evidence for the assumption that the utilization of ethanolamine and/or 1,2-propanediol is linked closely to intestinal proliferation and thus to the virulence of *L. monocytogenes*, enteropathogenic *E. coli* (EPEC), *Salmonella enterica* and *Enterococcus faecalis* (Becker *et al.*, 2006; Harvey *et al.*, 2011; Kendall *et al.*, 2012; Klumpp & Fuchs, 2007; Maadani *et al.*, 2007; Thiennimitr *et al.*, 2011; Toledo-Arana *et al.*, 2009). Two virulence regulators of *Salmonella*, CsrA and Fis, are known to control *eut* and *pdu* genes, thus further linking these metabolic pathways with infection (Kelly *et al.*, 2004; Lawhon *et al.*, 2003).

Genetics of ethanolamine utilization

Sequenced genomes of 84 bacteria belonging to different phyla (*Proteobacteria*, *Firmicutes*, *Actinobacteria*, *Acidobacteria*, *Bacteroidetes*, *Fusobacteria* and *Chlorophlexi*) were shown to harbour genes for ethanolamine utilization (*eut*) (Tsoy *et al.*, 2009). In addition to *Listeria*, *Salmonella*, *Shigella* and *Clostridium*, the commensal and opportunistic pathogenic *Enterococcus faecalis* as well as pathogenic *E. coli* are equipped with the *eut* genes. The *eut* gene cluster varies in size between the phylogenetic groups: the longer *eut* operon, which is present in *Firmicutes* and *Enterobacteriaceae* (Tsoy *et al.*, 2009), contains the genes *eutKLMNS*, whose products constitute an organelle-like structure or bacterial microcompartment reminiscent of carboxysomes (Kofoid *et al.*, 1999; Penrod & Roth, 2006). Those microcompartments are formed to optimize batched reactions by the spatial vicinity of substrates and enzymes, to protect the cell from damage from toxic intermediates such as acetaldehyde and to retain volatile intermediates (Garsin, 2010). A more effective utilization of ethanolamine may thus be especially important for pathogenic bacteria that live in competition with the commensal microbiota and are deprived of other energy sources. In contrast, *Actinobacteria* and most *Proteobacteria* have a short version of the *eut* operon containing only *eutB* and *eutC*, encoding the ethanolamine ammonia lyase subunits.

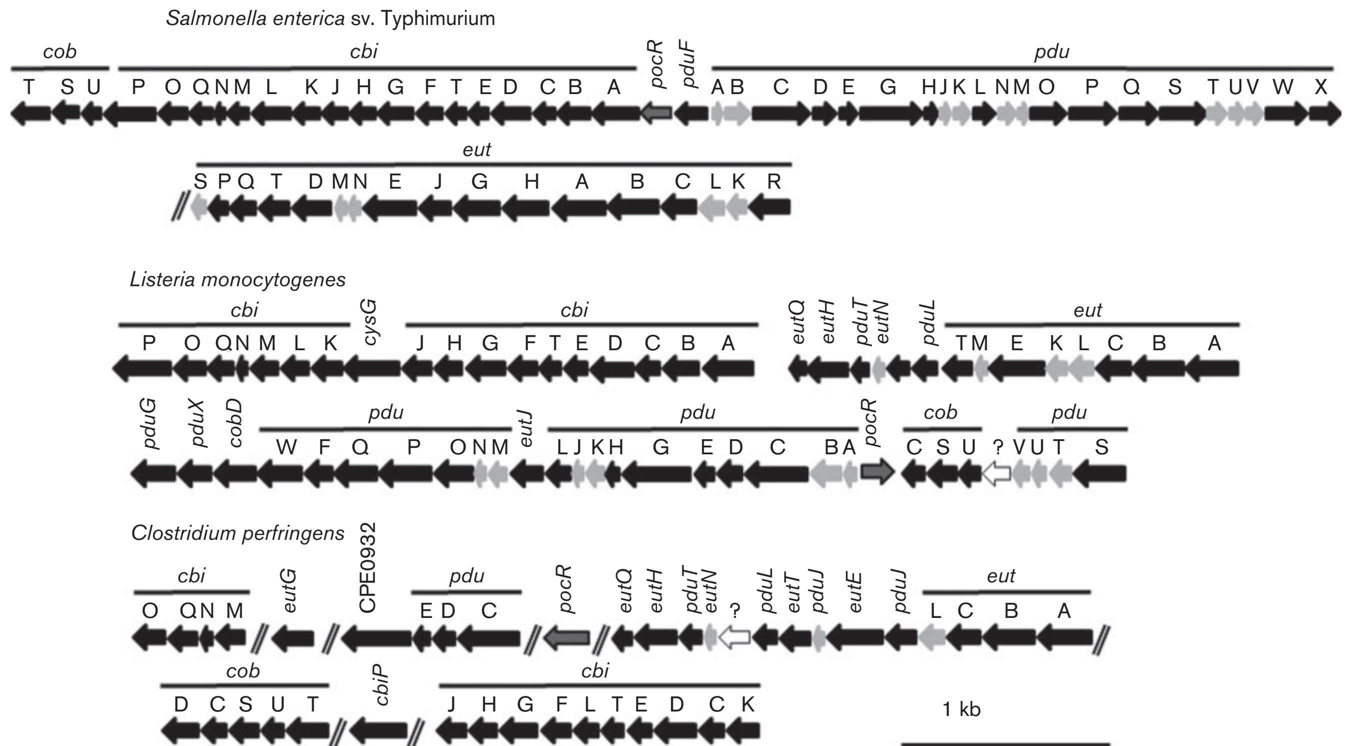

Fig. 2. Genetic organization of *eut*, *pdu* and *cob*/*cbi* genes in *Salmonella enterica* sv. Typhimurium LT2. The genomes of most *Salmonella enterica* serovars carry intact operons with most of the genes homologous to each other (genes depicted in black). The *cob* and *pdu* operons in the *Salmonella enterica* sv. Gallinarum strain 287/91 genome lack the genes *cbiO*/*K*/*D*/*C* and *pocR*, indicated in white. The organization of the *eut* operon within most *Salmonella* serovars is also shown. An exception is the *eut* operon of *Salmonella enterica* sv. Choleraesuis strain SC-B67 lacking *eutA*/*C*/*K*. Grey genes indicate gene replacement with respect to the LT2 genome.

Genes coding for proteins of the *eut* cluster were found in *Yersinia* species avirulent towards humans, but not in the pathogenic representatives of this genus, *Yersinia pseudotuberculosis* and *Yersinia pestis* (Chen *et al.*, 2010). In contrast to *Y. enterocolitica*, the systemic pathogens *Y. pseudotuberculosis*, *Salmonella enterica* sv. Typhi and *Salmonella enterica* sv. Parathyphi have not acquired or have lost the tetrathionate respiration pathway, presumably because they would not benefit significantly from tetrathionate reduction during extracellular growth. The putative loss of such a metabolic property is often interpreted as a consequence of the adaptation to a non-enteric life cycle, indicating that the energy burden of maintaining the respective chromosomal fragment exceeds the benefit for these pathogens (Rohmer *et al.*, 2011). In *Enterococcus faecalis*, *eut* gene expression is regulated via a TCS (EutVW) (Garsin, 2010). In this bacterium, the availability of cobalamin may be noticed by a riboswitch identified in the untranslated region of the *eut* operon (Fox *et al.*, 2009). In *Salmonella enterica*, the *eut* gene cluster (and also the *cob*/*cbi* cluster) are regulated positively by EutR, which is induced by the presence of ethanolamine and cobalamin (Sheppard & Roth, 1994).

Ethanolamine utilization *in vivo*

The host diet as well as the bacterial and epithelial cells in the intestine are abundant sources of ethanolamine, as phosphatidylethanolamine is a membrane lipid constituent in both mammalian and bacterial cell membranes. The highest concentrations of ethanolamine were found in the duodenum of mice, which were untreated or germ-free (Martin *et al.*, 2009). Ethanolamine can be readily broken down to ethanolamine and 1,2-diacyl-*sn*-glycerol by phosphatidylethanolamine hydrolases, and serves as a carbon, nitrogen and energy source (Garsin, 2010). Phospholipases specific for phosphatidylethanolamine are present in mammal tissue, but bacterial counterparts have not been identified so far, although broad-range phospholipases such as PlcB from *L. monocytogenes* might exhibit such an activity. The *eut* genes of *Salmonella enterica* sv. Typhimurium are upregulated in the intestine of chicken (Harvey *et al.*, 2011) and an *eut* mutant is attenuated in macrophages as well as in mice when administered *per os*, but not intraperitoneally (Stojiljkovic *et al.*, 1995), pointing to the role of ethanolamine utilization during proliferation in the gut. Similar findings were made for *L. monocytogenes*, which upregulates the *eut* genes in the intestine of

Table 2. *eut*, *pdu* and *cob*/*cbi* gene functions

Gene	Function
1,2-Propanediol utilization	
cobD	L-Threonine *O*-3-phosphate decarboxylase
eutJ	Unknown
pduA	Polyhedral body component
pduB	Polyhedral body component
pduC	Diol dehydratase large α subunit
pduD	Diol dehydratase medium β subunit
pduE	Diol dehydratase small γ subunit
pduF	Propanediol diffusion facilitator
pduG	Diol dehydratase reactivation factor large subunit
pduH	Diol dehydratase reactivation factor small subunit
pduJ	Polyhedral body component
pduK	Polyhedral body component
pduL	Phosphotransacylase
pduM	Unknown
pduN	Polyhedral body component
pduO	Adenosyltransferase
pduP	Propionaldehyde dehydrogenase
pduQ	Propanol dehydrogenase
pduS	NADH : ubiquinone oxidoreductase
pduT	Polyhedral body component
pduU	Polyhedral body component
pduV	Unknown
pduW	Propionate kinase
pduX	L-Threonine kinase
pocR	Transcriptional activator of *pdu* operon
Ethanolamine utilization	
eat	Ethanolamine permease
eutA	Reactivating factor
eutB	Ethanolamine ammonia lyase, large subunit
eutC	Ethanolamine ammonia lyase, small subunit
eutD	Phosphotransacylase
eutE	Aldehyde oxidoreductase
eutG	Alcohol dehydrogenase
eutH	Ethanolamine transport protein
eutJ	Putative chaperonin
eutK	Carboxysome structural protein
eutL	Carboxysome structural protein
eutM	Carboxysome structural protein
eutN	Carboxysome structural protein
eutP	Ethanolamine utilization protein
eutQ	Ethanolamine utilization protein
eutR	Transcriptional regulator
eutS	Carboxysome structural protein
eutT	Corrinoid cobalamin adenosyltransferase
eutV	Sensor histidine kinase
eutW	Response regulator
Cobalamin synthesis	
cbiA	Cobyrinic acid A,C-diamide synthase
cbiB	Cobalamin biosynthesis protein
cbiC	Precorrin-8X methylmutase
cbiD	Cobalt-precorrin-6A synthase
cbiE	Cobalt-precorrin-6Y C(5) methyltransferase
cbiT	Cobalt-precorrin-6Y C(15) methyltransferase
cbiF	Precorrin methylase
cbiG	Cobalamin biosynthesis protein

Table 2. cont.

Gene	Function
cbiH	Precorrin-3B C(17) methyltransferase
cbiJ	Cobalt-precorrin-6X reductase
cbiK	Cobalt chelatase
cbiL	Cobalt-precorrin-2 C(20) methyltransferase
cbiM	Cobalt transport protein
cbiN	Cobalt transport protein
cbiQ	Cobalt transport protein
cbiO	Cobalt transport protein
cbiP	Cobyric acid synthase
cobU	Adenosylcobinamide synthase
cobS	Cobalamin synthase
cobT	Nicotinate-nucleotide dimethylbenzimidazole phosphoribosyltransferase
cobA	Adenosyltransferase
cobC	α-Ribazole 5′-phosphate phosphatase
cobD	Threonine phosphate decarboxylase
btuB/tonB	Cobalamin transport over outer membrane
btuFCD	Cobalamin transport over inner membrane; *btuD* has ATPase function

mice and requires their activity during replication in human epithelial cells (Joseph *et al.*, 2006; Toledo-Arana *et al.*, 2009). EHEC uses ethanolamine as a molecule in cell-to-cell signalling that activates LEE genes (Kendall *et al.*, 2012) and also as a nitrogen source in the bovine intestinal content, thus providing a competitive growth advantage (Bertin *et al.*, 2011).

Intestinal inflammation upon *Salmonella enterica* infection allows the bacterium to grow with ethanolamine in the gut lumen due to the provoked formation of tetrathionate (Thiennimitr *et al.*, 2011; Winter *et al.*, 2010) – an intriguing example of pathogens exploiting the inflammatory response to compete with the intestinal microbiota, and thus obtaining an advantage for growth and colonization (Stecher *et al.*, 2008). Within the gut, tetrathionate required for anaerobic ethanolamine utilization is derived from endogenous sulphur compounds like thiosulphate, which is oxidized upon the activity of inflammation-triggered formation of nitric oxide radicals or reactive oxygen species. Thiosulphate is derived from hydrogen sulphide detoxification by the gut microbiota. Interestingly, the gene cluster *ttrRSBCA* for tetrathionate reduction contributes to the mosaic structure of SPI2 which otherwise encodes effector proteins and a type III secretion system (Hensel *et al.*, 1999a, b). Taken together, ethanolamine utilization well exemplifies the strategy of pathogens to use substrates not accessible for most members of the resident gut microbiota.

Utilization of 1,2-propanediol: distribution, regulation and *in vivo* relevance

1,2-Propanediol is the product of bacterial growth on fucose and/or rhamnose derived from mucosal glycoconjugates. In *Salmonella enterica*, eight genes of the *pdu* operon (Table 2) encode shell proteins of another microcompartment which might protect the cell from the toxic intermediate propionaldehyde, which is formed by cobalamin-dependent 1,2-propanediol dehydratase (*pduCDE*) and further processed to propanol or propionyl-coenzyme A (Havemann *et al.*, 2002). The microcompartment is also considered to be a barrier to cobalamin, as mutants unable to form microcompartments grew faster with limiting cobalamin compared with the WT (Cheng *et al.*, 2011). Glutathione is necessary for maximal transcription of *cob/pdu* when *Salmonella enterica* sv. Typhimurium grows aerobically, possibly by protecting proteins in the microcompartment from damage by aldehydes (Rondon *et al.*, 1995). In this enteropathogen, the expression of *pdu* (and the genes for cobalamin synthesis) seems to be regulated in a coordinated manner by the DNA-binding protein PocR, whose activity depends on the presence of 1,2-propanediol (Rondon & Escalante-Semerena, 1992, 1996). In addition to *Salmonella enterica*, the gene clusters for 1,2-propanediol utilization (*pdu*) and the synthesis of cobalamin (*cob/cbi*) (Fig. 2) are also found in the genomes of the foodborne pathogens *L. monocytogenes*, *Clostridium perfringens*, *Shigella sonnei*, EPEC, enterotoxigenic *E. coli* (ETEC) and *Y. enterocolitica* (Buchrieser *et al.*, 2003; Srikumar & Fuchs, 2011; Thomson *et al.*, 2006) (Table 1), but their ability to utilize this fermentation product lacks experimental demonstration. A homologue of *pocR* is also present in the genomes of *L. monocytogenes* and *Yersinia* spp., but not in *Clostridium* spp., and its upregulation was observed during intracellular replication of *L. monocytogenes*. The expression of *pdu* and *cob/cbi* in *Clostridium* is assumed to be regulated by a TCS, thus reminding us of *eut* gene control in *Firmicutes*. *Fusobacterium nucleatum* (Karpathy *et al.*, 2007) and commensal micro-organisms such as *Roseburia inulinivorans* and *Propionibacterium freudenreichii* also harbour the *pdu* and *cob/cbi* gene clusters. Fucose stimulates the expression of the genes involved in fucose and propanediol utilization in *R. inulinivorans*, resulting in the formation of propionate and propanol (Scott *et al.*, 2006). In contrast to

Salmonella, dehydration of the intermediate 1,2-propanediol involves a cobalamin-independent enzyme of *R. inulinivorans*.

The *pdu* operon is involved in pathogenicity of *Salmonella enterica* sv. Typhimurium, as the removal of the region resulted in a virulence defect (Conner *et al.*, 1998; Heithoff *et al.*, 1999). The *pdu* genes are also upregulated during growth in macrophages, epithelial tissue cells and in the gut of chicken (Harvey *et al.*, 2011; Hautefort *et al.*, 2008). Indeed, a *Salmonella enterica* sv. Typhimurium propanediol utilization mutant shows attenuated growth in mice macrophages (Klumpp & Fuchs, 2007). Therefore, when pathogenic micro-organisms such as *Listeria*, *Clostridium*, *Salmonella*, *Shigella* and *Yersinia* occupy anaerobic habitats such as the mammalian gut, the anaerobic degradation of 1,2-propanediol may provide a benefit over other bacteria not able to use such fermentation end products.

Inositol

Another example of the metabolic adaptation of enteric pathogens is the utilization of *myo*-inositol – a polyol that is abundant in soil. Its phosphorylated form, inositol hexakisphosphate or phytate, serves as a phosphorus store in plants. It can be utilized by livestock in the presence of phytases which are present in many representatives of the resident microbiota, such as *Bifidobacterium pseudocatenulatum* (Haros *et al.*, 2009). Phytic acid is naturally present in whole cereal grains, seeds, nuts and legumes, with up to 3–6 % phytic acid (Reddy, 2001). The daily intake of phytate was estimated to be 2000–2600 mg for vegetarian diets and 150–1400 mg for mixed diets (Reddy, 2001). Similar to ethanolamine, the duodenum has a higher content of *myo*-inositol than the other intestinal tissues (Martin *et al.*, 2009). Strikingly, the ability to grow with *myo*-inositol is found in the Gram-positive enteropathogens *Enterococcus faecalis*, *Bacillus cereus*, *L. monocytogenes* and *Clostridium perfringens*, all of which are found commonly in soil. Utilization of *myo*-inositol as a sole carbon and energy source by *Salmonella enterica* sv. Typhimurium *in vitro* has been characterized recently (Kröger & Fuchs, 2009). All *iol* genes involved in this degradation pathway are localized on a 22.6 kb genomic island (GEI4417/4436) that has so far been found in the genomes of several *Salmonella enterica* serovars and of *E. coli* ED1a (NC 011754). The *iol* genes, however, are absent in *Salmonella enterica* serovars such as Typhi, Parathypi A and Choleraesuis, indicating that the utilization of *myo*-inositol is not a common ability of *Salmonella* strains and does not play a role during systemic infection. An intriguing property of *Salmonella enterica* sv. Typhimurium growth on *myo*-inositol is the long lag phase of ~2 days, which is, however, reduced strongly upon the deletion of the repressor IolR or the addition of bicarbonate to simulate conditions in the intestine (Kröger *et al.*, 2011). Recent *in vivo* screening approaches indicate that *iol* genes play a role in *Salmonella enterica* sv. Typhimurium virulence in mice, pigs, chicken and calves (Carnell *et al.*, 2007; Chaudhuri *et al.*, 2009, 2013; Lawley *et al.*, 2006). The *srfJ* gene, also located on GEI4417/4436, encodes a putative glycosyl ceramidase or glycohydrolase. It is induced within host cells by the TCS SsrAB, which controls the expression of SPI2 genes, and negatively regulated by the repressor IolR (Cordero-Alba *et al.*, 2012; Worley *et al.*, 2000). Deletion of *srfJ* (STM4426) results in a slight attenuation with respect to the systemic virulence in mice (Ruiz-Albert *et al.*, 2002). Moreover, a yet unknown regulatory gene was shown to be upregulated in the gut using an enteritis mouse model (Rollenhagen & Bumann, 2006). Several gut pathogens carry *iol* gene homologues (Table 1), although a contribution of *myo*-inositol degradation to the virulence properties of *Clostridium perfringens* or *Y. enterocolitica* has not been demonstrated. Interestingly, the *iol* gene cluster is upregulated in *Enterococcus faecalis* during replication in monoassociated mice (Lindenstrauß, 2012).

Parallels to nutrient degradation and metabolite availability in food

An infection by foodborne pathogens starts with contamination of food in which the bacteria possibly proliferate before they are orally taken up by a mammalian host. In light of the findings reviewed above, it might be speculated that there are analogies between the food and the gut environments with respect to nutrient availability and the interdependencies or competition between pathogenic and non-pathogenic microbes. Indeed, most foods are considered nutrient-rich and provide partial anaerobic conditions. Muscle tissues of meat animals comprise 18 % protein and 3 % fat, and are a highly favourable growth medium for bacteria with readily available glycogen, peptides and amino acids, as well as metal ions and soluble phosphorus (Jay, 2000). Fruit and vegetable products are characterized by a high mean content of 8.6 % carbohydrates (polysaccharides, oligosaccharides, monosaccharides including L-rhamnose, L-fucose and gluconate), but contain only 1.9 % proteins and 0.3 % fat. On the one hand, there is a strong competition with spoilage bacteria, moulds and yeasts for nutrients, at least in raw meat or milk and on plants, eventually resulting in a nutrient-exhausted environment similar to that encountered in the gut. For example, glucose is known to be depleted in meat when bacterial populations exceed 10^6 c.f.u. cm^{-2} (Jackson *et al.*, 1997). On the other hand, foodborne pathogens also profit from the disintegrative enzymic activities of (non-pathogenic) spoilage micro-organisms. In milk, bacteria unable to utilize lactose depend on the lipolytic and proteolytic activities provided by other microbes that make milk fat available that is enclosed by the globule membrane. Plant-contaminating pathogens might take advantage of microbes producing enzymes such as pectinases and cellulases that degrade polysaccharides (Jay, 2000). Spoilage of freshly slaughtered meat occurs mainly by bacteria with lipolytic and proteolytic activities (*Clostridia*, *Pseudomonas* and members of the *Enterobacteriaceae*) and yeast. Proteolysis occurs at populations $>10^8$ c.f.u. cm^{-2}, when spoilage is well advanced and bacteria are approaching their maximal cell density (Dainty *et al.*, 1975). Lipases catalyse

the hydrolysis of phospholipids as an abundant component of the tissue membranes to glycerol and free fatty acids. In the case of phosphatidylethanolamine, ubiquitously present in food, this activity results in the release of ethanolamine. We recently chose utilization of this metabolite for the hypothesis that this metabolic adaptation required for full virulence properties of *Salmonella enterica* sv. Typhimurium also contributes to its proliferation in food. It was observed that growth of a mutant that lacks EutR, the inducer of the *eut* and *cob/cbi* genes, was reduced significantly in milk and in egg yolk (Srikumar & Fuchs, 2011). The *eutS* gene of *Salmonella enterica* sv. Typhimurium was shown to be upregulated strongly in pasteurized milk as well as in egg yolk and an *eutR* deletion mutant was significantly growth attenuated with both these substrates (Srikumar & Fuchs, 2011).

In the case of processed and fermented products, foodborne pathogens might contaminate a largely non-colonized and thus non-competitive milieu, but lack the help of spoilage bacteria to degrade otherwise non-accessible food macromolecules. Processed food is characterized by a mixture of anaerobic as well as aerobic microenvironments. Moreover, food processing and preservation methods, such as cooling, fermentation, heating, smoking or drying, often result in the lowering of pH or water activity, formation of a solid matrix, or carbohydrate depletion and thus in less favourable growth conditions for enteropathogens. In comparison with fluid milk, dairy products provide substantially different growth conditions that are less supportive for micro-organisms. Thus, foodborne pathogens growing on or in processed food have developed strategies to overcome those limitations, especially by broadening their temperature range for growth, and, as addressed here, by developing common and specific metabolic capacities.

Conclusions

Metabolic versatility under nutrient constraints is a prerequisite for pathogens that survive and proliferate successfully in different niches and compartments during their life cycle. The metabolites mentioned in the section ‘A

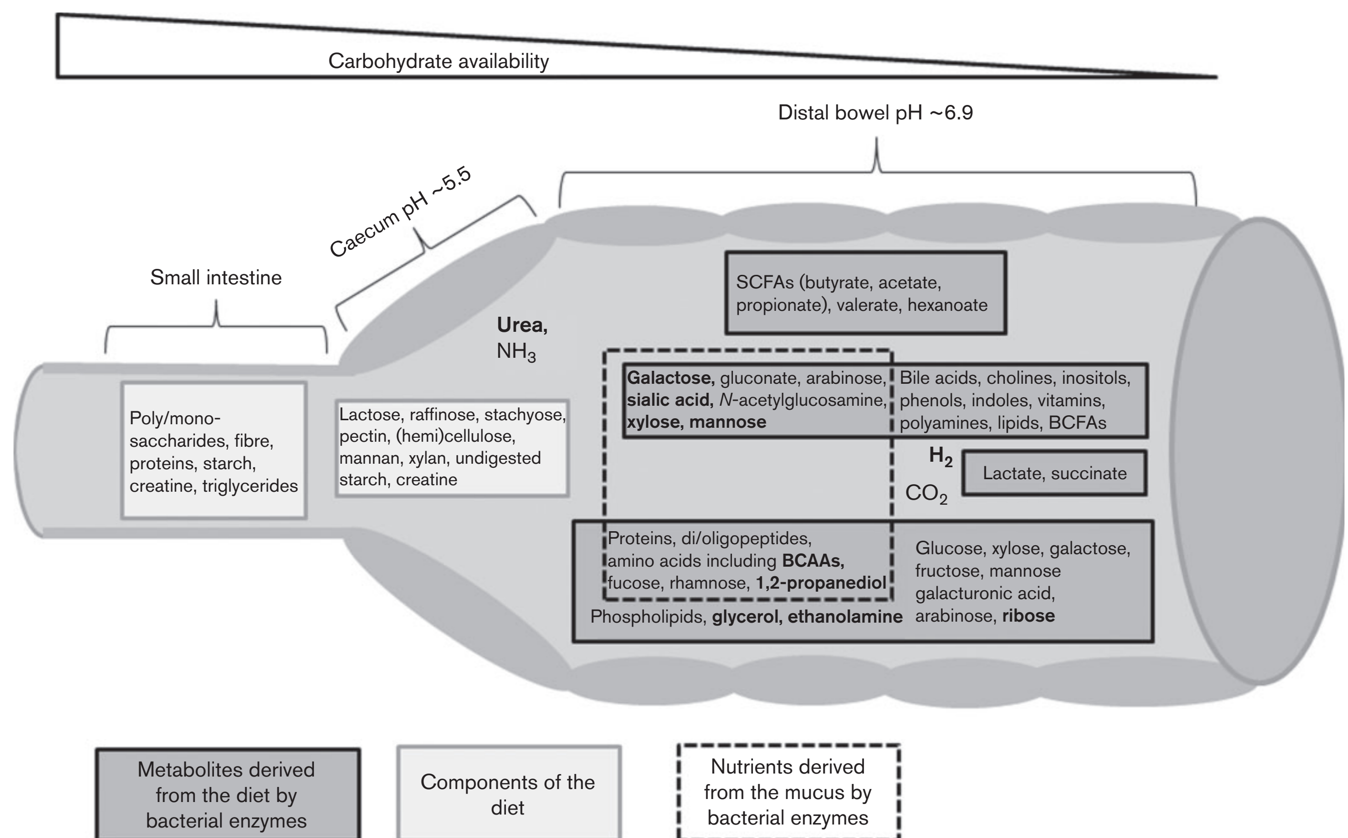

Fig. 3. Nutrient availability in the mammalian gut. The figure summarizes the metabolites that are potentially available for commensal and pathogenic bacteria during gut proliferation. Data were taken from the literature cited in the text. Metabolites specifically used by enteropathogens are indicated in bold letters. The stomach and colon of mice and rats have a two-layered glycocalyx, with an inner mucus layer of 50–100 μm closely attached to the epithelial cells and an outer loose mucus layer of up to 800 μm. In the small intestine, the monolayer reaches a thickness of 150–300 μm (Johansson *et al.*, 2010; McGuckin *et al.*, 2011). BCFA, branched-chain fatty acid; BCAA, branched-chain amino acid.

frugal or an opulent meal?' are readily available in the gut upon the activity of the commensal microbiota (Fig. 3). Their usage by enteropathogens only requires uptake systems and a standard repertoire of metabolic enzymes, and might help to overcome auxotrophies or bottlenecks in anabolic pathways. In contrast, the complex and more unusual degradation properties of enteric pathogens described in the further sections require larger gene sets that are encoded by distinct chromosomal regions. These constitute specific metabolic adaptations not common to members of the gut microbiota, and provide energy, carbon or nitrogen to pathogens under competitive circumstances and thus *in vivo* growth advantages over bacteria lacking this function. Due to their distinct G/C content, the genomic fragments responsible for the utilization of *myo*-inositol, ethanolamine, propanediol and sialic acids might be termed metabolic islands (Almagro-Moreno & Boyd, 2009a; Dobrindt *et al.*, 2004). Similar to pathogenicity islands contributing to virulence, it is assumed that these genetic determinants encoding metabolic functions have been acquired by horizontal gene transfer to expand the metabolite target spectrum of the enteropathogens (Rohmer *et al.*, 2011).

Depending on the diet, the microbiota and the host response, the carbon and energy sources mentioned above are available in varying amounts in the gut. Further research is required to delineate if, and to what extent, their utilization indeed contributes to proliferation of pathogens during infection. Due to their high metabolic flexibility, the enteric pathogens can be assumed to be well adapted under these conditions, and to exhibit a robust metabolism with respect to disturbances of the gut metabolome and nutrient limitations in intestinal microcompartments (Becker *et al.*, 2006). Such robustness is probably a synergistic result of a set of metabolic capacities and the knockout of only one pathway will at least partially be compensated by others. This explains why the *in vivo* relevance of several degradation pathways is still cryptic. In addition to common strategies, each of the Gram-positive and Gram-negative bacteria addressed here is characterized by an individual pattern of degradation pathways and uptake systems to fulfil its nutrient requirements (Table 1). For example, *L. monocytogenes* is especially adapted to proliferate in decaying plant or animal matter, and it might be assumed that such a saprophytic life style serves as a training ground for the competition for nutrients in the gut.

As delineated above, foodborne enteropathogens encounter comparable challenges in food and in the gut with respect to nutrient composition, content of oxygen, competition with dominating microbiota and dependency on other microbes to degrade macromolecules. We therefore conclude that the ability of enteric pathogens to utilize substrates such as inositol, ethanolamine, fucose or sialic acid provides a permanent selection advantage during proliferation in food and, following ingestion, during subsequent stages of infection, i.e. from food to cell.

Acknowledgements

We thank the German Research Foundation (Deutsche Forschungsgemeinschaft) for financial support of this review within the Research Training Program (Graduiertenkolleg) 1482.

References

Abu Kwaik, Y. & Bumann, D. (2013). Microbial quest for food *in vivo*: 'nutritional virulence' as an emerging paradigm. *Cell Microbiol* **15**, 882–890.

Almagro-Moreno, S. & Boyd, E. F. (2009a). Insights into the evolution of sialic acid catabolism among bacteria. *BMC Evol Biol* **9**, 118.

Almagro-Moreno, S. & Boyd, E. F. (2009b). Sialic acid catabolism confers a competitive advantage to pathogenic *Vibrio cholerae* in the mouse intestine. *Infect Immun* **77**, 3807–3816.

Alteri, C. J. & Mobley, H. L. (2012). *Escherichia coli* physiology and metabolism dictates adaptation to diverse host microenvironments. *Curr Opin Microbiol* **15**, 3–9.

Alteri, C. J., Smith, S. N. & Mobley, H. L. (2009). Fitness of *Escherichia coli* during urinary tract infection requires gluconeogenesis and the TCA cycle. *PLoS Pathog* **5**, e1000448.

Ashida, H., Miyake, A., Kiyohara, M., Wada, J., Yoshida, E., Kumagai, H., Katayama, T. & Yamamoto, K. (2009). Two distinct α-L-fucosidases from *Bifidobacterium bifidum* are essential for the utilization of fucosylated milk oligosaccharides and glycoconjugates. *Glycobiology* **19**, 1010–1017.

Backhed, F., Ley, R. E., Sonnenburg, J. L., Peterson, D. A. & Gordon, J. I. (2005). Host-bacterial mutualism in the human intestine. *Science* **307**, 1915–1920.

Badía, J., Ros, J. & Aguilar, J. (1985). Fermentation mechanism of fucose and rhamnose in *Salmonella typhimurium* and *Klebsiella pneumoniae*. *J Bacteriol* **161**, 435–437.

Barrett, E. L. & Clark, M. A. (1987). Tetrathionate reduction and production of hydrogen sulfide from thiosulfate. *Microbiol Rev* **51**, 192–205.

Barthel, M., Hapfelmeier, S., Quintanilla-Martínez, L., Kremer, M., Rohde, M., Hogardt, M., Pfeffer, K., Rüssmann, H. & Hardt, W. D. (2003). Pretreatment of mice with streptomycin provides a *Salmonella enterica* serovar Typhimurium colitis model that allows analysis of both pathogen and host. *Infect Immun* **71**, 2839–2858.

Becker, D. J. & Lowe, J. B. (2003). Fucose: biosynthesis and biological function in mammals. *Glycobiology* **13**, 41R–53R.

Becker, D., Selbach, M., Rollenhagen, C., Ballmaier, M., Meyer, T. F., Mann, M. & Bumann, D. (2006). Robust *Salmonella* metabolism limits possibilities for new antimicrobials. *Nature* **440**, 303–307.

Behari, J. & Youngman, P. (1998). Regulation of *hly* expression in *Listeria monocytogenes* by carbon sources and pH occurs through separate mechanisms mediated by PrfA. *Infect Immun* **66**, 3635–3642.

Bertin, Y., Girardeau, J. P., Chaucheyras-Durand, F., Lyan, B., Pujos-Guillot, E., Harel, J. & Martin, C. (2011). Enterohaemorrhagic *Escherichia coli* gains a competitive advantage by using ethanolamine as a nitrogen source in the bovine intestinal content. *Environ Microbiol* **13**, 365–377.

Bode, L. (2006). Recent advances on structure, metabolism, and function of human milk oligosaccharides. *J Nutr* **136**, 2127–2130.

Borezee, E., Pellegrini, E. & Berche, P. (2000). OppA of *Listeria monocytogenes*, an oligopeptide-binding protein required for bacterial growth at low temperature and involved in intracellular survival. *Infect Immun* **68**, 7069–7077.

Bry, L., Falk, P. G., Midtvedt, T. & Gordon, J. I. (1996). A model of host-microbial interactions in an open mammalian ecosystem. *Science* **273**, 1380–1383.

Buchrieser, C., Rusniok, C., Kunst, F., Cossart, P., Glaser, P. & Listeria Consortium (2003). Comparison of the genome sequences of *Listeria monocytogenes* and *Listeria innocua*: clues for evolution and pathogenicity. *FEMS Immunol Med Microbiol* **35**, 207–213.

Carnell, S. C., Bowen, A., Morgan, E., Maskell, D. J., Wallis, T. S. & Stevens, M. P. (2007). Role in virulence and protective efficacy in pigs of *Salmonella enterica* serovar Typhimurium secreted components identified by signature-tagged mutagenesis. *Microbiology* **153**, 1940–1952.

Chang, D. E., Smalley, D. J., Tucker, D. L., Leatham, M. P., Norris, W. E., Stevenson, S. J., Anderson, A. B., Grissom, J. E., Laux, D. C. & other authors (2004). Carbon nutrition of *Escherichia coli* in the mouse intestine. *Proc Natl Acad Sci U S A* **101**, 7427–7432.

Chatterjee, S. S., Hossain, H., Otten, S., Kuenne, C., Kuchmina, K., Machata, S., Domann, E., Chakraborty, T. & Hain, T. (2006). Intracellular gene expression profile of *Listeria monocytogenes*. *Infect Immun* **74**, 1323–1338.

Chaudhuri, R. R., Peters, S. E., Pleasance, S. J., Northen, H., Willers, C., Paterson, G. K., Cone, D. B., Allen, A. G., Owen, P. J. & other authors (2009). Comprehensive identification of *Salmonella enterica* serovar typhimurium genes required for infection of BALB/c mice. *PLoS Pathog* **5**, e1000529.

Chaudhuri, R. R., Morgan, E., Peters, S. E., Pleasance, S. J., Hudson, D. L., Davies, H. M., Wang, J., van Diemen, P. M., Buckley, A. M. & other authors (2013). Comprehensive assignment of roles for *Salmonella typhimurium* genes in intestinal colonization of food-producing animals. *PLoS Genet* **9**, e1003456.

Chen, Y. M., Zhu, Y. & Lin, E. C. (1987). NAD-linked aldehyde dehydrogenase for aerobic utilization of L-fucose and L-rhamnose by *Escherichia coli*. *J Bacteriol* **169**, 3289–3294.

Chen, P. E., Cook, C., Stewart, A. C., Nagarajan, N., Sommer, D. D., Pop, M., Thomason, B., Thomason, M. P., Lentz, S. & other authors (2010). Genomic characterization of the *Yersinia* genus. *Genome Biol* **11**, R1.

Cheng, S., Sinha, S., Fan, C., Liu, Y. & Bobik, T. A. (2011). Genetic analysis of the protein shell of the microcompartments involved in coenzyme B12-dependent 1,2-propanediol degradation by Salmonella. *J Bacteriol* **193**, 1385–1392.

Cocks, G. T., Aguilar, T. & Lin, E. C. (1974). Evolution of L-1,2-propanediol catabolism in *Escherichia coli* by recruitment of enzymes for L-fucose and L-lactate metabolism. *J Bacteriol* **118**, 83–88.

Conner, C. P., Heithoff, D. M., Julio, S. M., Sinsheimer, R. L. & Mahan, M. J. (1998). Differential patterns of acquired virulence genes distinguish *Salmonella* strains. *Proc Natl Acad Sci U S A* **95**, 4641–4645.

Contag, C. H., Contag, P. R., Mullins, J. I., Spilman, S. D., Stevenson, D. K. & Benaron, D. A. (1995). Photonic detection of bacterial pathogens in living hosts. *Mol Microbiol* **18**, 593–603.

Corazziari, E. S. (2009). Intestinal mucus barrier in normal and inflamed colon. *J Pediatr Gastroenterol Nutr* **48** (Suppl. 2), S54–S55.

Cordero-Alba, M., Bernal-Bayard, J. & Ramos-Morales, F. (2012). SrfJ, a *Salmonella* type III secretion system effector regulated by PhoP, RcsB, and IolR. *J Bacteriol* **194**, 4226–4236.

Cummings, J. H. & Macfarlane, G. T. (1991). The control and consequences of bacterial fermentation in the human colon. *J Appl Bacteriol* **70**, 443–459.

Cummings, J. H., Pomare, E. W., Branch, W. J., Naylor, C. P. & Macfarlane, G. T. (1987). Short chain fatty acids in human large intestine, portal, hepatic and venous blood. *Gut* **28**, 1221–1227.

Dainty, R. H., Shaw, B. G., De Boer, K. A. & Scheps, E. S. (1975). Protein changes caused by bacterial growth on beef. *J Appl Bacteriol* **39**, 73–81.

Dalebroux, Z. D., Svensson, S. L., Gaynor, E. C. & Swanson, M. S. (2010). ppGpp conjures bacterial virulence. *Microbiol Mol Biol Rev* **74**, 171–199.

De Filippo, C., Cavalieri, D., Di Paola, M., Ramazzotti, M., Poullet, J. B., Massart, S., Collini, S., Pieraccini, G. & Lionetti, P. (2010). Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc Natl Acad Sci U S A* **107**, 14691–14696.

Deriu, E., Liu, J. Z., Pezeshki, M., Edwards, R. A., Ochoa, R. J., Contreras, H., Libby, S. J., Fang, F. C. & Raffatellu, M. (2013). Probiotic bacteria reduce *Salmonella typhimurium* intestinal colonization by competing for iron. *Cell Host Microbe* **14**, 26–37.

Derrien, M., Vaughan, E. E., Plugge, C. M. & de Vos, W. M. (2004). *Akkermansia muciniphila* gen. nov., sp. nov., a human intestinal mucin-degrading bacterium. *Int J Syst Evol Microbiol* **54**, 1469–1476.

Dobrindt, U., Hochhut, B., Hentschel, U. & Hacker, J. (2004). Genomic islands in pathogenic and environmental microorganisms. *Nat Rev Microbiol* **2**, 414–424.

Dominguez-Bello, M. G., Costello, E. K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N. & Knight, R. (2010). Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci U S A* **107**, 11971–11975.

Dupuy, B., Daube, G., Popoff, M. R. & Cole, S. T. (1997). *Clostridium perfringens* urease genes are plasmid borne. *Infect Immun* **65**, 2313–2320.

Eisenreich, W., Dandekar, T., Heesemann, J. & Goebel, W. (2010). Carbon metabolism of intracellular bacterial pathogens and possible links to virulence. *Nat Rev Microbiol* **8**, 401–412.

Eylert, E., Schär, J., Mertins, S., Stoll, R., Bacher, A., Goebel, W. & Eisenreich, W. (2008). Carbon metabolism of *Listeria monocytogenes* growing inside macrophages. *Mol Microbiol* **69**, 1008–1017.

Fabich, A. J., Jones, S. A., Chowdhury, F. Z., Cernosek, A., Anderson, A., Smalley, D., McHargue, J. W., Hightower, G. A., Smith, J. T. & other authors (2008). Comparison of carbon nutrition for pathogenic and commensal *Escherichia coli* strains in the mouse intestine. *Infect Immun* **76**, 1143–1152.

Forsythe, S. J. & Parker, D. S. (1985). Nitrogen metabolism by the microbial flora of the rabbit caecum. *J Appl Bacteriol* **58**, 363–369.

Fox, K. A., Ramesh, A., Stearns, J. E., Bourgogne, A., Reyes-Jara, A., Winkler, W. C. & Garsin, D. A. (2009). Multiple posttranscriptional regulatory mechanisms partner to control ethanolamine utilization in *Enterococcus faecalis*. *Proc Natl Acad Sci U S A* **106**, 4435–4440.

Freter, R., Brickner, H., Botney, M., Cleven, D. & Aranki, A. (1983). Mechanisms that control bacterial populations in continuous-flow culture models of mouse large intestinal flora. *Infect Immun* **39**, 676–685.

Fuchs, T. M., Eisenreich, W., Heesemann, J. & Goebel, W. (2012a). Metabolic adaptation of human pathogenic and related nonpathogenic bacteria to extra- and intracellular habitats. *FEMS Microbiol Rev* **36**, 435–462.

Fuchs, T. M., Eisenreich, W., Kern, T. & Dandekar, T. (2012b). Toward a systemic understanding of *Listeria monocytogenes* metabolism during infection. *Front Microbiol* **3**, 23.

Gantois, I., Ducatelle, R., Pasmans, F., Haesebrouck, F., Hautefort, I., Thompson, A., Hinton, J. C. & Van Immerseel, F. (2006). Butyrate specifically down-regulates *Salmonella* pathogenicity island 1 gene expression. *Appl Environ Microbiol* **72**, 946–949.

Garsin, D. A. (2010). Ethanolamine utilization in bacterial pathogens: roles and regulation. *Nat Rev Microbiol* **8**, 290–295.

Giel, J. L., Sorg, J. A., Sonenshein, A. L. & Zhu, J. (2010). Metabolism of bile salts in mice influences spore germination in *Clostridium difficile*. *PLoS ONE* **5**, e8740.

Gill, S. R., Pop, M., Deboy, R. T., Eckburg, P. B., Turnbaugh, P. J., Samuel, B. S., Gordon, J. I., Relman, D. A., Fraser-Liggett, C. M. & Nelson, K. E. (2006). Metagenomic analysis of the human distal gut microbiome. *Science* **312**, 1355–1359.

Golding, G. R., Olson, A. B., Doublet, B., Cloeckaert, A., Christianson, S., Graham, M. R. & Mulvey, M. R. (2007). The effect of the *Salmonella* genomic island 1 on in vitro global gene expression in *Salmonella enterica* serovar Typhimurium LT2. *Microbes Infect* **9**, 21–27.

Gu, Y., Ding, Y., Ren, C., Sun, Z., Rodionov, D. A., Zhang, W., Yang, S., Yang, C. & Jiang, W. (2010). Reconstruction of xylose utilization pathway and regulons in Firmicutes. *BMC Genomics* **11**, 255.

Hansson, G. C. (2012). Role of mucus layers in gut infection and inflammation. *Curr Opin Microbiol* **15**, 57–62.

Haros, M., Carlsson, N. G., Almgren, A., Larsson-Alminger, M., Sandberg, A. S. & Andlid, T. (2009). Phytate degradation by human gut isolated *Bifidobacterium pseudocatenulatum* ATCC27919 and its probiotic potential. *Int J Food Microbiol* **135**, 7–14.

Harvey, P. C., Watson, M., Hulme, S., Jones, M. A., Lovell, M., Berchieri, A., Jr, Young, J., Bumstead, N. & Barrow, P. (2011). *Salmonella enterica* serovar Typhimurium colonizing the lumen of the chicken intestine grows slowly and upregulates a unique set of virulence and metabolism genes. *Infect Immun* **79**, 4105–4121.

Hautefort, I., Thompson, A., Eriksson-Ygberg, S., Parker, M. L., Lucchini, S., Danino, V., Bongaerts, R. J. M., Ahmad, N., Rhen, M. & Hinton, J. C. D. (2008). During infection of epithelial cells *Salmonella enterica* serovar Typhimurium undergoes a time-dependent transcriptional adaptation that results in simultaneous expression of three type 3 secretion systems. *Cell Microbiol* **10**, 958–984.

Havemann, G. D., Sampson, E. M. & Bobik, T. A. (2002). PduA is a shell protein of polyhedral organelles involved in coenzyme B_{12}-dependent degradation of 1,2-propanediol in *Salmonella enterica* serovar Typhimurium LT2. *J Bacteriol* **184**, 1253–1261.

Heithoff, D. M., Conner, C. P., Hentschel, U., Govantes, F., Hanna, P. C. & Mahan, M. J. (1999). Coordinate intracellular expression of *Salmonella* genes induced during infection. *J Bacteriol* **181**, 799–807.

Hensel, M., Hinsley, A. P., Nikolaus, T., Sawers, G. & Berks, B. C. (1999a). The genetic basis of tetrathionate respiration in *Salmonella typhimurium*. *Mol Microbiol* **32**, 275–287.

Hensel, M., Nikolaus, T. & Egelseer, C. (1999b). Molecular and functional analysis indicates a mosaic structure of *Salmonella* pathogenicity island 2. *Mol Microbiol* **31**, 489–498.

Hooper, L. V. & Gordon, J. I. (2001). Glycans as legislators of host–microbial interactions: spanning the spectrum from symbiosis to pathogenicity. *Glycobiology* **11**, 1R–10R.

Hooper, L. V., Xu, J., Falk, P. G., Midtvedt, T. & Gordon, J. I. (1999). A molecular sensor that allows a gut commensal to control its nutrient foundation in a competitive ecosystem. *Proc Natl Acad Sci U S A* **96**, 9833–9838.

Hooper, L. V., Midtvedt, T. & Gordon, J. I. (2002). How host–microbial interactions shape the nutrient environment of the mammalian intestine. *Annu Rev Nutr* **22**, 283–307.

Hugdahl, M. B., Beery, J. T. & Doyle, M. P. (1988). Chemotactic behavior of *Campylobacter jejuni*. *Infect Immun* **56**, 1560–1566.

Jackson, T. C.,, Acuff, G. R. & Dickson, J. D. (1997). Meat, poultry, and seafood. In *Food Microbiology: Fundamentals and Frontiers*, pp. 83–100. Edited by M. P. Doyle, L. R. Beuchat & T. J. Montville. Washington, DC: American Society for Microbiology.

Jay, J. (2000). *Modern Food Microbiology*, 6th edn. Gaithersburg, MD: Aspen.

Johansson, M. E., Phillipson, M., Petersson, J., Velcich, A., Holm, L. & Hansson, G. C. (2008). The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria. *Proc Natl Acad Sci U S A* **105**, 15064–15069.

Johansson, M. E., Larsson, J. M. & Hansson, G. C. (2011). The two mucus layers of colon are organized by the MUC2 mucin, whereas the outer layer is a legislator of host–microbial interactions. *Proc Natl Acad Sci U S A* **108** (Suppl. 1), 4659–4665.

Jones, S. A., Chowdhury, F. Z., Fabich, A. J., Anderson, A., Schreiner, D. M., House, A. L., Autieri, S. M., Leatham, M. P., Lins, J. J. & other authors (2007). Respiration of *Escherichia coli* in the mouse intestine. *Infect Immun* **75**, 4891–4899.

Joseph, B., Przybilla, K., Stühler, C., Schauer, K., Slaghuis, J., Fuchs, T. M. & Goebel, W. (2006). Identification of *Listeria monocytogenes* genes contributing to intracellular replication by expression profiling and mutant screening. *J Bacteriol* **188**, 556–568.

Juge, N. (2012). Microbial adhesins to gastrointestinal mucus. *Trends Microbiol* **20**, 30–39.

Kaiser, P., Diard, M., Stecher, B. & Hardt, W. D. (2012). The streptomycin mouse model for *Salmonella* diarrhea: functional analysis of the microbiota, the pathogen's virulence factors, and the host's mucosal immune response. *Immunol Rev* **245**, 56–83.

Karpathy, S. E., Qin, X., Gioia, J., Jiang, H., Liu, Y., Petrosino, J. F., Yerrapragada, S., Fox, G. E., Haake, S. K. & other authors (2007). Genome sequence of *Fusobacterium nucleatum* subspecies polymorphum – a genetically tractable fusobacterium. *PLoS ONE* **2**, e659.

Katayama, T., Sakuma, A., Kimura, T., Makimura, Y., Hiratake, J., Sakata, K., Yamanoi, T., Kumagai, H. & Yamamoto, K. (2004). Molecular cloning and characterization of *Bifidobacterium bifidum* 1,2-α-L-fucosidase (AfcA), a novel inverting glycosidase (glycoside hydrolase family 95). *J Bacteriol* **186**, 4885–4893.

Keeney, K. M. & Finlay, B. B. (2011). Enteric pathogen exploitation of the microbiota-generated nutrient environment of the gut. *Curr Opin Microbiol* **14**, 92–98.

Kelly, A., Goldberg, M. D., Carroll, R. K., Danino, V., Hinton, J. C. & Dorman, C. J. (2004). A global role for Fis in the transcriptional control of metabolism and type III secretion in *Salmonella enterica* serovar Typhimurium. *Microbiology* **150**, 2037–2053.

Kendall, M. M., Gruber, C. C., Parker, C. T. & Sperandio, V. (2012). Ethanolamine controls expression of genes encoding components involved in interkingdom signaling and virulence in enterohemorrhagic *Escherichia coli* O157 : H7. *MBio* **3**, e00050-12.

Klose, K. E. & Mekalanos, J. J. (1997). Simultaneous prevention of glutamine synthesis and high-affinity transport attenuates *Salmonella typhimurium* virulence. *Infect Immun* **65**, 587–596.

Klumpp, J. & Fuchs, T. M. (2007). Identification of novel genes in genomic islands that contribute to *Salmonella typhimurium* replication in macrophages. *Microbiology* **153**, 1207–1220.

Kobata, A. (2010). Structures and application of oligosaccharides in human milk. *Proc Jpn Acad, Ser B, Phys Biol Sci* **86**, 731–747.

Kofoid, E., Rappleye, C., Stojiljkovic, I. & Roth, J. (1999). The 17-gene ethanolamine (*eut*) operon of *Salmonella typhimurium* encodes five homologues of carboxysome shell proteins. *J Bacteriol* **181**, 5317–5329.

Korbel, J. O., Doerks, T., Jensen, L. J., Perez-Iratxeta, C., Kaczanowski, S., Hooper, S. D., Andrade, M. A. & Bork, P. (2005). Systematic association of genes to phenotypes by genome and literature mining. *PLoS Biol* **3**, e134.

Kröger, C. & Fuchs, T. M. (2009). Characterization of the *myo*-inositol utilization island of *Salmonella enterica* serovar Typhimurium. *J Bacteriol* **191**, 545–554.

Kröger, C., Srikumar, S., Ellwart, J. & Fuchs, T. M. (2011). Bistability in *myo*-inositol utilization by *Salmonella enterica* serovar Typhimurium. *J Bacteriol* **193**, 1427–1435.

Lamichhane-Khadka, R., Benoit, S. L., Maier, S. E. & Maier, R. J. (2013). A link between gut community metabolism and pathogenesis: molecular hydrogen-stimulated glucarate catabolism aids *Salmonella* virulence. *Open Biol* **3**, 130146.

Lawhon, S. D., Frye, J. G., Suyemoto, M., Porwollik, S., McClelland, M. & Altier, C. (2003). Global regulation by CsrA in *Salmonella typhimurium*. *Mol Microbiol* **48**, 1633–1645.

Lawley, T. D., Chan, K., Thompson, L. J., Kim, C. C., Govoni, G. R. & Monack, D. M. (2006). Genome-wide screen for *Salmonella* genes required for long-term systemic infection of the mouse. *PLoS Pathog* **2**, e11.

Lawrence, J. G. & Roth, J. R. (1996). Evolution of coenzyme B12 synthesis among enteric bacteria: evidence for loss and reacquisition of a multigene complex. *Genetics* **142**, 11–24.

Le Bouguénec, C. & Schouler, C. (2011). Sugar metabolism, an additional virulence factor in enterobacteria. *Int J Med Microbiol* **301**, 1–6.

Lindenstrauß, A. (2012). *Distribution of virulence factors in Enterococcus faecalis and its adaptation to conditions in the intestinal tract.* Dissertation, Technische Universität München, Germany.

Lupp, C., Robertson, M. L., Wickham, M. E., Sekirov, I., Champion, O. L., Gaynor, E. C. & Finlay, B. B. (2007). Host-mediated inflammation disrupts the intestinal microbiota and promotes the overgrowth of Enterobacteriaceae. *Cell Host Microbe* **2**, 119–129.

Maadani, A., Fox, K. A., Mylonakis, E. & Garsin, D. A. (2007). *Enterococcus faecalis* mutations affecting virulence in the *Caenorhabditis elegans* model host. *Infect Immun* **75**, 2634–2637.

Maccaferri, S., Biagi, E. & Brigidi, P. (2011). Metagenomics: key to human gut microbiota. *Dig Dis* **29**, 525–530.

Maier, R. J. (2005). Use of molecular hydrogen as an energy substrate by human pathogenic bacteria. *Biochem Soc Trans* **33**, 83–85.

Maier, R. J., Olczak, A., Maier, S., Soni, S. & Gunn, J. (2004). Respiratory hydrogen use by *Salmonella enterica* serovar Typhimurium is essential for virulence. *Infect Immun* **72**, 6294–6299.

Maier, L., Vyas, R., Cordova, C. D., Lindsay, H., Schmidt, T. S. B., Brugiroux, S., Periaswamy, B., Bauer, R., Sturm, A. & other authors (2013). Microbiota-derived hydrogen fuels *Salmonella* Typhimurium invasion of the gut ecosystem. *Cell Host Microbe* **14**, 641–651.

Maltby, R., Leatham-Jensen, M. P., Gibson, T., Cohen, P. S. & Conway, T. (2013). Nutritional basis for colonization resistance by human commensal *Escherichia coli* strains HS and Nissle 1917 against *E. coli* O157 : H7 in the mouse intestine. *PLoS ONE* **8**, e53957.

Marteyn, B., West, N. P., Browning, D. F., Cole, J. A., Shaw, J. G., Palm, F., Mounier, J., Prévost, M.-C., Sansonetti, P. & Tang, C. M. (2010). Modulation of *Shigella* virulence in response to available oxygen *in vivo*. *Nature* **465**, 355–358.

Martin, F. P., Wang, Y., Yap, I. K., Sprenger, N., Lindon, J. C., Rezzi, S., Kochhar, S., Holmes, E. & Nicholson, J. K. (2009). Topographical variation in murine intestinal metabolic profiles in relation to microbiome speciation and functional ecological activity. *J Proteome Res* **8**, 3464–3474.

Martins dos Santos, V., Müller, M. & de Vos, W. M. (2010). Systems biology of the gut: the interplay of food, microbiota and host at the mucosal interface. *Curr Opin Biotechnol* **21**, 539–550.

Matsumoto, M., Kibe, R., Ooga, T., Aiba, Y., Kurihara, S., Sawaki, E., Koga, Y. & Benno, Y. (2012). Impact of intestinal microbiota on intestinal luminal metabolome. *Sci Rep* **2**, 233.

Maynard, C. L., Elson, C. O., Hatton, R. D. & Weaver, C. T. (2012). Reciprocal interactions of the intestinal microbiota and immune system. *Nature* **489**, 231–241.

McCormick, B. A., Stocker, B. A., Laux, D. C. & Cohen, P. S. (1988). Roles of motility, chemotaxis, and penetration through and growth in intestinal mucus in the ability of an avirulent strain of *Salmonella typhimurium* to colonize the large intestine of streptomycin-treated mice. *Infect Immun* **56**, 2209–2217.

McGuckin, M. A., Lindén, S. K., Sutton, P. & Florin, T. H. (2011). Mucin dynamics and enteric pathogens. *Nat Rev Microbiol* **9**, 265–278.

McNeil, N. I. (1984). The contribution of the large intestine to energy supplies in man. *Am J Clin Nutr* **39**, 338–342.

Miller, C. P. & Bohnhoff, M. (1963). Changes in the mouse's enteric microflora associated with enhanced susceptibility to *Salmonella* infection following streptomycin treatment. *J Infect Dis* **113**, 59–66.

Miura, T., Okamoto, K. & Yanase, H. (2005). Purification and characterization of extracellular 1,2-α-L-fucosidase from *Bacillus cereus*. *J Biosci Bioeng* **99**, 629–635.

Muraoka, W. T. & Zhang, Q. (2011). Phenotypic and genotypic evidence for L-fucose utilization by *Campylobacter jejuni*. *J Bacteriol* **193**, 1065–1075.

Ng, K. M., Ferreyra, J. A., Higginbottom, S. K., Lynch, J. B., Kashyap, P. C., Gopinath, S., Naidu, N., Choudhury, B., Weimer, B. C. & other authors (2013). Microbiota-liberated host sugars facilitate post-antibiotic expansion of enteric pathogens. *Nature* **502**, 96–99.

Nicholson, J. K., Holmes, E., Kinross, J., Burcelin, R., Gibson, G., Jia, W. & Pettersson, S. (2012). Host-gut microbiota metabolic interactions. *Science* **336**, 1262–1267.

Njoroge, J. W., Nguyen, Y., Curtis, M. M., Moreira, C. G. & Sperandio, V. (2012). Virulence meets metabolism: Cra and KdpE gene regulation in enterohemorrhagic *Escherichia coli*. *MBio* **3**, e00280–12.

Obradors, N., Badía, J., Baldomà, L. & Aguilar, J. (1988). Anaerobic metabolism of the L-rhamnose fermentation product 1,2-propanediol in *Salmonella typhimurium*. *J Bacteriol* **170**, 2159–2162.

Pacheco, A. R., Curtis, M. M., Ritchie, J. M., Munera, D., Waldor, M. K., Moreira, C. G. & Sperandio, V. (2012). Fucose sensing regulates bacterial intestinal colonization. *Nature* **492**, 113–117.

Parkhill, J., Wren, B. W., Mungall, K., Ketley, J. M., Churcher, C., Basham, D., Chillingworth, T., Davies, R. M., Feltwell, T. & other authors (2000). The genome sequence of the food-borne pathogen *Campylobacter jejuni* reveals hypervariable sequences. *Nature* **403**, 665–668.

Penrod, J. T. & Roth, J. R. (2006). Conserving a volatile metabolite: a role for carboxysome-like organelles in *Salmonella enterica*. *J Bacteriol* **188**, 2865–2874.

Pham, T. A. & Lawley, T. D. (2014). Emerging insights on intestinal dysbiosis during bacterial infections. *Curr Opin Microbiol* **17**, 67–74.

Poncet, S., Milohanic, E., Mazé, A., Nait Abdallah, J., Aké, F., Larribe, M., Deghmane, A.-E., Taha, M.-K., Dozot, M. & other authors (2009). Correlations between carbon metabolism and virulence in bacteria. *Contrib Microbiol* **16**, 88–102.

Power, J. (1967). The L-rhamnose genetic system in *Escherichia coli* K-12. *Genetics* **55**, 557–568.

Price-Carter, M., Tingey, J., Bobik, T. A. & Roth, J. R. (2001). The alternative electron acceptor tetrathionate supports B12-dependent anaerobic growth of *Salmonella enterica* serovar typhimurium on ethanolamine or 1,2-propanediol. *J Bacteriol* **183**, 2463–2475.

Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K. S., Manichanh, C., Nielsen, T., Pons, N., Levenez, F. & other authors (2010). A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* **464**, 59–65.

Reddy, N. (2001). Occurrence, distribution, content, and dietary intake of phytate. In *Food Phytates*, pp. 25–51. Edited by N. R. Reddy & S. K. Sathe. Boca Raton, FL: CRC Press.

Robbe, C., Capon, C., Coddeville, B. & Michalski, J. C. (2004). Structural diversity and specific distribution of *O*-glycans in normal human mucins along the intestinal tract. *Biochem J* **384**, 307–316.

Rohmer, L., Hocquet, D. & Miller, S. I. (2011). Are pathogenic bacteria just looking for food? Metabolism and microbial pathogenesis. *Trends Microbiol* **19**, 341–348.

Rollenhagen, C. & Bumann, D. (2006). *Salmonella enterica* highly expressed genes are disease specific. *Infect Immun* **74**, 1649–1660.

Rondon, M. R. & Escalante-Semerena, J. C. (1992). The *poc* locus is required for 1,2-propanediol-dependent transcription of the cobalamin biosynthetic (*cob*) and propanediol utilization (*pdu*) genes of *Salmonella typhimurium*. *J Bacteriol* **174**, 2267–2272.

Rondon, M. R. & Escalante-Semerena, J. C. (1996). *In vitro* analysis of the interactions between the PocR regulatory protein and the promoter region of the cobalamin biosynthetic (*cob*) operon of *Salmonella typhimurium* LT2. *J Bacteriol* **178**, 2196–2203.

Rondon, M. R., Kazmierczak, R. & Escalante-Semerena, J. C. (1995). Glutathione is required for maximal transcription of the cobalamin biosynthetic and 1,2-propanediol utilization (*cob*/*pdu*) regulon and for the catabolism of ethanolamine, 1,2-propanediol, and propionate in *Salmonella typhimurium* LT2. *J Bacteriol* **177**, 5434–5439.

Roth, J. R., Lawrence, J. G. & Bobik, T. A. (1996). Cobalamin (coenzyme B12): synthesis and biological significance. *Annu Rev Microbiol* **50**, 137–181.

Ruiz-Albert, J., Yu, X. J., Beuzón, C. R., Blakey, A. N., Galyov, E. E. & Holden, D. W. (2002). Complementary activities of SseJ and SifA regulate dynamics of the *Salmonella typhimurium* vacuolar membrane. *Mol Microbiol* **44**, 645–661.

Ruiz-Palacios, G. M., Cervantes, L. E., Ramos, P., Chavez-Munguia, B. & Newburg, D. S. (2003). *Campylobacter jejuni* binds intestinal H(O) antigen (Fucα1, 2Galβ1, 4GlcNAc), and fucosyloligosaccharides of human milk inhibit its binding and infection. *J Biol Chem* **278**, 14112–14120.

Salazar, J. K., Wu, Z., McMullen, P. D., Luo, Q., Freitag, N. E., Tortorello, M. L., Hu, S. & Zhang, W. (2013). PrfA-like transcription factor gene lmo0753 contributes to L-rhamnose utilization in *Listeria monocytogenes* strains associated with human food-borne infections. *Appl Environ Microbiol* **79**, 5584–5592.

Salyers, A. A. & Pajeau, M. (1989). Competitiveness of different polysaccharide utilization mutants of *Bacteroides thetaiotaomicron* in the intestinal tracts of germfree mice. *Appl Environ Microbiol* **55**, 2572–2578.

Sampson, E. M. & Bobik, T. A. (2008). Microcompartments for B12-dependent 1,2-propanediol degradation provide protection from DNA and cellular damage by a reactive metabolic intermediate. *J Bacteriol* **190**, 2966–2971.

Savage, D. C. (1977). Microbial ecology of the gastrointestinal tract. *Annu Rev Microbiol* **31**, 107–133.

Schär, J., Stoll, R., Schauer, K., Loeffler, D. I., Eylert, E., Joseph, B., Eisenreich, W., Fuchs, T. M. & Goebel, W. (2010). Pyruvate carboxylase plays a crucial role in carbon metabolism of extra- and intracellularly replicating *Listeria monocytogenes*. *J Bacteriol* **192**, 1774–1784.

Schauer, K., Geginat, G., Liang, C., Goebel, W., Dandekar, T. & Fuchs, T. M. (2010). Deciphering the intracellular metabolism of *Listeria monocytogenes* by mutant screening and modelling. *BMC Genomics* **11**, 573.

Scott, K. P., Martin, J. C., Campbell, G., Mayer, C. D. & Flint, H. J. (2006). Whole-genome transcription profiling reveals genes up-regulated by growth on fucose in the human gut bacterium "*Roseburia inulinivorans*". *J Bacteriol* **188**, 4340–4349.

Sela, D. A., Chapman, J., Adeuya, A., Kim, J. H., Chen, F., Whitehead, T. R., Lapidus, A., Rokhsar, D. S., Lebrilla, C. B. & other authors (2008). The genome sequence of *Bifidobacterium longum* subsp. infantis reveals adaptations for milk utilization within the infant microbiome. *Proc Natl Acad Sci U S A* **105**, 18964–18969.

Severi, E., Hood, D. W. & Thomas, G. H. (2007). Sialic acid utilization by bacterial pathogens. *Microbiology* **153**, 2817–2822.

Sheppard, D. E. & Roth, J. R. (1994). A rationale for autoinduction of a transcriptional activator: ethanolamine ammonia-lyase (EutBC) and the operon activator (EutR) compete for adenosyl-cobalamin in *Salmonella typhimurium*. *J Bacteriol* **176**, 1287–1296.

Snider, T. A., Fabich, A. J., Conway, T. & Clinkenbeard, K. D. (2009). *E. coli* O157 : H7 catabolism of intestinal mucin-derived carbohydrates and colonization. *Vet Microbiol* **136**, 150–154.

Sonnenburg, J. L., Xu, J., Leip, D. D., Chen, C. H., Westover, B. P., Weatherford, J., Buhler, J. D. & Gordon, J. I. (2005). Glycan foraging *in vivo* by an intestine-adapted bacterial symbiont. *Science* **307**, 1955–1959.

Spees, A. M., Wangdi, T., Lopez, C. A., Kingsbury, D. D., Xavier, M. N., Winter, S. E., Tsolis, R. M. & Bäumler, A. J. (2013). Streptomycin-induced inflammation enhances *Escherichia coli* gut colonization through nitrate respiration. *MBio* **4**, e00430-13.

Srikumar, S. & Fuchs, T. M. (2011). Ethanolamine utilization contributes to proliferation of *Salmonella enterica* serovar Typhimurium in food and in nematodes. *Appl Environ Microbiol* **77**, 281–290.

Stahl, M., Friis, L. M., Nothaft, H., Liu, X., Li, J., Szymanski, C. M. & Stintzi, A. (2011). L-Fucose utilization provides *Campylobacter jejuni* with a competitive advantage. *Proc Natl Acad Sci U S A* **108**, 7194–7199.

Stahl, M., Butcher, J. & Stintzi, A. (2012). Nutrient acquisition and metabolism by *Campylobacter jejuni*. *Front Cell Infect Microbiol* **2**, 5.

Stams, A. J. (1994). Metabolic interactions between anaerobic bacteria in methanogenic environments. *Antonie van Leeuwenhoek* **66**, 271–294.

Stecher, B. & Hardt, W. D. (2008). The role of microbiota in infectious disease. *Trends Microbiol* **16**, 107–114.

Stecher, B., Robbiani, R., Walker, A. W., Westendorf, A. M., Barthel, M., Kremer, M., Chaffron, S., Macpherson, A. J., Buer, J. & other authors (2007). *Salmonella enterica* serovar typhimurium exploits inflammation to compete with the intestinal microbiota. *PLoS Biol* **5**, e244.

Stecher, B., Barthel, M., Schlumberger, M. C., Haberli, L., Rabsch, W., Kremer, M. & Hardt, W. D. (2008). Motility allows *S.* Typhimurium to benefit from the mucosal defence. *Cell Microbiol* **10**, 1166–1180.

Steeb, B., Claudi, B., Burton, N. A., Tienz, P., Schmidt, A., Farhan, H., Mazé, A. & Bumann, D. (2013). Parallel exploitation of diverse host nutrients enhances *Salmonella* virulence. *PLoS Pathog* **9**, e1003301.

Steyert, S. R. & Kaper, J. B. (2012). Contribution of urease to colonization by Shiga toxin-producing *Escherichia coli*. *Infect Immun* **80**, 2589–2600.

Stojiljkovic, I., Bäumler, A. J. & Heffron, F. (1995). Ethanolamine utilization in *Salmonella typhimurium*: nucleotide sequence, protein expression, and mutational analysis of the *cchA cchB eutE eutJ eutG eutH* gene cluster. *J Bacteriol* **177**, 1357–1366.

Thiennimitr, P., Winter, S. E., Winter, M. G., Xavier, M. N., Tolstikov, V., Huseby, D. L., Sterzenbach, T., Tsolis, R. M., Roth, J. R. & Bäumler, A. J. (2011). Intestinal inflammation allows *Salmonella* to use ethanolamine to compete with the microbiota. *Proc Natl Acad Sci U S A* **108**, 17480–17485.

Thomson, N. R., Howard, S., Wren, B. W., Holden, M. T. G., Crossman, L., Challis, G. L., Churcher, C., Mungall, K., Brooks, K. & other authors (2006). The complete genome sequence and comparative genome analysis of the high pathogenicity *Yersinia enterocolitica* strain 8081. *PLoS Genet* **2**, e206.

Toledo-Arana, A., Dussurget, O., Nikitas, G., Sesto, N., Guet-Revillet, H., Balestrino, D., Loh, E., Gripenland, J., Tiensuu, T. & other authors (2009). The *Listeria* transcriptional landscape from saprophytism to virulence. *Nature* **459**, 950–956.

Tsoy, O., Ravcheev, D. & Mushegian, A. (2009). Comparative genomics of ethanolamine utilization. *J Bacteriol* **191**, 7157–7164.

Turnbaugh, P. J., Hamady, M., Yatsunenko, T., Cantarel, B. L., Duncan, A., Ley, R. E., Sogin, M. L., Jones, W. J., Roe, B. A. & other authors (2009). A core gut microbiome in obese and lean twins. *Nature* **457**, 480–484.

Varki, A. (1993). Biological roles of oligosaccharides: all of the theories are correct. *Glycobiology* **3**, 97–130.

Velayudhan, J., Jones, M. A., Barrow, P. A. & Kelly, D. J. (2004). L-Serine catabolism via an oxygen-labile L-serine dehydratase is essential for colonization of the avian gut by *Campylobacter jejuni*. *Infect Immun* **72**, 260–268.

Wang, Y., Holmes, E., Comelli, E. M., Fotopoulos, G., Dorta, G., Tang, H., Rantalainen, M. J., Lindon, J. C., Corthésy-Theulaz, I. E. & other authors (2007). Topographical variation in metabolic signatures of human gastrointestinal biopsies revealed by high-resolution magic-angle spinning ^{1}H NMR spectroscopy. *J Proteome Res* **6**, 3944–3951.

Wexler, H. M. (2007). Bacteroides: the good, the bad, and the nitty-gritty. *Clin Microbiol Rev* **20**, 593–621.

Winter, S. E. & Bäumler, A. J. (2014). Dysbiosis in the inflamed intestine: chance favors the prepared microbe. *Gut Microbes* **5**, 1–3.

Winter, S. E., Thiennimitr, P., Winter, M. G., Butler, B. P., Huseby, D. L., Crawford, R. W., Russell, J. M., Bevins, C. L., Adams, L. G. & other authors (2010). Gut inflammation provides a respiratory electron acceptor for *Salmonella*. *Nature* **467**, 426–429.

Winter, S. E., Winter, M. G., Xavier, M. N., Thiennimitr, P., Poon, V., Keestra, A. M., Laughlin, R. C., Gomez, G., Wu, J. & other authors (2013). Host-derived nitrate boosts growth of *E. coli* in the inflamed gut. *Science* **339**, 708–711.

Worley, M. J., Ching, K. H. & Heffron, F. (2000). *Salmonella* SsrB activates a global regulon of horizontally acquired genes. *Mol Microbiol* **36**, 749–761.

Zhang, Y., Rodionov, D. A., Gelfand, M. S. & Gladyshev, V. N. (2009). Comparative genomic analyses of nickel, cobalt and vitamin B12 utilization. *BMC Genomics* **10**, 78.

Zheng, X., Xie, G., Zhao, A., Zhao, L., Yao, C., Chiu, N. H. L., Zhou, Z., Bao, Y., Jia, W. & other authors (2011). The footprints of gut microbial–mammalian co-metabolism. *J Proteome Res* **10**, 5512–5522.

Zúñiga, M., Comas, I., Linaje, R., Monedero, V., Yebra, M. J., Esteban, C. D., Deutscher, J., Pérez-Martínez, G. & González-Candelas, F. (2005). Horizontal gene transfer in the molecular evolution of mannose PTS transporters. *Mol Biol Evol* **22**, 1673–1685.

Edited by: S. Spiro