The gut microbiome: the role of a virtual organ in the endocrinology of the host

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Abstract

The human microbiome contains a vast array of microbes and genes that show greater complexity than the host's own karyome; the functions of many of these microbes are beneficial and show co-evolution with the host, while others are detrimental. The microbiota that colonises the gut is now being considered as a virtual organ or emergent system, with properties that need to be integrated into host biology and physiology. Unlike other organs, the functions that the gut microbiota plays in the host are as yet not fully understood and can be quite easily disrupted by antibiotics, diet or surgery. In this review, we look at some of the best-characterised functions that only the gut microbiota plays and how it interacts with the host's endocrine system and we try to make it clear that the 21st-century biology cannot afford to ignore this facet of biology, if it wants to fully understand what makes us human.

Key Words

- ▶ human microbiome
- ▶ cross-talk
- ▶ gut microbiome
- ▶ endocrine system

Journal of Endocrinology
(2013) **218**, R37–R47

Introduction

In the many years of studying the human body, it has become accepted that all the organs are known and well characterised in terms of their main functions. The whole discipline of anatomy has been focused on documenting the fine structure of these organs, while physiology and biochemistry have been determining their functions and specific chemical reactions. In the last 10 years, a significant revolution has been progressing, which started with the notion that for the best part of a hundred years we have been trying to describe how mammals function while ignoring one of the main organs in the body. However, this organ is not found or described in any conventional textbook and there are no clinical experts who can understand its functions and the pathologies that arise when it becomes diseased. This dearth of information is because this organ does not conform to the current

definition of being an organ, i.e. 'a fully differentiated and functional unit', and should probably best be thought of as a virtual organ (O'Hara & Shanahan 2006) since it is composed of microbes and all its functions are derived from these parts. In fact, it most probably should be considered as a system in the same way we look at our immune system, which is made of different cells, each having its own set of functions and roles. This paradigm shift is still undergoing some refinement, but it does beg the question 'what would biologists do if they were suddenly presented with a whole new organ/system?' Furthermore, why should we even think of it as an organ or system? To answer the last question first, we see this as a virtual organ/system due to the genetic and metabolic diversity that resides within it.

Microbiologists have coined a phrase for this system, the microbiome, which is defined as the 'the genetic

material (DNA) within a microbial community'; this can also be referred to as the metagenome of the microbiota. The largest contributors to the human microbiome are the bacteria present in the intestinal tract, which have been estimated to be in the range of 100 trillion cells, ten times more cells than there are human cells in the host's body. In terms of the total non-redundant genetic load found in the human gut microbiome, it is 150 times larger than the host's karyome ((Qin *et al.* 2010)), which is between 20 000 and 26 000 genes (Pennisi 2003, Collins *et al.* 2004)), and each individual has ~540 000 bacterial genes in the gut (21–27×the human karyome). While the karyome is generally regarded as fixed with respect to the gene catalogue, and at this stage ignoring any epigenetic mechanisms, the gut microbiome is far more random and each individual will contain a unique collection of microbes that are easily altered (see below). Humans are born either sterile or colonised with a very basic microbiome, and analysis of the meconium has shown that any microbes that are present are not necessarily those that ultimately colonise the adult gut (Koenig *et al.* 2011). The microbiome that is obtained is partly inherited from the mother and partly from the exposure to the environment in the first 2 years of life. Hence, there is a degree of determinism (both by exposure to the mother and due to genetic selection (Tims *et al.* 2013)) and also a significant proportion of random colonisation. However, it is striking that after 2 years of age, all adults' colons will be predominantly colonised with members of two phyla, namely *Bacteroidetes*: Gram-negative, anaerobic, non-spore-forming bacteria, which are enriched with carbohydrate-degrading enzymes, and *Firmicutes*: Gram-positive, formerly called 'the low-GC bacteria', anaerobic, spore-forming bacteria, which ferment simple sugars to produce a variety of short-chain fatty acids (SCFAs), such as butyrate, acetate and propionate (Fischbach & Sonnenburg 2011). Between them, these phyla can constitute over 90% of the bacteria present in the large intestinal lumen (Turnbaugh *et al.* 2009, Qin *et al.* 2010, Claesson *et al.* 2011, HMPC *et al.* 2012) and mucosa (Eckburg *et al.* 2005, Chen *et al.* 2012, Harrell *et al.* 2012), and the proportion of each phylum in the colon ranges from being nearly 90% *Firmicutes*, at one end of the continuum, to 90% *Bacteroidetes*, at the other end. What dictates this distribution is unclear, and the consequences for the host are also unclear. Furthermore, our view of the intestinal environment is skewed towards the large intestine and is predominantly focused on faecal material, and even then we are very bacteria centric (Marchesi 2010). Bearing this biased view of the intestinal

environment in mind, we have begun to determine what functions this collection of organisms plays in the host.

A virtual organ/system with functions of importance to the host

In the last 10 years, it has become increasingly apparent that the gut microbiota plays a significant role in host biology. We have a substantial body of evidence that these functions can be beneficial or detrimental to the host, and if they were assets, we would wish to maximise the former and somehow offset the latter. A significant portion of the evidence that supports a role for the gut microbiota in host development and function comes from studying sterile animals, especially rodents (Fig. 1). A recent comprehensive review of the use of such animals has shown how widespread the impact of not having a gut microbiota is (Smith *et al.* 2007). Some of the best studied of these bacterial functions include providing the host with energy in the form of SCFAs such as butyrate (Louis & Flint 2009) and propionate (Macfarlane & Macfarlane 2011), bile salt metabolism (Jones *et al.* 2008, Swann *et al.* 2011) and role in the brain–gut axis (Collins *et al.* 2012). Many ecological analyses of the colonic microbiota have shown that while it is relatively stable (Scanlan *et al.* 2006, Jalanka-Tuovinen *et al.* 2011, Kolmeder *et al.* 2012), it can be significantly perturbed by antibiotics (Dethlefsen *et al.* 2008, Jernberg *et al.* 2010), diet (Claesson *et al.* 2012, Ravussin *et al.* 2012) and surgery (Zhang *et al.* 2009, Li *et al.* 2011). Unlike a conventional organ, the functions of this virtual organ can be significantly altered or removed due to these environmental factors, which can result in disease in the host, e.g. *Clostridium difficile*-associated diarrhoea (Kachrimanidou & Malisiovas 2011), or a significant alteration of the host's metabolite profile (Yap *et al.* 2008), the significance of which still remains unclear. The variability in the gut microbiome and its functions are important in two respects: the functions that one inherits and acquires are driven mainly by a random process and once established they can be perturbed by interventions.

Bile metabolism and gut bacteria

Bile acids/salts are cholesterol-derived host metabolites that play a role in several host processes (Fig. 2). Their principal functions are to aid in fat adsorption and prevent small intestinal bacterial overgrowth. Both these functions can be explained by the fact that bile acids are surfactants (not detergents), with a hydrophilic taurine or glycine group covalently bound to a hydrophobic steroid

Figure 1

Schematic representation of areas of the rodent system that are significantly impacted by the absence of a normal microbiome; all the changes are those that are measured/observed in the sterile animal (adapted from Smith K,

McCoy KD & Macpherson AJ 2007 Use of axenic animals in studying the adaptation of mammals to their commensal intestinal microbiota. *Seminars in Immunology* 19 59–69. (doi:10.1016/j.smim.2006.10.002)).

(predominantly a C₂₄ structure (Russell 2003))-derived moiety that is wholly derived from cholesterol. This surfactant nature allows them to associate with fat molecules to form micelles, which are ultimately absorbed by the host, thus facilitating fat metabolism. Additionally, being a surfactant allows them to be antimicrobial also, as they can disrupt the plasma membrane of the bacteria, causing them to lyse and die; thus in a niche where food is plentiful, bile helps to prevent the bacteria in the small intestine from overgrowing and becoming a health issue. A secondary role for bile involves regulating the host's cholesterol levels, on a typical day, ~0.5 g of this steroid is used to synthesise bile acids in hepatocytes and accounts for 90% of the cholesterol usage (Russell 2003). Once the hormonal signal has been sent to the gall bladder, the bile acids are excreted into the small intestine, where they interact with the dietary lipids and fat-soluble vitamins. These complexes are eventually reabsorbed in the terminal ileum; this process is part of the enterohepatic circulation that ensures that 95% of the bile acids are recovered from the gut. The remaining 5% that escapes this pathway

enters the large intestine, where it becomes available for metabolism by bacteria. Interestingly, the gut bacteria have evolved several enzymes capable of modifying the primary bile acids such as the taurine- and glycine-conjugated cholic and chenodeoxycholic acids and removing the taurine and glycine parts of the molecules to produce secondary bile salts, such as cholic, lithocholic and deoxycholic acids. While some of these secondary bile acids are excreted in the faeces, a significant proportion are passively absorbed and returned to the liver. These secondary bile acids then enter the enterohepatic circulation and the general bile metabolite pool. The bacterial enzymes responsible for the deconjugation of either taurine or glycine are collectively known as bile salt hydrolases (BSHs), choloylglycine hydrolases or bile acid hydrolases (EC 3.5.1.24) and catalyse the hydrolytic removal of taurine or glycine from the corresponding primary bile acids. However, as with many gut functions, the diversity and abundance of BSHs are highly variable as are their substrate ranges (Jones *et al.* 2008). Additionally, studies on germ-free rodents (i.e. sterile or gnotobiotic)

Figure 2

Schematic representation of some of the functions that the gut microbiota plays in the host. The four functions shown, those of bile salt hydrolases, bacterial fermentation, amino acid decarboxylases and glucuronidases, can

play a role in producing molecules that interact with the host's endocrine system. The red/green colour scheme implies that it is still unclear whether these functions are beneficial or detrimental to the host's physiology.

have shown that the bile pool is significantly and dramatically altered in other non-liver or non-gut compartments too, e.g. heart tissue (Fig. 3), which begs the question of the significance of having a specific BSH profile in the gut and the host's own physiology. Bile acids interact at an endocrinological level via three major signalling mechanisms, as ligands for the

G-protein-coupled receptor TGR₅, activators of the MAPK pathways and activators of the nuclear hormone receptors such as farnesoid X receptor α (FXR α ; NR1H4). While the primary bile acids are of significant interest as they have been shown to regulate lipid, energy and glucose metabolism, the secondary bile acids can also interact with these receptors. However, the availability of the

****P<0.01; ***P<0.001** (modified from Swann JR, Want EJ, Geier FM, Spagou K, Wilson ID, Sidaway JE, Nicholson JK & Holmes E 2011 Systemic gut microbial modulation of bile acid metabolism in host tissue compartments. *PNAS* **108**(Suppl 1) 4523–4530. (doi:10.1073/pnas.1006734107)). Unconjugated bile acids are those that are produced by bacterial metabolism of the host conjugated acids.

(Warnecke *et al.* 2007) and ruminants (Brulc *et al.* 2009) have evolved a mutualistic relationship with the organisms that synthesise SCFAs, and it seems that humans too have co-evolved with these bacterial functions. The G-protein-coupled receptors free fatty acid receptor 2 (FFAR2, GPR43) and FFAR3 (GPR41) are the two endogenous receptors that have been identified to interact with SCFAs (Brown *et al.* 2003, Le Poul *et al.* 2003, Nilsson *et al.* 2003). FFAR2 and FFAR3 interact with the SCFAs (μM – mM range) with a carbon chain length greater than six atoms and are those that are most likely to have evolved in response to the fermentation products of the gut bacteria. Both receptors are found in a variety of tissues including the gut and have been shown to be expressed in enteroendocrine cells that are producing peptide YY (PYY; Table 1). SCFAs have been shown to stimulate the release of PYY and 5-hydroxytryptamine (5-HT) from the

One of the most fundamental contributions that the gut microbiota makes to host function is the provision of SCFAs. These relatively simple molecules, predominantly butyrate, acetate and propionate, are all produced when certain classes of bacteria ferment a variety of carbon sources anaerobically. Although SCFAs are the end products of metabolism for some bacteria, they are a significant source of energy for the host. Both termites

Table 1 Characteristics of free fatty acid receptor 2 and free fatty acid receptor 3

Nomenclature	FFAR2	FFAR3
Agonist (FFA)	Short-chain C3~C4~C2	Short-chain C3>C4>>C2
Gene	<i>GPR43</i>	<i>GPR41</i>
Localisation	19q13.1	19q13.1
Expression outside of the gut	Adipose tissue	Adipose tissue
Physiological role	PYY secretion 5-HT secretion	Leptin production PYY secretion

ileum and colon (Cherbut *et al.* 1998, Fukumoto *et al.* 2003). Mice that have had their FFAR3 knocked out (Samuel *et al.* 2008) show an associated reduction in the expression of PYY, increased intestinal transit rate and reduced harvest of energy (SCFAs) from the diet. These authors concluded that FFAR3 is involved in the regulation of host energy balance, which is ultimately driven by the gut microbiota and its metabolites. Additionally, the FFARs have been proposed to be involved in glucose intolerance and thus diabetes (Tolhurst *et al.* 2012). Tolhurst *et al.* have shown in their study that both FFAR2 and FFAR3 are more greatly expressed in glucagon-like peptide-1 (GLP1)-secreting cells. Additionally, when mice that were homozygous negative for both FFARs were exposed to SCFAs, there was a significant reduction in SCFA-triggered GLP1 secretion. The other significant role that these bacterially derived metabolites play is the stimulation of leptin production in adipocytes (Xiong *et al.* 2004); however, the exact mechanism is still being elucidated (Zaibi *et al.* 2010). Since leptin is involved in a wide range of physiological processes, such as feeding behaviour, reproduction and metabolic rate, any molecules that stimulate its production are of significant interest. All of the SCFAs have been shown to stimulate plasma leptin levels (Yonekura *et al.* 2003, Xiong *et al.* 2004), and when propionate is delivered orally, these levels are raised and the effect can be blocked by small-interfering RNAs targeted towards GPR41 in Ob-Luc cells (Xiong *et al.* 2004).

Although SCFAs have been shown to interact with their own cognate receptors, they have also been shown to modulate hepatic glucose production in humans (Thorburn *et al.* 1993). The intake of fibre, which acts as a prebiotic and is only metabolised by the gut bacteria, has been reported to be inversely associated with the risk of type 2 diabetes and heart disease (Pereira *et al.* 2002). The hypothesis that fibre is digested eventually to SCFAs is an important one in the area of the gut microbiota, because it

assumes that fibre ingested will be digested to SCFAs and that this leads to eventual benefits to the host. However, this treats the gut microbiota as a 'black box' and does not consider that individuals' capacity to metabolise the different components of the fibre and to ferment these degradation products to SCFAs is conditional on them having the necessary bacterial functions present in the first place. Bearing this in mind, it may be explained why the evidence is not strong as to the beneficial role of fibre in the reduction of the risk of developing diabetes and other diseases (Williams 2012, Caricilli & Saad 2013).

The brain-gut axis

The hypothalamic–pituitary–adrenal (HPA) axis has received much attention in recent years, in particular, its association with the gut and its resident microbiota. It is becoming increasingly apparent that this association can both positively and negatively affect host health, with implications for the gut microbiota itself and the endocrine system.

Studies using *in vitro* and *in vivo* models have hinted at the possible underlying mechanisms of the effect of stress on the gut through the HPA axis. It has been shown that this axis responds to stress (Herman *et al.* 2003) through the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus, in turn triggering the release of ACTH from the pituitary gland and driving the release of catecholamines and cortisol from the cortex (Mawdsley & Rampton 2005). CRH has been shown to stimulate the release of pro-inflammatory cytokines such as TNF α , IL1 β and IL6 in *in vitro* and *in vivo* murine models (Agelaki *et al.* 2002), while the *in vivo* stimulation of β -adrenergic receptor, a receptor for the catecholamines nor-epinephrine and epinephrine, has been shown to increase the levels of circulating IL1 and IL6 (Johnson *et al.* 2005). The production of cytokines, in particular, TNF α , has been shown to affect the gut epithelial barrier function in both *in vitro* (Schmitz *et al.* 1999) and in human studies, where one study has shown the restoration of the gut epithelial barrier function in Crohn's disease patients through the administration of infliximab, a chimeric MAB against TNF α (Suenae *et al.* 2002). Bacterial cells can also disrupt the function of the gut epithelial membrane through lipopolysaccharide (LPS) and its interaction with myosin light chain kinase, a regulator of tight junctions (Shen *et al.* 2006). It has also been shown that the stress response of the HPA axis and 'leakiness' of the gut epithelial barrier in mice can be attenuated through feeding of the probiotic organism *Lactobacillus farciminis* (Ait-Belgnaoui *et al.*

2012). This highlights the two-way nature of the HPA axis and our resident gut microbiota.

A very common diagnosis in gastroenterological practice worldwide is irritable bowel syndrome (IBS), which is characterised by abnormal bowel function, bloating and abdominal pain or discomfort relieved by defaecation (Spiller *et al.* 2007). IBS significantly affects quality of life (Simren *et al.* 2006) and is a substantial economic burden to healthcare systems (Nyrop *et al.* 2007). IBS has been reported to be present in up to 10% of the population and responsible for 3.6% of GP consultations. So, understanding this syndrome is an important goal, and recently, in a landmark study, Dinan *et al.* (2006) have shown that in an IBS cohort the levels of cortisol and the pro-inflammatory cytokines IL6 and IL8 are elevated. Prior to this study, they had also used a bacterial intervention, in the form of two separate probiotics (*Lactobacillus salivarius* UCC4331 or *Bifidobacterium infantis* 35624), and shown that *B. infantis* is able to normalise the IL10:IL12 ratio. Hence, this again leads us to the conclusion that the variable levels of some organisms in the gut may be responsible for diseases/syndromes as they signal to a variety of host effectors.

Microbially derived endocrine molecules

Endocrine molecules are not solely produced by the human body; gut microbes can also produce these molecules. It has been shown previously that there is a significant level of dopamine production in the human gut (Eisenhofer *et al.* 1997). The importance of the gut microbiota in the generation of this compound has been overlooked, and in a subsequent piece of work, it has been shown that the gut microbiota plays a critical role in the production of norepinephrine and dopamine in the gut (Asano *et al.* 2012). This production is due to the expression of β -glucuronidases by commensal gut bacteria, generating dopamine and norepinephrine through the cleavage of their inactive conjugated forms. Gut microbes can also produce non-noradrenergic, non-cholinergic transmitters such as nitric oxide, which plays a pivotal role in the regulation of gastric emptying (Orihata & Sarna 1994), through the anaerobic reduction of nitrate to nitrogen (Sobko *et al.* 2005, Cutruzzolà 2012). The inhibitory transmitter γ -aminobutyric acid can be generated by *Lactobacillus brevis* and *Bifidobacterium dentium* (Barrett *et al.* 2012); both of these organisms can be isolated from humans (Rönkä *et al.* 2003, Ventura *et al.* 2009). Studies such as these are highlighting the previously unrealised importance of our own gut microbiota in generating compounds that interact with our own endocrine system.

Diabetes and gut bacteria

Diabetes is a chronic metabolic disorder that affects an estimated 347 million people throughout the world (WHO 2012). Type 1 diabetes, also known as juvenile diabetes, is a state of absolute deficiency of insulin, while type 2 diabetes is a state of relative insulin deficiency in the presence of obesity and insulin resistance; the prevalence of the latter is increasing among children due to the adoption of a sedentary lifestyle. There is increasing evidence that the gut microbiota plays a role in the development of this disorder. In the non-obese diabetic (NOD) murine model, which was also deficient for the adapter protein MYD88, researchers have shown that the gut microbiota plays a role in the development of type 1 diabetes (Wen *et al.* 2008). In this study, the islets of Langerhans of germ-free, specific pathogen-free and altered Schaedler flora (Dewhirst *et al.* 1999) *Myd88* knockout NOD mice were histologically compared; the germ-free mice exhibited a greater level of islet infiltration. The authors showed that the gut commensal bacteria can modify the development of this disease. With this in mind, research has been carried out to determine which bacterial species and groups in humans are most prevalent in the sufferers of type 1 diabetes. In a recent study (Giongo *et al.* 2011), the distal gut microbiota of four children with autoimmunity, who went on to develop type 1 diabetes, has been compared with that of four healthy children through pyrosequencing of faecal DNA extracted at three time points. The results highlighted differences between the two major phyla in the gut, *Bacteroidetes* and *Firmicutes*. There was an increase in the number of DNA sequences from the *Bacteroidetes* phylum as autoimmunity developed to type 1 diabetes and a reduction in the number of DNA sequences obtained from the *Firmicutes* phylum. In contrast, the four healthy children exhibited the opposite pattern, with the number of *Bacteroidetes* sequences decreasing and that of *Firmicutes* sequences increasing as each time point was analysed. It was also shown that the healthy control children had a higher diversity of bacterial species than the children with autoimmunity, suggesting a link between low bacterial species diversity and type 1 diabetes. This low diversity is indicative of a non-normal gut microbiota, which has been suggested to combine with intestinal leakiness and altered intestinal immune responsiveness to generate a 'perfect storm' for the development of type 1 diabetes (Vaarala *et al.* 2008).

The gut microbiota, through LPS, has been shown to exert a pro-inflammatory effect and when combined with

a high-fat diet leads to the onset of insulin resistance and, therefore, the development of type 2 diabetes in a mouse model (Cani *et al.* 2007, 2008). In accordance with what has been observed in type 1 diabetes, a metagenomic analysis of faecal samples of type 2 diabetes sufferers has shown a slight level of dysbiosis in their gut bacterial make-up; type 2 diabetes sufferers exhibited higher levels of opportunistic pathogens (Qin *et al.* 2012). Arguably more important is the fact that this research showed a reduction in the number of butyrate-producing bacteria, a SCFA that modulates the activity of NF- κ B (Inan *et al.* 2000), hinting that the loss of bacterial species may not be as important as the loss of functions that they play.

Microbial modulation of neurotransmitters: serotonin

One metabolic pathway of interest is the metabolism of tryptophan, a precursor for a number of metabolites, but particularly for the production of serotonin or 5-HT. Serotonin is a well-documented monoamine neurotransmitter that has been extensively studied due to its hypothesised role in the regulation of learning, mood, sleep, anxiety and other psychiatry-related afflictions. In recent years, serotonin has also gained increasing interest for its role in the area of gut pathophysiology (Gershon & Tack 2007) and its role as a signalling molecule linking the brain and the gut. Research has been fairly conclusive in demonstrating that bacteria can affect serotonin levels indirectly by stimulating secretion. However, recent evidence suggests a role for the gut microbiota in actually modulating the levels of the serotonin precursor tryptophan and hence having a control over serotonin levels in the host. Research by Desbonnet *et al.* (2008) has suggested a role for tryptophan producers such as *B. infantis* as probiotics specifically to aid in combating psychiatric disorders such as depression. Other groups have also shown a role for bacteria in modulating neurotransmitter precursors (Rhee *et al.* 2009, Wikoff *et al.* 2009, Heijtz *et al.* 2011).

Around 90% of serotonin is located in the enterochromaffin cells of the human gastrointestinal tract (Keszthelyi *et al.* 2009) and, therefore, must be intimately associated with the gastrointestinal mucosa and its microbiota. Enterochromaffin cells release serotonin in response to certain bacterial stimuli such as LPS, enzymes and other bacterial toxins to help increase gastric transit and rid the host of the toxin as quickly as possible (result is often diarrhoea). As a result of a bacterial stimulus, there is release of serotonin, which acts as a signalling molecule to activate primary sensory neurons to communicate with

the brain and ultimately alter secretory reflexes. Consequently, an ongoing brain–gut interaction is developed, exerting various effects on gut physiology. This relationship has resulted in serotonin potentially being one of the most significant molecules related to the pathophysiology of intestinal disorders such as inflammatory bowel disease and IBS and is also intrinsically linked to the anxiety and depression associated with such disorders.

If serotonin is in charge of mood and sleep and low levels are associated with the onset of depression, etc., then varying levels of its precursor, tryptophan, are likely to have an effect on available serotonin levels (Heijtz *et al.* 2011). Studies have shown that germ-free rats have depleted levels of tryptophan, but upon administration of certain bacteria, such as bifidobacterial species, tryptophan levels are increased (Desbonnet *et al.* 2008), thus suggesting that bacteria can alter the available serotonin pool and ultimately elicit communication between the gut and the brain. Some microbes, such as *Candida* spp., *Streptococcus* spp., *Escherichia* spp. and *Enterococcus* spp., have been shown to directly produce serotonin (Cryan & Dinan, 2012), although much more research is needed into the impact that this has on the host.

Conclusions

In the last decade, the paradigm that the human genome is the predominant driver of host health has shifted towards a more superorganism-based viewpoint, with the microbiome playing a significant role in influencing host physiology and function. This review has not sought to cover all the areas where there is evidence for a role of the host's microbiota and has unapologetically focused on the gut microbiota, since the gut is the best-studied and most densely populated niche. There are numerous other niches in the human body that are colonised and in which the adapted microbiome interacts with the host, and in due course, these will be explored and their interactions with the host described. We hope to have made it more obvious to the reader that the microbiome needs to be understood in more depth and integrated into the endocrine system as it is being integrated into the immune system. In the future, more 'omic' approaches will further uncover more associations between the human microbiome and the endocrine system, which may be drugable and thus modulated to the benefit of the host.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Author contribution statement

All authors contributed equally to the writing of this manuscript.

Acknowledgements

The authors thank the BBSRC (for funding L S M's studentship) and Knowledge Economy Skills Scholarships (KESS; for funding J M E's studentship).

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Received in final form 3 July 2013

Accepted 5 July 2013

Accepted Preprint published online 5 July 2013