The microbiota and helminths

REVIEW ARTICLE

The microbiota and helminths: sharing the same niche in the human host

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(*Received 30 November 2013; revised 27 February and 1 April 2014; accepted 3 April 2014; first published online 5 June 2014*)

SUMMARY

Human gastrointestinal bacteria often share their environment with parasitic worms, allowing physical and physiological interaction between the two groups. Such associations have the potential to affect host health as well as the bacterial and helminth populations. Although still in its early stages, research on the interaction between the microbiome and parasitic helminths in humans offers the potential to improve health by manipulating the microbiome. Previously, supplementation with various nutritional compounds has been found to increase the abundance of potentially beneficial gut commensal bacteria. Thus, nutritional microbiome manipulation to produce an environment which may decrease malnutrition associated with helminth infection and/or aid host recovery from disease is conceivable. This review discusses the influence of the gut microbiota and helminths on host nutrition and immunity and the subsequent effects on the human host's overall health. It also discusses changes occurring in the microbiota upon helminth infections and the underlying mechanisms leading to these changes. There are still significant knowledge gaps which need to be filled before meaningful progress can be made in translating knowledge from studying the human gut microbiome into therapeutic strategies. Ultimately this review aims to discuss our current knowledge as well as highlight areas requiring further investigation.

Key words: microbiota, helminths, bacteria, nutrition, immunology, co-infection, homoeostasis, public health.

INTRODUCTION

Numerous microbes colonize the tissues and systems of humans such as the skin, gut, mouth and genitals. Most of these microbes are bacterial (Rajilić-Stojanović *et al*. 2007) with smaller numbers of Archaea, fungi, viruses, protozoa and arguably helminths during asymptomatic infections. Within the human gut alone there are around 10^{13}–10^{14} commensal bacterial cells (Gill *et al*. 2006; Ley *et al*. 2006*a*; Sekirov *et al*. 2010) with diverse populations and quantities occupying the jejunum, ileum, caecum and rectum (Hayashi *et al*. 2005). A significant proportion of these species belong to the Gram-positive Firmicutes and Gram-negative Bacteroidetes phyla, with a relatively greater amount of cell turnover and metabolic activity within the Firmicutes (Maurice *et al*. 2013). There are also smaller numbers of the Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia groups (Yatsunenko *et al*. 2012).

There is now a concerted global effort to characterize the gut microbiome of different human populations e.g. The Human Microbiome Consortium, The European Commission's Metagenomics of Human Intestinal Tract Project, The US National Institutes of Health Microbiome Project and The Canadian Microbiome Initiative. Already the predominant and/or medically important bacteria occupying the human gastrointestinal tract and their major function have been characterized (see Table 1). Now the major focus of research is to understand how these different bacterial groups function as a community in the human gut and how changes in the composition of this community impact on the host's health.

The gut flora plays a significant role in human health including the development and maturation of the immune system (Chung *et al*. 2012), the repair of damaged epithelial tissues (Scales and Huffnagle, 2013), the production of new blood vessels (Reinhardt *et al*. 2012) and protection against

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doi:10.1017/S0031182014000699

Table 1. The predominant and/or medically significant bacterial genera represented in the human gut

Phylum	Genus	Description
Bacteroidetes	*Alistipes*	A bile resistant Gram-negative genus, common in the guts of elderly Europeans (Claesson *et al*. 2012)
	Bacteroides	A dominant Gram-negative member of the gut microbiota in Western individuals (Arumugam *et al*. 2011). Dominance related to eating high levels of sugars and animal fats
	Odoribacter	A common genus in the guts of elderly Europeans (Claesson *et al*. 2012). *O. splanchnicus* has the potential to be an opportunistic pathogen of the gut (Göker *et al*. 2011)
	Prevotella	Constitute an appreciable proportion of the intestinal microbiota of Burkinabé children but not Italian children (De Filippo *et al*. 2010). Able to digest complex plant polysaccharides such as xylan and cellulose
	Xylanibacter	A dominant Gram-negative member of the gut microbiota in Western individuals (Arumugam *et al*. 2011). Dominance related to eating high levels of sugars and animal fats
Firmicutes	*Butyrivibrio*	A dominant Gram-positive member of the gut microbiota in Western individuals (Arumugam *et al*. 2011). Dominance related to eating high levels of sugars and animal fats
	Clostridium	A common low abundance member of the gut flora. Contains the common antibiotic treatment-associated pathogen *C. difficile*
	Enterococcus	*E. faecalis* and *E. faecium* are both common members of the gut microbiota
	Eubacterium	Common members of the gut flora. Are significantly reduced in patients with ulcerative colitis (Fite *et al*. 2013)
	Oscillibacter	A common genus in the guts of elderly Europeans (Claesson *et al*. 2012). Members of this genus have also been extracted from the rumen of cattle (Lee *et al*. 2012)
	Peptostreptococcus	Several species are able to infect human hosts, with the most predominant being *P. magnus*. Significantly elevated in patients with colorectal cancer (Wang *et al*. 2011*a*)
	Ruminococcus	Abundant in the human colon. Degrade complex plant polysaccharides (Flint *et al*. 2008)
	Streptococcus	A predominant member of the ileal microbiome (Hayashi *et al*. 2005)
Actinobacteria	*Atopobium*	A common member of the vaginal microbiome which is commonly found in the guts of babies delivered vaginally (Fallani *et al*. 2010). Elevated in children with coeliac disease (Collado *et al*. 2007)
	Bifidobacterium	A predominant bacterium colonizing the infant (van Nimwegen *et al*. 2011). It has been suggested as a probiotic due to its anti-inflammatory properties (Imaoka *et al*. 2008)
	Lactobacillus	Has been suggested as a probiotic due to its anti-inflammatory effect (Macho Fernandez *et al*. 2011). High in abundance in the infant gut (Fallani *et al*. 2010)
	Propionibacterium	Common members of the skin microbiota which also compromise a portion of the infant gut flora (Sharon *et al*. 2013)
Proteobacteria	*Campylobacter*	*C. jejuni* is a major food-borne pathogen
	Enterobacter	Opportunistic pathogens sometimes seen in Crohn's patients (Martinez-Medina *et al*. 2006). More likely to inhabit the gut microbiome of infants delivered by caesarean section (Conroy *et al*. 2009)
	Escherichia	The majority of *Escherichia* are harmless commensals but some strains of *E. coli* can cause severe gastrointestinal illness
	Haemophilus	Contains opportunistic pathogens sometimes seen in Crohn's patients (Martinez-Medina *et al*. 2006)
	Helicobacter	Contains the human gastrointestinal pathogen *H. pylori*
	Klebsiella	Opportunistic pathogens sometimes seen in Crohn's patients (Martinez-Medina *et al*. 2006). More likely to inhabit the gut microbiome of infants delivered by caesarean section (Conroy *et al*. 2009)
	Proteus	Contains opportunistic pathogens sometimes seen in Crohn's patients (Martinez-Medina *et al*. 2006)
	Salmonella	Can cause the infection salmonellosis. Infection can lead to changes in the composition of the gut microbiome including an increase in other Proteobacteria genera (Stecher *et al*. 2007)
	Vibrio	Contains the pathogen *V. cholerae* which has been shown to decrease the proportion of Firmicutes and Bacteroidetes during infection while increasing Proteobacteria genera (Monira *et al*. 2013)
Verrucomicrobia	*Akkermansia*	*A. muciniphila* is currently the only known species of this genus and is common in the gastrointestinal tract (Derrien *et al*. 2008)
Fusobacteria	*Fusobacterium*	Species from this genus are enriched in colorectal carcinomas (Kostic *et al*. 2012) and appendicitis (Swidsinski *et al*. 2012)
Spirochaetes	*Treponema*	A dominant corkscrew-shaped member of the gut microbiota in Western individuals (Arumugam *et al*. 2011). Dominance related to eating high levels of sugars and animal fats

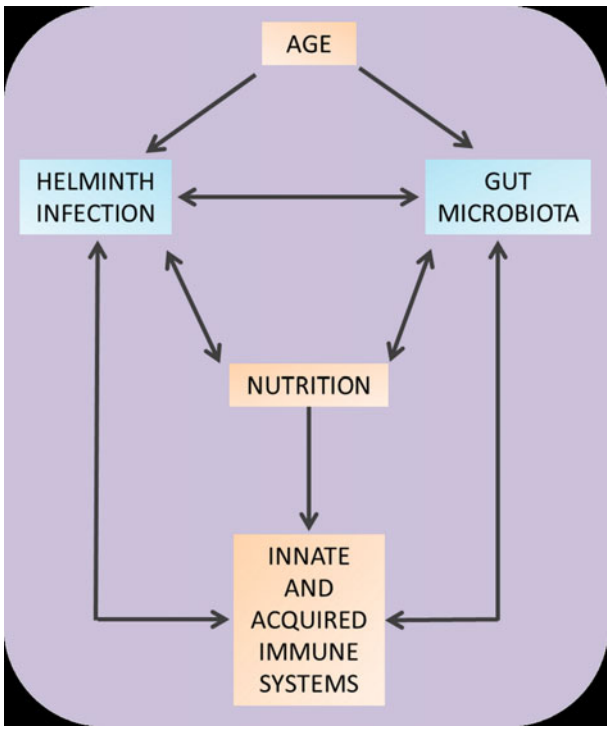

Fig. 1. Potential interactions between the gut microbiota and helminth infection.

pathogens including viruses, bacteria and eukaryotes, termed colonization resistance (Lawley and Walker, 2013). It also plays a role in nutrition by increasing the potential of the host to harvest energy from its diet (Tremaroli and Bäckhed, 2012). For these reasons, it is advantageous for the host to cultivate a large population of commensal gut bacteria. However, correlation studies suggest that not all commensal populations may be advantageous. Different microbial colonizations are associated with disease states in humans including metabolic disorders, autoimmune diseases and allergies, as summarized by Bäckhed *et al*. (2012), although the causal mechanisms/pathways of these relationships have yet to be elucidated. Thus, the 'healthy' host maintains a homoeostatic relationship with the gut microbiota, where infection by pathogens can be prevented while allowing for a diverse community of microorganisms to be present within the gut lumen.

However, other pathogens can co-exist in the gut with the gut microbiota. Of particular importance in tropical countries are helminths. Helminths are eukaryotic, multi-cellular organisms which parasitize a wide range of hosts. Several species are able to cause disease in humans including soil-transmitted helminths such as roundworms, whipworms and hookworms; the schistosomes and food-borne pathogens such as the pork and beef tapeworms. Several mechanisms exist by which these helminths could interact with the microbiota (see Fig. 1), with multi-way interactions between host factors (such as age-related physiological changes and diet), helminth effects (e.g. effects on nutrition and host immune system) and finally microbe effects (also on host immune status and nutrition) and vice versa which may shape both the microbiome landscape and host health.

Helminths are able to modulate the host immune response to allow their survival and also reduce immunopathology (McSorley and Maizels, 2012). However, unlike the gut flora, helminth infection often has a negative impact upon host nutrition (Stephenson *et al*. 2000; Lwanga *et al*. 2012). This is a particular problem in children where malnutrition associated with helminths can lead to fatigue, growth stunting, decreased cognitive development and thereby a general failure to thrive (King and Dangerfield-Cha, 2008).

If possible, the manipulation of the host's microbiota to a composition favourable to nutrition (greater nutrient availability to the host) or helminth clearance could help reduce helminth-related pathology and morbidity. This would have the advantage of being non-invasive and relatively inexpensive as the microbiota is able to be manipulated by nutritional or probiotic supplementation which could accompany standard treatment. Several countries where helminth infections are common already follow the WHO recommendations on supplementation of micronutrients such as vitamin A (see http://www.who.int/nutrition/publications/micronutrients/guidelines//vas_6to59_months/en/), meaning that nutritional supplementation for a healthy microbiome is a feasible consideration for improving paediatric health. Thus, associations between helminths and gut bacteria and their collective impact on human health present an urgent area of research. Harnessing the knowledge from studies on the human gut bacteria and helminths has the potential of providing/cultivating immune therapeutics as well as growth promoters in children exposed to helminthic infection. However, there is still a significant knowledge gap that has to be closed before dietary or immunological therapeutics that target the gut microbiome can be developed and translated to human disease. To this end, the work presented here reviews the current knowledge of the interactions between the gut bacteria and helminths and their potential for manipulation to improve host health in helminth endemic areas, while also highlighting important knowledge gaps and emphasizing the difficulties inherent in microbiome research.

DIVERSITY OF THE HUMAN GUT BACTERIA

A healthy or 'normal' microbiota has yet to be defined and may most likely not be a useful reference point due to the high geographical and temporal variability of bacterial communities between individuals and populations. The search for a 'core microbiome' which most people share has led to the discovery of only 18 bacterial species which were found in all

124 European participants in an initial MetaHIT (Metagenomics of the Human Intestinal Tract project) study (Qin *et al*. 2010). Even within human communities which are closely genetically related and share similar diets, such as the Old Order Amish, there is still variability between individuals (Zupancic *et al*. 2012). In particular, *Prevotella*, which are able to metabolize complex plant carbohydrates, are more abundant in the gut microbiota of Amish farmers than Amish of different occupations, which could be explained by their closeness to livestock whose gut microbiotas tend to be dominated by this bacterial group (Stevenson and Weimer, 2007; Kim and Yu, 2012). The microbiota does not easily lend itself to categorization and variation within even closely related populations is often high at the sub-phylum level (Jeffery *et al*. 2012).

What studies attempting to define a 'healthy' microbiome have suggested is that it is the 'function' rather than the diversity/composition of the microbiota that ultimately influences the host's health. This function has been elucidated by clustering microbiotas in one of three distinct 'enterotypes' based upon their ratios of *Bacteroides*, which primarily derive their energy from fermentation of carbohydrates and proteins, and *Prevotella* and *Ruminococcus* which are able to degrade host mucins (Arumugam *et al*. 2011). This 'classification' into enterotypes has proved useful in simplifying the otherwise diverse characteristics of the individual gut microbiome, but the clustering methodologies to identify the different enterotypes are still being developed (Koren *et al*. 2013).

Thus, for therapeutic interventions, these early studies suggest that focusing on manipulating the function of the gut microbiome could overcome some of the confounding effects of host heterogeneities, as reviewed in Bäckhed *et al*. (2012). Nonetheless, it is important to understand the factors influencing the composition of the gut microbiome. There is now cumulative evidence that the gut microbiome is influenced by several environmental factors including mode of delivery, antibiotic exposure, neonatal nutrition, parent nutrition, stress, age, degree of hygiene, nutrition/diet and co-infections (see review by Brown *et al*. 2012) as detailed below. Understanding the relative impact of these factors on the gut microbiome structure, composition and function is essential to allow predictions of the effects of any intervention aimed at altering the ecology of the gut.

FACTORS GIVING RISE TO THE DIVERSITY OF THE HUMAN GUT BACTERIA

Nutrition/diet

Experimental studies in mice suggest that diet accounts for a larger proportion of the structural variation in gut bacteria compared with genetic factors (57 *vs* 12%; Zhang *et al*. 2010) and several experimental studies (some using gut communities from humans in humanized or germ-free mice) have demonstrated diet-induced dysbiosis in gut bacterial structure (see review by Brown *et al*. 2012). The recent studies demonstrating that the human gut microbiota clusters into functional groups (enterotypes), regardless of host age, nationality, gender and body mass index, suggest that these enterotypes may respond differently to diet.

Gut microbiomes from people consuming a Western diet and from people in rural communities consuming a predominantly plant-based diet were recently compared from a broad range of age groups amongst three populations from rural Venezuela, rural Malawi and the urban USA (Yatsunenko *et al*. 2012). The differences found in the gut microbiota compositions between the two rural communities were found to be far less than the differences between the urban and rural populations. This indicates that nutritional factors are more important in influencing the composition of the gut microbiota than geographical or genetic differences. A previous study by this group also highlighted the importance of environment over genetics by showing that the gut microbiomes of monozygotic twins were as similar to each other as those of dizygotic twins (Turnbaugh *et al*. 2009).

In another study, comparing the gut microbiomes of Italian children and children from rural Burkina Faso (De Filippo *et al*. 2010), Burkinabé children were found to have significantly different microbiotas from children living an Italian urban lifestyle. This included a decrease in the proportion of Bacteroidetes spp. and an increase in Firmicutes spp. in the Italian group (Fig. 2). Obesity has been correlated with changes in the ratios of these two phyla where individuals with low Bacteroidetes to Firmicutes ratios were found to be more likely to be obese (Ley *et al*. 2006*b*). The children from rural Burkina Faso had diets containing higher amounts of starch, fibre and plant polysaccharides and lower amounts of fat and animal proteins than the Italian children. This was thought to be the main reason for gut bacterial differences as the gut microbiomes in children who were still being breast-fed in both groups were relatively similar. Changes were also found between the two populations in the ability of their gut microbiomes to harvest energy from food. Unlike the children fed a Western diet, the Burkinabé children were found to harbour the genera *Xylanibacter, Prevotella, Butyrivibrio* and *Treponema* which are able to degrade xylan and cellulose and are therefore able to utilize more energy from a plant-based diet.

Interestingly, very short-term changes in diet can still impact the composition of the microbiome. Subjects who ate a diet consisting either only of

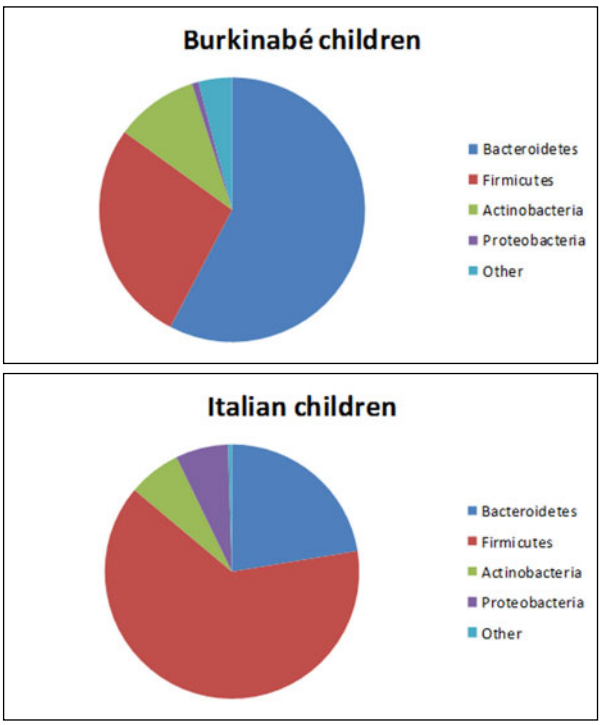

Fig. 2. The composition of the gut microbiota in African (Burkinabé) and European (Italian) children. Data adapted from De Filippo *et al*. (2010) showing the major bacterial phyla composing the gut microbiotas of urban European and rural African children displayed as a pie-chart representation of the total bacterial microbiome.

plants or only of meat/dairy foods over a 5-day period showed significant changes in the proportions of several groups of bacteria in their gastrointestinal tracts (David *et al*. 2014). The meat/dairy group showed more changes in microbiome composition and more closely mirrored the Western urban groups in the above studies than the plant-based diet group, which showed fewer changes and more similarities to the rural groups. This demonstrates that altering the microbiome through diet to treat disease would not necessarily need to take place over a lengthy period of time.

Recently, the relationship between malnutrition and the gut microbiota has been addressed in a study of Malawian children suffering from kwashiorkor (a form of acute malnutrition caused by a lack of dietary protein but sufficient calorie intake) (Smith *et al*. 2013). Significant differences were found between the gut microbiomes in twins where one twin was diagnosed with kwashiorkor and the other twin was healthy. The faecal microbiotas of several pairs of twins were transplanted into gnotobiotic mice (microbe-free mice which are then colonized by a specified microbial community) that were supplied with a Malawian-style diet followed by a standard peanut-based ready to use therapeutic food (RUTF) often used to treat malnutrition in children (Yang *et al*. 2013). Upon returning the kwashiorkor mice to a Malawian-style diet, dietary metabolites were found to fall to pre-treatment levels in 'kwashiorkor' mice while those in 'healthy' mice were higher. This suggests that those with an originally kwashiorkor-associated gut microbiome would benefit less from RUTF treatment than those with a normal microbiome.

There are also significant differences between the gut microbiotas of children who are breast-fed and those who are not (Harmsen *et al*. 2006; Fallani *et al*. 2010). Breast-fed infants develop a less diverse gut microbiota dominated by Bifidobacteria while formula-fed infants develop a more complex bacterial community which more closely resembles that of adults.

Several nutritional supplements have previously been shown to increase the abundance of bacterial species such as *Bifidobacterium* spp. and *Lactobacillus* spp. in humans, which are regularly used as probiotic supplements in their own right. These supplements include the plant polysaccharide inulin (Ramirez-Farias *et al*. 2009), oligosaccharides from human breast milk (Yu *et al*. 2013) and pomegranate extracts (Bialonska *et al*. 2010). Bacterial species which have been associated with colon cancer initiation have also been found to be reduced in humans by the consumption of polydextrose (Costabile *et al*. 2012).

Caution must be taken when introducing new nutritional strategies as dietary supplementation does not always produce a beneficial change in the microbiota. For example, the impact of iron supplementation upon the gut microbiota of rural children from Côte d'Ivoire (Zimmermann *et al*. 2010) was shown to increase the Gram-negative Enterobacteriaceae family of bacteria which contains potentially pathogenic species such as *Salmonella* spp., *Shigella* spp. and *Escherichia coli* while a decrease in the Lactobacilli family was found. This could be explained by the presence of siderophores which are often present amongst the Enterobacteriaceae (Reissbrodt and Rabsch, 1988) but are absent amongst the Lactobacilli, which do not require iron to achieve growth (Archibald, 1983; Pandey *et al*. 1994). Siderophores are secreted by microorganisms in order to sequester iron from the environment and transform it into soluble complexes which can more easily be absorbed into the bacterial cells by active transport (Ferguson *et al*. 1998). Indeed recent studies also show that diet can cause dysbiosis which can lead to inflammatory conditions detrimental to human health, and the possibility of promoting microbes that can prevent or control these inflammatory-mediated diseases, through the manipulation of host diet, is already being discussed (Brown *et al*. 2012).

Age

Microbial colonization of individuals commences from birth with maternal, childhood and

environmental conditions establishing a lifelong effect on the individual's gut microbiome (Collado *et al*. 2010; Gareau *et al*. 2010; Manco *et al*. 2010). In general, there is heterogeneity in the infant gut microbiome within the first months, stabilizing with a mix of the major bacterial phyla as previously described; the next changes occur when the infant is weaned, with the microbiome composition remaining relatively stable for life after the age of about 3 (Palmer *et al*. 2007; Yatsunenko *et al*. 2012). A study comparing the gut microbiotas of infants (3 weeks to 10 months), adults (25–45 years) and the elderly (70–90 years) eating a Western diet (Mariat *et al*. 2009) found significant differences between the three age groups. The average ratios of Firmicutes to Bacteroidetes in the elderly and infants were found to be more similar to each other than when either group was compared with adults. It has also been found that when comparing the diversity between children and adults, the variation between children's microbiotas within the same population tends to be larger than that of adults regardless of geography (Yatsunenko *et al*. 2012).

Environment

One of the few studies conducted in an African population recently showed that different species of hosts sharing the same environment shared the different bacterial taxa present in their guts, as sampled by faecal samples collected from humans, cattle and semi-captive chimpanzees (Ellis *et al*. 2013). As already discussed, environmental factors are thought to significantly influence the gut microbiome structure. As more research is conducted it will become clearer which environmental factors can be more readily manipulated for improved host health.

Co-infections

In a healthy individual, the gut microbiota is able to protect the host against several gut pathogens due to colonization resistance which is maintained by multiple factors. Any invading gut pathogen must compete with the gut microbiota for available nutrients. This has been shown to be a significant factor in the inability of pathogens such as *Clostridium difficile* to cause disease in a non-antibiotic treated host (Britton and Young, 2012). The microbiota is also able to metabolize polysaccharides present in the gut environment into short chain fatty acids (Breznak and Kane, 1990; Louis and Flint, 2009; Hosseini *et al*. 2011) whose production can lead to reduced host deaths during *E. coli* infection (Fukuda *et al*. 2011) and the down-regulation of virulence genes located in the *Salmonella* pathogenicity island 1 (Gantois *et al*. 2006). The production of these fatty acids also leads to a decreased pH which is less well tolerated by pathogens than by the normal gut flora (Cherrington *et al*. 1991). The overall reduction in available oxygen by microbial metabolism in the gut can also lead to an unfavourable environment for facultatively anaerobic pathogens such as the Enterobacteriaceae (Altier, 2005), in comparison to the majority of the gut flora which are obligate anaerobes (Marteau *et al*. 2001). Apart from other bacteria, there are several parasites ranging from viruses, fungi, protozoans and helminths that can share the gastro-intestinal niche with bacteria (McKenna *et al*. 2008; Parfrey *et al*. 2011; Hoffmann *et al*. 2013). Their life history and clinical management can affect the composition and structure of the gut microbiome (Khoruts *et al*. 2010; Dethlefsen and Relman, 2011). This review focuses on helminth parasites.

HELMINTHS OCCUPYING THE GASTROINTESTINAL TRACT AND SURROUNDING TISSUES

Helminths from two main phyla, the Nematoda and Platyhelminthes, occupy different niches within the gut for all or part of their life cycle, as is detailed in Table 2. The most important members of the Trematode 'fluke' class of platyhelminths are the schistosomes (Muller, 2001), which cause the disease schistosomiasis. In humans this disease can be caused by several species, predominantly *Schistosoma haematobium* whose adults reside in the bladder venous plexus and *Schistosoma mansoni* and *Schistosoma japonicum* whose adults reside in the mesentery arteries of the intestines. The disease takes either a urogenital form as is the case with *S. haematobium* or a gastrointestinal form in the case of the other two species (Mahmoud, 2001).

The Cestode 'tapeworm' class of platyhelminths also play an important role in human health and several are highly important food-borne pathogens (Dorny *et al*. 2009). The most important species to human health belong to the genus *Taenia*, which includes several pork and beef tapeworms, and the genus *Echinococcus*.

Several nematodes also occupy the human intestinal tract including the soil-transmitted nematodes (geohelminths) which include roundworms, whipworms and hookworms, all of which cumulatively currently infect over 1·5 billion people (World Health Organization, 2012). The most prevalent nematodes are *Trichuris trichiura* (whipworm), *Ascaris lumbricoides* (round worms), *Necator americanus* (hookworms) and *Ancylostoma duodenale* (hookworms) all of which occupy the human intestinal tract (Hotez *et al*. 2008). While infection with these nematodes is often asymptomatic they are also associated with diarrhoea, abdominal pain and malaise during heavier infections and anaemia (hookworm) and intestinal obstruction (*Ascaris* spp.) in extreme cases.

Table 2. Helminths which are able to cause infection in human hosts and share a niche with the gut microbiota

Helminth	Human disease	Human host status	Gut lifecycle stage	Gut niche
Trematodes				
Clonorchis sinensis	Clonorchiasis, Chinese Liver-Fluke	Definitive host	Metacercariae, eggs	Small intestine (especially duodenum)
Fasciolopsis buski	Fasciolopsiasis, Busk's Fluke infection	Definitive host	Adult worms, eggs	Small intestine. Stomach and colon (severe infection)
Fasciola hepatica	Fasciolosis, Liver-Fluke	Definitive host	Metacercariae, eggs	Small intestine (especially duodenum)
Gastrodiscoides hominies	Gastrodiscoidiasis	Definitive host	Metacercariae, adult worms, eggs	Caecum and ascending colon
Heterophyes heterophyes	Heterophyiasis, Dwarf-Fluke Infection	Definitive host	Metacercariae, adult worms, eggs	Jejunum and upper ileum
Metagonimus yokogawai	Metagonimiasis, Yokogawa's Fluke infection	Definitive host	Metacercariae, adult worms, eggs	Jejunum. Rarely in the duodenum, ileum and caecum
Opisthorchis felineus	Opisthorchiasis, Cat Liver-Fluke	Definitive host	Metacercariae, eggs	Small intestine (especially duodenum)
Opisthorchis viverrini	Opisthorchiasis, Southeast Asian Liver-Fluke	Definitive host	Metacercariae, eggs	Small intestine (especially duodenum)
Paragonimus westermani	Paragonimiasis, Oriental Lung-Fluke	Definitive host	Metacercariae, eggs	Small intestine (especially duodenum)
Schistosoma haematobium	Schistosomiasis, Bilharzia	Definitive host	Eggs	Rectum, appendix and lower colon. Upper colon and ileum (severe infection)
Schistosoma mansoni	Schistosomiasis, Bilharzia	Definitive host	Adult worms/eggs	Mesenteric or rectal veins/Gut lumen
Schistosoma japonicum	Schistosomiasis, Bilharzia	Definitive host	Adult worms/eggs	Mesenteric or rectal veins/Gut lumen
Cestodes				
Diphyllobothrium latum	Diphyllobothriasis, Broad Fish Tapeworm	Definitive host	Adult worms, eggs	Head located in small intestine
Echinococcus granulosus	Cystic Echinococcosis	Dead-end host	Eggs, oncosphere	Small intestine
Echinococcus multilocularis	Alveolar Echinococcosis	Dead-end host	Eggs, oncosphere	Small intestine
Echinococcus oligarthus	Polycystic Echinococcosis	Dead-end host	Eggs, oncosphere	Small intestine
Echinococcus vogeli	Polycystic Echinococcosis	Dead-end host	Eggs, oncosphere	Small intestine
Hymenolepis diminuta (rare)[a]	Hymenolepiasis, Rat Tapeworm	Definitive host	Adult worms, eggs	Head located in ileum
Taenia asiatica	Taeniasis	Definitive host	Adult worms, eggs	Head located in ileum
Taenia solium	Taeniasis	Definitive host	Adult worms, eggs	Head located in ileum
Taenia saginata	Taeniasis	Definitive host	Adult worms, eggs	Head located in ileum
Nematodes				
Ancylostoma duodenale	Ancylostomiasis, Hookworm	Definitive host	Adult worms, eggs	Jejunum. Rarely the duodenum and caecum
Anisakis spp.	Anisakiasis or Anisakidosis	Dead end host	Larvae	Stomach wall and occasionally the small intestine and colon walls
Ascaris lumbricoides	Ascariasis	Definitive host	Larvae/Adult worms, eggs	Duodenum/Small intestinal lumen
Enterobius vermicularis	Enterobiasis, Pinworm (US), Threadworm (UK)	Definitive host	Adult worms, eggs	Lumen of caecum and appendix. Rarely the colon and ileum
Necator americanus	Ancylostomiasis, Hookworm	Definitive host	Adult worms, eggs	Jejunum. Rarely the duodenum and caecum
Parastrongylus cantonensis	Parastrongyliasis, Angiostrongyliasis	Dead end host	Larvae	Small intestine. occasionally the appendix or caecum
Parastrongylus costaricensis	Parastrongyliasis, Angiostrongyliasis	Dead end host	Adult	Ileocolic arteries
Oesophagostomum bifurcum[b]	Oesophagostomiasis	Definitive host	Juvenile and adult worms, eggs	Caecum and colon
Strongyloides stercoralis	Strongyloidiasis	Definitive host	Adult female worms, eggs	Mucosa of the small intestine
Ternidens deminutus	False Hookworm infection	Definitive host	Adult worms, eggs	Colon. Occasionally the ileum
Toxocaridae spp.	Toxocariasis, Visceral Larva Migrans	Definitive host	Larvae, eggs	Small intestine
Trichostrongylus spp.	Wire worms	Definitive host	Adult worms, eggs	Wall of the duodenum and jejunum
Trichuris trichiura	Trichuriasis, Whipworm	Definitive host	Adult worms, eggs	Caecum. Occasionally also appendix, rectum and upper colon

[a] Hamrick *et al*. (1990).
[b] Polderman *et al*. (1991).

EPIDEMIOLOGY OF HELMINTH INFECTION AND GUT BACTERIA

As already discussed, the relative effects of the host and environmental factors on the human gut microbiome structure and function are currently under investigation. In comparison, the effects of host and environment on the health impact of helminth infection have been studied for several decades (Gazzinelli *et al*. 2012). Several features of the epidemiology of helminth infections are of relevance in the establishment and maintenance of the gut bacterial structure as well as overall health of the host.

As is detailed above, nutrition/diet is important in the ecology of the gut bacteria. While there is no clear evidence that diet/nutrition makes children susceptible to helminth infection, malnourishment has been suggested to increase susceptibility to disease caused by helminths in children, due to impaired immune responses and a decreased ability to repair damage caused by the parasites (Hall *et al*. 2012). Helminthic diseases have also been linked to generalized malnutrition (Stephenson *et al*. 2000) and reduced host micronutrients such as iron (Gilles *et al*. 1964; Friedman *et al*. 2005) and vitamin A (Friis *et al*. 1996; Haque *et al*. 2010). Several mechanisms by which helminths may cause malnutrition have been suggested including damage to the gut epithelium and anorexia (Symons, 1985). Thus as previously suggested, it may be possible to manipulate the gut microbiome to avoid these pathologies as the gut flora composition is highly linked to nutrition. With more research it may be possible to manipulate the host microbiome through cheap, non-complex nutritional strategies maintained in at-risk human populations. For example, if malnourishment, associated with helminth infection, induces dysbiosis leading to a reduced ability to extract nutrients from food for host absorption, supplementation would be a useful therapeutic tool to accompany standard helminth treatment, particularly in children.

Host age is an important factor in the epidemiology of helminth infection, where infections are typically acquired in childhood and rise to peak in late childhood/early adulthood (Anderson and May, 1992). Levels of environmental contamination influence the rate and level of infection. In some cases, children's first exposure to helminth infection occurs before their microbiotas stabilize and reflect adult gut microbial communities, at around 3 years of age (Yu *et al*. 1995; Odogwu *et al*. 2006; Stothard *et al*. 2013). This provides the potential of the already established helminth infections to affect significantly the structure of the microbial community, as detailed below.

In the case of the schistosomes and some of the nematodes, there is a decline in infection levels which has been attributed to the gradual development of protective acquired immunity (Woolhouse, 1998). The effector responses induced during helminth infection are a complex combination of inflammatory and anti-inflammatory responses. Protective anti-helminth immunity is characterized by a balance between regulatory and effector responses. However, bacterial infections may alter this balance and may indeed skew the responses towards a different effector phenotype (see below). Thus, the time of gut colonization by bacteria relative to helminth colonization may be of importance in determining the health outcome for the host. Already human studies have begun to suggest that gut colonization by nematode infection (*A. lumbricoides*) may be associated with dysbiosis of the gut microbiome (Cooper *et al*. 2013). Of particular interest are those experimental studies suggesting that both history of helminth infection (even in animals that have cleared infection) and helminth infection intensity can affect the gut microbiome ecology (Broadhurst *et al*. 2012; Wu *et al*. 2012).

THE EFFECT OF HELMINTH INFECTION ON GUT BACTERIAL POPULATIONS

The effect of helminth infections on the composition of the gut microbiota has mainly been studied in animal models, specifically *Heligmosomoides polygyrus bakeri* infection in mice and *Trichuris suis* infection in pigs. Significant differences have been observed between the ratios of bacterial families present in the proximal colon of pigs infected with *T. suis* in comparison with controls (Li *et al*. 2012). Several genera demonstrated significant decreases in prevalence upon infection including *Oscillibacter* which is the second most abundant genus in the porcine colon. In contrast, the three genera *Mucispirillum, Paraprevotella* and *Desulfovibrio* all significantly increased in prevalence, although the overall diversity of the porcine colon remained unchanged. These changes were related to differences in the metabolic potential of the gut microbiota between the two groups. Amongst the changes in genes associated with bacterial metabolism were significant decreases in genes relating to carbohydrate metabolism and the biosynthesis of the amino acids lysine, cysteine and methionine upon helminth infection. This finding indicates that during infection the proximal colonic bacteria are less able to utilize carbohydrates effectively. It has also previously been suggested that there is a need for increased sulphur-containing amino acids during infection with intestinal parasites in order to combat parasitic infection (MacRae, 1993), potentially due to decreased cysteine and methionine production by the microbiome.

The changes in the gut microbiome following helminth infection and subsequent clearance were still apparent 53 days post-infection (Wu *et al*. 2012), with significantly higher proportions of *Campylobacter* occurring in pigs that were infected

but did not clear infection compared with those that had been infected but had low worm burdens or were worm free. This agrees with previous findings that *T. suis* infection can exacerbate campylobacteriosis (Rutter and Beer, 1975; Mansfield and Urban, 1996; Shin *et al*. 2004).

In contrast to the above studies where helminths are shown to increase the quantity of a pathogenic bacterial species, investigations in *H. polygyrus bakeri* infection have shown an increase in commensal bacterial species. *Heligmosomoides polygyrus bakeri* infection was examined in two duplicate experiments to attempt to explain the ability of the helminth to ameliorate the symptoms of IBDs in model IL-10 deficient mice inducing chronic colitis (Walk *et al*. 2010). While no significant difference was found in the caecum of infected mice the group did note a significant 1·8-fold increase in bacterial numbers within the ileum where the parasites were located. Infection was also associated with a change in the families of bacteria occupying the ileum, with members of the *Lactobacillaceae* family increasing in both experiments. *The Lactobacillaceae* group has been found to produce reactive oxygen species which inhibit activation of the transcription factor NF-κB in neonatal mouse intestines (Lin *et al*. 2009), reverse intestinal injury (Mañé *et al*. 2009) and offer protection against graft-versus-host disease (Jenq *et al*. 2012). This may lead to a symbiotic relationship between infecting helminths and the microbes to reduce intestinal inflammation. However at this level of bacterial taxonomic hierarchy the mouse gut microbiota is significantly different from the human microbiota (Ley *et al*. 2005) and the study was conducted in a mouse disease model which cannot easily be compared with healthy humans.

It is not necessarily the case that helminths would only influence the microbiota occupying the same niche as them. While *Opisthorchis viverrini* primarily occupies the bile ducts it has been shown to alter the microbiome of hamster colorectal faeces (Plieskatt *et al*. 2013). There have been indications that the gut microbiota is also affected by schistosomiasis infection in both mice and humans as the urinary host metabolites associated with the gut microbiota are changed upon infection (Wang *et al*. 2004; Balog *et al*. 2011). It has also been shown that the absence of a gut microbiome during *S. mansoni* infection in mice significantly reduces the amount of intestinal granulomas and gut inflammation, potentially influencing the ability of the helminth to excrete eggs into the gut lumen (Holzscheiter *et al*. 2014).

The effect of the gut microbiota on the establishment, maintenance and pathology of helminth infections in the gut has mainly been addressed in studies investigating gnotobiotic/germ-free animals (Wescott, 1968; Chang and Wescott, 1972; Johnson and Reid, 1973) and in relation to egg-hatching of *Trichuris muris* (Hayes *et al*. 2010).

Hayes *et al*. compared *T. muris* hatching in eggs incubated with explant from a mouse caecum (upper large intestine) with eggs incubated with separate cultures of *E. coli, Staphylococcus aureus, Salmonella typhimurium, Pseudomonas aeruginosa* and *Saccharomyces cerevisiae* (Hayes *et al*. 2010). All of the tested microbial cultures produced hatching at 37 °C after 2 h, at similar levels to hatching in the mouse caecum, while filtered cultures failed to cause hatching. The importance of bacterial contact with eggs was established with the use of transwells with *E. coli* and *S. cerevisiae* cultures, which when used failed to elicit hatching when pores were too small for passage of cells through to the eggs (0·4 μm). This indicated that the factor affecting egg hatching was unlikely to be a microbially derived part of the supernatant. The study also established the necessity of having an intact bacterial structure in the case of *E. coli* as clustering of green-fluorescent tagged *E. coli* around the poles of the helminth eggs where worms emerge was observed (Preston and Jenkins, 1985), demonstrating that a component of the bacterial cell surface played a role.

The group hypothesized that the Type 1 fimbriae of *E. coli* which bind the cells to surfaces in a mannose-dependent manner may play a role in *T. muris* hatching. While they found that purified Type 1 fimbriae did not elicit hatching, the addition of mannose decreased hatching and several other experiments pointed to it playing a key role. However, it is unlikely that this is the only mechanism at play as *S. aureus* and *P. aeruginosa* do not contain these proteins but are still able to induce *T. muris* hatching.

To establish whether the microbiota had an effect *in vivo* the team treated a group of mice with antibiotics and measured the worm-burden 21 days after infection. The worm-burden was found to be significantly decreased and the host's Th2 response was significantly increased with elevated amounts of IL-4 and IL-13. However, the decrease in worm numbers was found not to be caused by this increase in the Th2 response due to decreased worm numbers still occurring in severe combined immunodeficient mice. This study indicates that the absence of the gut microbiota causes a decrease in the helminth's ability to establish infection but does not necessarily decrease its ability to survive within the host.

While the above study did show that the presence of bacterial species played a role in initiating egg-hatching and germ-free/gnotobiotic studies have indicated a relationship between the presence of a microbiome and the ability of helminths to establish chronic infection, the contribution of specific commensal bacterial groups has not currently been addressed. Limited information can therefore be drawn from these studies about how the microbiota interacts with helminth pathogens although they do indicate that colonization resistance by the gut

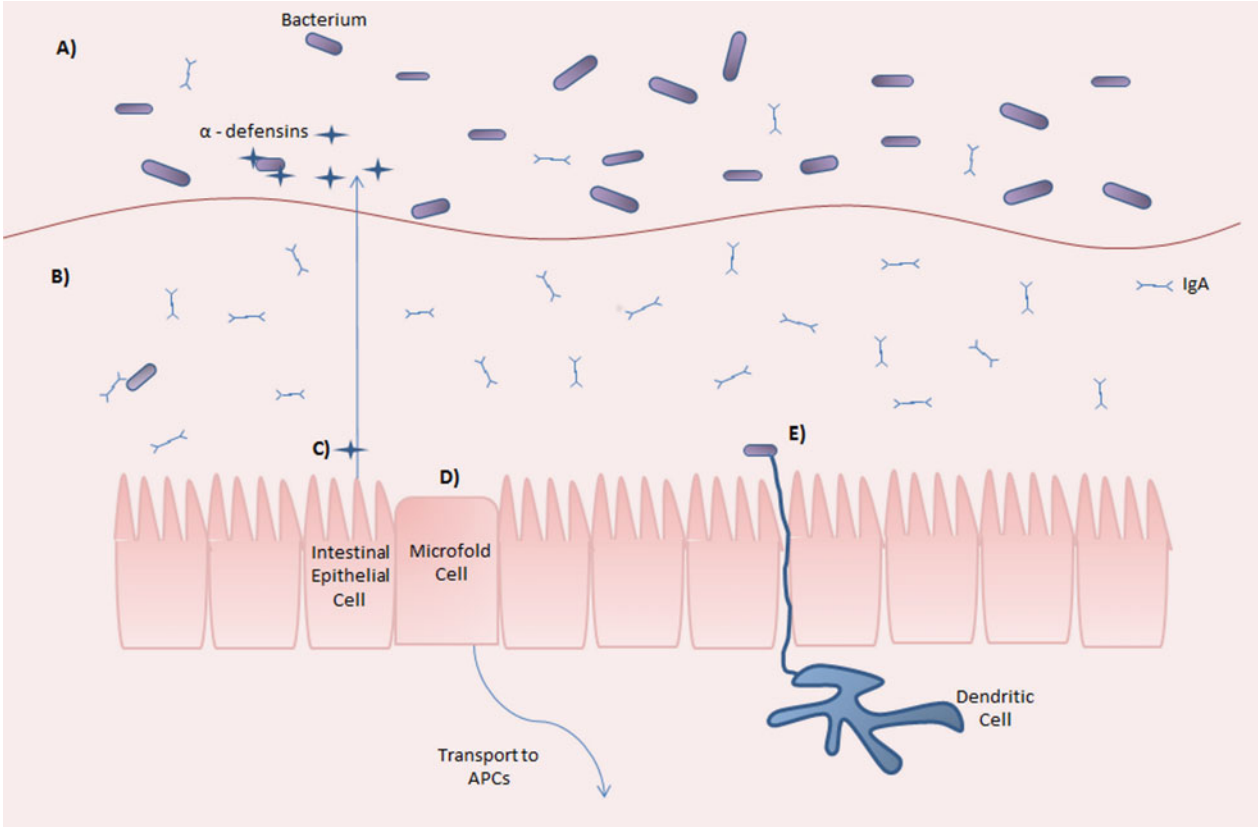

Fig. 3. The interaction of the microbiota with the host immune system. The first layer of protection for the gut epithelium is a double layer of mucus comprising an easily invaded loose outer layer with low quantities of IgA where the majority of the gut microbiome resides (A) and a denser layer containing larger amounts of IgA which lies next to the epithelium and is less conducive to microbial growth (B) (McAuley *et al*. 2007). Intestinal epithelial cells also secrete a large amount of antimicrobial peptides called defensins (C) which broadly act upon bacteria, fungi and some enveloped viruses to increase the permeability of their membranes (Ganz, 2003). The gut constantly samples the surrounding microbial communities via microfold cells (D), contained within specialized Peyer's patches, and lymphoid follicles which sample the surrounding antigens and microbes and transport them to the sub-epithelial dome which contains many antigen-presenting cells. Dendritic cells sample microbes from within the gut lumen (E) (Niess and Reinecker, 2005), and contain pattern recognition receptors that can detect a wide variety of microbe-associated molecular patterns.

microbiome may not play a role in preventing these helminth infections.

THE EFFECTS OF GUT BACTERIA AND HELMINTHS ON THE HOST IMMUNE SYSTEM

A potential mechanism by which helminth infection could alter the gut microbiota composition is its effect upon the host immune system, which could disrupt the homeostatic relationship established between the gut flora and the host.

The majority of bacteria present within the intestines are commensals which despite their large numbers do not cause disease, nor do they generate a predominantly pro-inflammatory environment (Chinen and Rudensky, 2012). This is true despite the presence of pattern recognition receptors (PRRs) within the intestinal epithelium, which recognize broadly distributed bacterial antigens and are able to initiate an inflammatory response to bacterial cells (Philpott and Girardin, 2004). Pathogenic bacteria also often produce molecular factors which are not present in commensal microbes, which can induce specific immune responses (Franchi *et al*. 2012; Larsen *et al*. 2012; Rizzetto *et al*. 2012).

The host gut is able to create a degree of separation between its immune cells and the gut flora by maintaining a dense mucus layer which separates most of the commensal bacteria from the gut epithelium (Fig. 3). However, this mechanism is insufficient to explain the lack of a pathology associated with commensal bacteria as cells lining the epithelium are constantly sampling microbes from within the lumen. The gut microbiota have been found to inhibit NF-κB activation (Kelly *et al*. 2004; Kumar *et al*. 2007; Kaci *et al*. 2011; Lakhdari *et al*. 2011) and in a non-diseased state it has been noted that intestinal epithelial cells express few lipopolysaccharide recognizing molecules such as Toll-like receptor (TLR) co-receptor CD14, TLR2 and TLR4 (Abreu *et al*. 2001). This suggests that the immune response to gut commensal bacteria is low when pathogenic bacteria are not present or that there

is a reduced ability to initiate responses through innate receptors.

Individual bacterial species also possess mechanisms to induce an anti-inflammatory response which may help to reduce immunopathology related to the gut bacterial flora. These include the human commensal bacteria *Bacteroides fragilis* (Round and Mazmanian, 2010), *Faecalibacterium prausnitzii* (Sokol *et al*. 2008), several *Lactobacillus* spp. (Jenq *et al*. 2012; Shimazu *et al*. 2012; van Baarlen *et al*. 2013) and *Bifidobacterium* spp. (Imaoka *et al*. 2008; Khokhlova *et al*. 2012).

It has also been suggested that diet-dependent nutrients and metabolites produced by the gut microbiota can have an immunomodulatory effect. This has been reviewed recently in some detail (Brestoff and Artis, 2013). The microbiota has been implicated in the production of secondary bile acids (Sayin *et al*. 2013) which interact with monocytes and macrophages to produce an anti-inflammatory response via the G protein-coupled bile acid receptor 1 (Wang *et al*. 2011*b*) and the nuclear receptor subfamily 1, group H, member 4 (Attinkara *et al*. 2012). Various other compounds produced by the microbiota influence the development and/or regulation of the immune system such as essential amino acids, short chain fatty acids and vitamins (Jose and Good, 1973; Chandra, 1992; Gill *et al*. 2006; Maslowski *et al*. 2009; LeBlanc *et al*. 2013).

The avoidance of inflammation by the microbiota helps maintain the homoeostasis of the gut and helminths reinforce this stability by excreting/secreting anti-inflammatory molecules. As a result, helminths and their products are being investigated as potential therapies for inflammatory bowel diseases (IBDs). Several trials of *T. suis* treatment have been carried out for IBDs in humans (Summers *et al*. 2005*a*,*b*) which have shown positive results. The hookworm *N. americanus* has also been tested as a therapy for IBDs (Croese *et al*. 2006; Feary *et al*. 2010; Daveson *et al*. 2011) and has been separately shown to alter the gut microbiota in Syrian hamsters (Wang *et al*. 2009).

Mechanisms by which helminths decrease the immune response to bacterial antigens

Several mechanisms have been suggested for how helminths are able to reduce the immune response to bacterial antigens translocating across the gut epithelium during infection. Schistosomiasis infections have been linked to an increase in B-cell expression of Toll-like receptors specific for Gram-negative (TLR4) and Gram-positive (TLR2) bacteria where TLR4 in this case causes an anti-inflammatory response in humans (Onguru *et al*. 2011). This heightened expression of TLR2 and TLR4 has also been observed in epithelial cells in rats infected with the tapeworm *Hymenolepis diminuta* (Kosik-Bogacka *et al*. 2012). TLR mediated targeting of bacterial antigens has also been studied during nematode infection, with an up-regulation of TLR2, TLR4 and TLR9 observed in *H. polygyrus bakeri* infection in mice (Friberg *et al*. 2013).

It is also possible that helminths could impact the immune response to gut bacterial antigens through their induction of specific T-cell responses. Helminth infection is usually characterized by a strong T helper 2 cell (Th2) type response characterized by an increase in IL-4, IL-5 and IL-13; the expansion of CD4+ Th2 cells, eosinophils, mast cells, basophils and alternatively activated macrophages and an increased secretion of IgE (Anthony *et al*. 2007). In contrast, antibacterial immune responses tend to be dominated by a T helper 1 (Th1) cell type response characterized by increased levels of IFN-γ and IL-2 (Lorvik *et al*. 2013). Helminths also decrease the amount of bacterial translocation across the gut epithelium through the induction of a Th2 type response which leads to faster tissue healing (Chen *et al*. 2012) and thereby fewer bacterial antigens coming into contact with immune cells.

An antibacterial immune response has been observed during several helminth infections including a model of hookworm infections in mice (*Nippostrongylus brasiliensis*) which has been shown to stimulate mast cells to increase their innate responses to bacteria by the induction of IL-4 (Sutherland *et al*. 2011). In *T. muris* infection in mice, expression of mouse angiogenin 4 (a goblet cell derived antimicrobial peptide) was found to be increased (Forman *et al*. 2012), indicating a targeted immune response to bacteria during infection.

IL-22 has also been implicated in the induction of an antimicrobial response during helminth infections (Leung and Loke, 2013). This cytokine is produced by a variety of immune cells, both innate and adaptive (Sabat *et al*. 2013), and regulates the production of numerous antimicrobial peptides (Wolk *et al*. 2004; Liang *et al*. 2006). The lack of IL-22 has been implicated in more severe pathologies of several bacterial infections including infections with *Citrobacter rodentium* (Zheng *et al*. 2008) and *Salmonella enterica* (Schulz *et al*. 2008). It has been noted that during helminth treatment for inflammatory bowel diseases, both *N. americanus* excretory proteins (NaES) (McSorley *et al*. 2011) and *T. trichiura* (Broadhurst *et al*. 2010) caused an increase in IL-22 expression, although no difference was observed between IL-22 deficient and wild-type mice infected with *S. mansoni* (Wilson *et al*. 2010), indicating that IL-22 does not play a significant role during schistosomiasis.

This evidence points to a significant increase in the immune response to bacterial antigens upon helminth infection, which may potentially lead to changes in the gut microbiota composition in infected individuals. While this would not

necessarily negatively affect host health, depending upon the bacterial species affected it could cause a decrease in host nutrition or lead to bacterial disease.

CONCLUSIONS/FUTURE DIRECTIONS

Experimental studies show that helminths influence the composition of the microbiota during infection and that this is mediated through different mechanisms including alteration of immunological and metabolic pathways. Helminth infection may result in changes in the ability of the host to extract nutrients from their diet, particularly in malnourished children, and could also affect the numbers of potentially pathogenic bacteria within the gut, causing bacterial co-infection.

Currently there is a paucity of data on the interactions between the microbiota and helminths in humans, but this should soon change with increasing technologies and tools to carry out more large-scale and detailed human studies.

With more understanding of how modern living and medical interventions (e.g. use of antibiotics) have affected the human immune system and the role played by helminths and the gut microbiome (and the mechanisms/pathways involved) in maintaining immune and metabolic homoeostasis, it may be possible to manipulate the microbiota in order to reduce morbidity (e.g. malnutrition) and pathology caused by helminth infection and metabolic diseases arising from dysbiosis of the gut microbiome. Although the realization of this prospect is far from immediate, it presents an exciting prospect that warrants further investigation.

ACKNOWLEDGEMENTS

The authors would like to thank the Parasite Immunoepidemiology Group and Julien Sindt, both at the University of Edinburgh, for their feedback during the writing of this review.

FINANCIAL SUPPORT

The review was prepared as part of laboratory studies which were funded by the Thrasher Research Fund (www.thrasherresearch.org) and the University of Edinburgh.

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