Evolution, human-microbe interactions and life history plasticity

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Abstract

A bacterium was a component of the ancestor of all eukaryotic cells, and much of the human genome originated in microorganisms. Today, all vertebrates harbour large communities of microorganisms (microbiota), particularly in the gut, while at least 20% of the small molecules in human blood are products of the microbiota. Changing human lifestyles and medical practices are disturbing the content and diversity of the microbiota, while simultaneously reducing our exposures to the "Old Infections" and to organisms from the natural environment with which we co-evolved. Meanwhile population growth is increasing exposures to novel pathogens, particularly the crowd infections that were not part of our evolutionary history. Thus some microbes have co-evolved with us, and play crucial roles in our physiology and metabolism, whereas others are entirely intrusive. Our metabolism therefore manifests a tug-of-war between managing beneficial microbes, excluding detrimental ones, and channeling as much energy as is available into other essential functions (growth, maintenance, reproduction). This tug-of-war shapes the passage of each individual through life history 'decision nodes' (how fast to grow, when to mature, how long to live). We describe how changing microbiota and changing microbial exposures are contributing to the dysregulation of metabolic and immune pathways that are involved in the contemporary increases in chronic inflammatory, metabolic and psychiatric disorders. We then discuss how human behaviour is modifying the evolution of pathogens and endangering our efforts to combat them. Finally we suggest how medical practices might change to exploit human-microbe co-evolution and its role in life history plasticity.

Introduction: Humans as products of their evolutionary history

Since the evolution of cellular life (~3.8 billion years ago, bya) the biosphere has been dominated by the Bacteria, Archaea, and eukaryotic microbes.[1] A consideration of the major milestones in evolution, and their relationship to the microbial world can provide insight into the position of humans in the history and diversity of the biosphere. Animal, plant, and fungal life exist as a patina on this microscopic landscape and represent a very minor portion of the biosphere's diversity. We humans live in a microbial world, and this has shaped all aspects of our biology (Figure 1).[2] Here we review how some microbes have co-evolved with us and constitute crucial components of our physiology and metabolism, whereas others such as the more recently evolved "Crowd infections" are new consequences of our changing lifestyles. Our metabolism must therefore achieve optimal allocation of energy to multiple competing functions. The activity of the immune system is energy-intensive, but we have to manage beneficial microbes such as microbiota and exclude detrimental ones while simultaneously providing energy for other essential functions such as growth, maintenance, sexual maturation, reproduction and brain activity. Our behavior, changing lifestyles and medical efforts shape these consequences. This paper aims to explore these issues from a microbiological point of view.

Evolution of eukaryotes

The early biosphere was inhabited only by Bacteria and Archaea.[3] Then about 1.5 bya the eukaryotic cell came on the scene. Existing data suggest that this new cell type arose as the result of an endosymbiotic event in which an alpha-proteobacterium gave rise to the mitochondrion. Interestingly molecular signatures provide evidence that this event occurred only once in evolution; i.e., all eukaryotes have mitochondria derived from that original endosymbiotic incident.[4] The radiation of microbial eukaryotes was accompanied by a vast expansion of genome size and increase in metabolic efficiency.[4] About 540-520 mya, nearly one million years later, the Cambrian 'explosion' resulted in the appearance of nearly all of the ~38 animal phyla.

Evolution of vertebrates and their microbial partners

Although we tend to think of them as much younger, vertebrates came on the scene early in the evolution of animals, at ~500 mya, only about 20-30 my following the major radiation of the animal kingdom.[5] Using new genomic tools, bioinformaticians have resolved the trajectory of evolution leading to humans into a series of 19 steps in which, with each successive step, new genes arise.[6] This analysis provides evidence that ~65% of our genes originated with the Bacteria, Archaea, and unicellular eukaryotes (Figure 1), including those genes that enabled animal-microbe interactions. Thus all vertebrates harbor complex communities of microbial partners that probably necessitated the evolution of a complex adaptive immune system.[7] Biologists have traditionally defined vertebrates as a group with neural crest tissue and 10 organ systems. Actually, the microbiota (the naturally-occurring set of microorganisms that inhabit body organs, especially the gut) is considered a newly recognized 11th vertebrate organ system (Figure 2) that influences all the others, and communicates with them through the metabolome (the collection of metabolites). A significant percentage of the metabolic products in human blood is microbial in origin. This startling finding reveals to us that each cell of the body that is serviced by blood is now, and has been over evolutionary time, influenced by microbes. Consequently the signature of microbes can be found in all aspects of human biology, from our molecular makeup to such central functions as our sleep cycles, circadian rhythms,[8] and mental health.[9] Thus an individual vertebrate is a "holobiont" composed of multiple different microbes and macrobes (bionts) in symbiotic relationships. Organisms that can switch between mutualistic and pathogenic relationships are often known as pathobionts.

Other components of the microbiota

While this review focuses on bacteria, which are the most studied, the microbiota also contains fungi, sometimes protozoa and helminths and always far more viruses than bacteria or archaea. Many of these viruses are phages that may influence the composition of the bacterial microbiota. A recent study has revealed large variations in the rates of turnover of gut bacteria, and suggests that this can be as relevant clinically as absolute abundance.[10] Interestingly the loss of bacterial biodiversity that is seen in Crohn's disease and ulcerative colitis is accompanied by an increase in the taxonomic complexity of the bacteriophages.[11] Moreover bacteriophages mediate horizontal transfer of virulence factors (cholera, pertussis and shiga toxin) and antibiotic resistance.
The gut also contains a variety of eukaryotic viruses that can influence the local immune system and therefore, the microbiota. Following a norovirus infection some individuals develop a long-term distortion of the microbiota with reduced Bacteroidetes and increased *Escherichia coli*.[12] Similarly some persistent norovirus strains infect Paneth cells bearing a human Crohn's disease susceptibility gene *(ATG16L1)* and drive an abnormal gene transcription pattern that in turn leads to susceptibility to inflammation driven by the microbiota, or experimentally, by dextran sulphate.[13]

Microbiota and life history plasticity

The microbiota influences development of most organ systems,[2] including the immune system, and modulates metabolism and development as summarized in Table 1 and supplementary online Table 1s. Evolutionary biologists consider that life-history variables (such as litter size, birth weight, age at sexual maturity, adult weight and height) can be crucial developmental adaptations to a changing environment.[14, 15] Such changes can occur stepwise over several generations.[15] Epigenetic and developmental mechanisms are invoked to explain these generational effects, but stepwise changes in the relationship between the immune system and the microbiotas provide an additional explanation. An altered microbiota will drive changes in the immune system and in epigenetic programming, leading to further changes in the immune system and microbiota in the next generation, and so on. In reality the microbiota should be considered part of the epigenetic inheritance of the infant and a potential mediator of life history plasticity. For example, sex steroids are conjugated with sulphate or glucuronide in the liver and secreted into the gut. These conjugated forms are mostly lost in the faeces, but enzymes expressed by the microbiota can alter the balance of metabolites, and also deconjugate these so that they are reabsorbed. In a mouse model, transfer of adult male gut microbiota to immature females resulted in elevated testosterone in the female recipients.[16] These processes are sensitive to modulation of the microbiota by antibiotics.[17] In post-menopausal women the ratio of estrogen metabolites relevant to breast cancer risk was found to correlate with composition and diversity of the microbiota.[18] Large changes in the microbiota that occur during pregnancy probably modulate the endocrinological changes that occur.[19]

Co-regulation of immune system and metabolism

The gut microbiota defends against pathogen colonisation by production of anti-microbial substances, occupation of ecological niches, nutrient competition, reinforcement of intestinal barrier function and enhancement of IgA secretion. Some microbiota-derived signals (Figure 3), notably those that signal via ''metabolite-sensing'' G-protein-coupled receptors (GPCR) or by inhibiting histone deacetylase (HDAC) and so driving epigenetic changes, are equally relevant to metabolism and to immunoregulation.[20] This close link might be due to the large metabolic costs of immune responses that therefore need coordinated regulation of energy harvest. There is evidence for a critical window of opportunity during early life when an appropriate and diverse microbiota must be

present to allow correct setting of metabolic[21] and immune system pathways.[22] The microorganisms in the human gut are well-adapted to this environment and are mainly from two dominant phyla: Firmicutes and Bacteroidetes. Diet is a major factor in shaping the gut microbiota.[23] Diets rich in fat and protein enrich bacteria belonging to Bacteroides, whereas diets rich in fibre increase the abundance of Prevotella, which are the two dominant genera within Bacteroidetes.[23, 24] Accordingly, one major difference between the microbiome and the human genome is that the microbiome changes to a much larger extent than the human genome over the course of a lifetime and can contribute to life history plasticity. Such changes can have severe consequences. For example, one reason that the malnutrition of kwashiorkor is difficult to reverse is the presence of a grossly abnormal gut microbiome that is not easily corrected and that fails to promte growth.[25] Interestingly, sialylated milk oligosaccharides act via the infant microbiota to promote growth and mitigate effects of malnutrition.[26]

However in large areas of the world obesity rather than malnutrition is a growing problem and compelling evidence suggests that the gut microbiota is contibuting to energy harvest from our diet.[27, 28] These points emphasise the importance of the microbiota in life history plasticity and energy budgeting.

Metabolism of macronutrients may require the coordination of processes encoded by the human genome and the microbiome.[27] For example the gut microbiota plays an essential role in disposal of cholesterol from the body by affecting host bile acid metabolism. Cholesterol is oxidized in the liver to primary conjugated bile acids which are released into the small intestine. The primary bile acids are metabolized by microbiota into more hydrophobic secondary bile acids such as deoxycholic acid and lithocholoic acid, which can be secreted in the feces.[28] Importantly, both primary and secondary bile acids are agonists for host receptors including both GPCRs such as TGR5 and nuclear hormone receptors such as FXR-α, both important regulators of host metabolism. So gut microbiota may contribute to host metabolism and physiology by modulating cell signaling through FXR and other receptors.[29]
The gut microbiota also contributes to the synthesis of trimethylamines generated from choline and carnitine, which are further oxidized to trimethylamineoxide (TMAO) by flavin monooxygenases in the liver.[30, 31] Serum levels of TMAO are strongly correlated with cardiovascular events and may provide a mechanism by which the gut microbiota contributes to cardiovascular disease (CVD).[32] Importantly, the gut microbiota can acquire new genes and functions through horizontal gene transfer (HGT) in order, for example, to adapt to dietary components and thus contribute to human adaptability.[33, 34] Enzymes accquired by HGT from marine bacteria enable Japanese gut microbiota to metabolize seaweed carbohydrates.[33] The natural environment thus constitutes a resource of genetic diversity for the microbiota though the time scale of such adaptation is unclear.[34, 35] There is some controversial evidence that HGT from bacteria and protists to vertebrates has also occurred, usually involving genes encoding metabolic enzymes.[36]

Microbes and immune system function

Because studies of the adaptive immune system began as an outgrowth of pathogenic microbiology, its principal function had been thought to be for 'non-self' recognition, and its evolution driven by pathogenesis. With our recent awareness of the sustained interactions with a coevolved microbiota, immunologists are beginning to entertain the possibility that the principal evolutionary pressure on the adaptive vertebrate immune system has been the requirement to manage and maintain a stable microbiota (Figure 2), while simultaneously protecting from infection (discussed in [37]). Thus the immune system co-evolved with the microbiota that provides crucial signals driving

development,[38, 39] expansion, level of background activation,[40] and memory repertoire,[41] of the lymphoid system. Crucially in the context of this review, the microbiota (and other organisms discussed below) needed to be tolerated (i.e. integrated within the ecosystem) and so co-evolved to drive expansion of the regulatory pathways that control the immune system and prevent it from attacking inappropriate targets, and also shut it down when inflammation is not required.

But humans evolved as a grassland species in small hunter-gatherer groups and the various microbiotas were obviously not the only organisms with which they co-evolved (Table 1 and supplementary online Table 1s). They were also exposed to microorganisms from animals and the natural environment, some of which were probably able to establish themselves within the microbiotas.[42-44] Moreover, approximately 1/3 of the gut microbiota are spore-forming so it can be hypothesized that wherever humans have lived, the environment has been seeded with spores of human gut-adapted strains.[44] Finally, there were certain "Old Infections" that could regulate the immune system and establish long-term infections and so were able to survive within small hunter-gatherer groups.[45] Ancestral forms of *M. tuberculosis*, *Helicobacter pylori*, gut helminths and blood nematodes all fall into this category. Analysis of the phylogenetic trees of *M. tuberculosis* and *H. pylori* and comparison with the human phylogenetic tree reveal how these Old Infections co-evolved and spread with human populations.[45-47] *H. pylori* is a notable example of a pathobiont that can contribute to immunoregulation, but under some circumstances triggers stomach ulcers and influences oesophageal cancer.[48] Some of the most studied mechanisms involved in immunoregulation by microbiota and Old Infections (we use helminths and *Helicobacter pylori* as an illustration of the latter) are described in Figure 3.[42, 49-56]

Lack of microbes and immune system dysfunction

Modern life, especially in urban settings, causes human microbial experience to deviate from the co-evolved pattern (Table 1 and supplementary online Table 1s). Modern medicine eliminates the Old Infections, at least from the wealthier sections of society. Meanwhile trans-generational transmission of the microbiota is compromised by caesarean deliveries,[57] lack of breast-feeding,[58] and inappropriate hygiene.[59] The microbiota is further disrupted by antibiotics,[60, 61] and by dietary changes.[20, 24] Finally contact with the natural world is diminished, particularly in people of low socioeconomic status living in modern cities.[62, 63]

Since these microbial exposures have evolved critical roles in setting up immunoregulatory circuits (Figure 3),[42, 49-56] diminished exposure to them is likely to be relevant to the sharp rise in chronic inflammatory disorders (allergies, autoimmunity and inflammatory bowel disease) in high-income settings.[64] These are all at least partly disorders of immunoregulation, where the immune system is attacking inappropriate targets. From a life history point of view this can be seen as erroneous allocation of energy to the immune system. Disturbed immunoregulation also plays a role in long-term background inflammation manifested as persistently raised C-reactive protein (CRP) in the absence of detectable medical cause. In terms of energy budgeting and life history strategy the maintenance of unnecessary background inflammation is a misdirection of resources, but raised CRP is common in high-income countries,[65] and is associated over time with increased risk of cardiovascular disease, metabolic syndrome, insulin resistance, obesity,[66, 67] some inflammation-associated types of cancer,[68, 69] and depression.[44, 70] Major depressive disorder (MDD) is rapidly becoming the major cause of human disability so it deserves emphasis here.[71] Some studies suggest that the prevalence is increasing though this is difficult to prove.[72] It is clear however that some cases of depression (and of some other psychiatric disorders) are associated with raised background levels of biomarkers of inflammation (Table 2 and supplementary online Table 2s), and commonly associated with chronic inflammatory disorders.[73] Similarly some cases of depression, especially

those cases that are accompanied by raised biomarkers of inflammation, can benefit clinically from anti-inflammatory therapies.[74, 75] Recent data show that raised C-reactive protein (CRP) or Interleukin-6 (IL-6) can *predict* later depression in children,[76] and adults,[77] and also *predict* later susceptibility to Post-Traumatic Stress Disorder (PTSD) in army recruits.[78] New non-invasive techniques can demonstrate the presence of inflammation in the brains of depressed individuals.[79] Similarly inflammation during pregnancy, from any cause, increases the risk of autism and schizophrenia in the child.[80] It is hypothesized that diminished immunoregulation can increase this risk further.[81] Tables 2 and 2s list examples of links between chronic inflammatory states and psychiatric disease, using where possible examples where the role of infection or disturbed microbiota in the immunoregulatory dysfunction is apparent.

Crowd Infections

Although the inhabitants of modern cities have distorted microbiota, encounter fewer of the Old Infections and have less contact with the natural environment, they are increasingly exposed to the more recently evolved "crowd infections". These affected humans much later as populations grew, and settled into large communities. "Crowd infections" can only persist in populations larger than around 300,000 because people are infectious for only a short time before they recover (or die), and they are subsequently immune for a very long time. These infections tend to occur in epidemic waves with dramatic outbreaks in which large numbers of susceptible people become infectious and ill. Then the number of cases falls, as dramatically as it once rose. In small populations stochastic effects can cause "fade-outs" where one last infectious individual recovers before passing infection to anyone else. Infection can be reintroduced to subsequent generations by the arrival of an infected person. Measles is the canonical example of a "crowd infection" and the pattern outlined above was documented by Bartlett[82, 83] and Black[84] in classic papers from the pre-vaccination era. Other infectious diseases (including those of childhood) also have these behaviours. When might these crowd infections have evolved? Phylogenetic analyses attempt to date the emergence of measles by studying the sequence divergence between measles and its two closest relatives, rinderpest and peste-des-petits-ruminants. One such study dates the emergence of measles to the 11th or 12th century.[85] However others suggest that purifying selection can mask the more ancient origins of RNA viruses and suggest that measles emerged a few hundred years earlier.[86] Either way, the increasing prevalence of crowd infections as populations increased will have diverted energy resources (particularly in childhood) towards the immune system, and away from growth, whereas more recently, measures such as vaccines will be enabling the use of these resources for growth. These recently evolved "crowd infections" were clearly not major drivers of the evolution of the mechanisms that regulate the immune system, and epidemiological studies show that unlike microbiota and "Old Infections", they do not protect from the chronic inflammatory disorders that are increasing in developed high-income countries.[87-89]

Managing our microbial exposures

Which microbial exposures need to be restored, and how do we do it? Widespread misunderstanding of the current status of the "hygiene hypothesis" is leading to a worrying tendency for the media, and even the medical profession, to suggest the abandonment of hygiene and hand-washing. However a close examination of what we now know indicates that hygiene plays a minor role in the diminishing contact with beneficial microbes, and plays a crucial role in shielding us from the crowd infections.

Microbiota

Behaviours that inhibit transmission of microbiota from mother to child were discussed earlier and we need to limit these practices where we can, particularly excessive use of antibiotics in pregnancy or infancy.[21] But once the microbiota is established, maintaining it is largely a matter of diet.[20] A diverse diet helps to maintain the biodiversity of the gut microbiota, which decreases in institutionalized individuals.[90] Plant polyphenols such as flavonoids and resveratrol also help to maintain biodiversity.[91] In an animal model, a diet lacking fibre (polysaccharides that are fermented by microbiota rather than by the human host) leads to progressive loss of biodiversity of the microbiota, and over several generations, to irreversible extinctions of important species.[92] These findings tend to support studies indicating the health benefits of the "Mediterranean diet".[93] However the complex interactions between the gut microbiota and diet are only just beginning to be unravelled and it is clear that microbiota contribute to metabolic diseases such as obesity, diabetes and CVD,[94-97] as well as to inflammatory diseases and behavioral effects. But we don't yet know whether studying the microbiota can also predict who will develop disease. Nor do we know whether modulating the gut microbiota can provide novel treatments. Interestingly, gastric bypass surgery can lead to rapid metabolic improvement and weight loss, accompanied by changes to the microbiota that might be mediating these effects.[98] Faecal transplantation can be used to treat *Clostridium difficile*-associated colitis and there are indications that such transplantation may also improve metabolic parameters.[99, 100] These findings open up possibilities for using the microbiota as a therapeutic target. We know that the microbiota influences development and life-history plasticity but we do not yet know what is optimal, or how this needs to accommodate differing diets and genetic backgrounds.[101] Much regulatory and clinical work remains to be done.

Organisms from the natural environment

Contact with microbial diversity from animals and the environment appears to explain the fact that exposure to farms, dogs in the home, green space, livestock or animal faeces in early childhood (see Table 1) provide some protection against chronic inflammatory disorders.[62, 65, 102, 103] New evidence indicates that exposure to such organisms via the airways is a critical factor, at least where protection from asthma and hay fever are concerned. Plant and microbial components interact with a range of receptor systems in the airways, including PI3K/Akt/mTOR[104], the aryl hydrocarbon receptor (AhR),[105, 106] Toll-like receptors[107, 108] and pulmonary neuroendocrine cells.[109] The overall effects of these sensors are likely to be immunoregulatory.[104] For example, exposure to bacterial components causes increased expression of A20 (*tnfaip3*) in the airways.[110, 111] This protein inhibits the inflammatory pathway that attracts dendritic cells to the sites of allergen deposition in the airways, and so limits the initiation of the Th2 response.[110] These considerations all lead to the view that we need to design our homes and cities to optimize contact with the natural environment, but they do not suggest the abandonment of hygiene.

Helminths

Do we also need to recover our ancestors' exposure to helminths? This is controversial. In order to persist in small hunter-gatherer groups these organisms needed to minimise potentially fatal host immunopathology by downregulating the host's immune system. Some authors suggest that, like the microbiota, this helminth-mediated immunoregulation might have evolved to become a physiological necessity.[112] However, greatly varying prevalence of infection[113] and the diverse range of immunoregulatory mechanisms exerted by the helminths[49, 114, 115] render the argument for helminth driven evolution of human immune regulation less convincing. Interestingly, there is some evidence that helminth exposure,[116] by driving immunoregulation,[52] is effective in patients with multiple sclerosis in Argentina where helminth infections are common, but results have so far been disappointing using *Trichuris suis* in a high-income setting where the subjects might have been helminth-free for several generations.[117] This might simply mean that *T. suis* is inappropriate. But it is equally possible that immune systems developing in the babies of helminth-infected mothers are epigenetically programmed to require the continuing presence of the relevant helminths, but that this

requirement is lost in subsequent generations. We hope that ongoing clinical trials will resolve this dilemma.

Pathogens, antibiotics and vaccines

While we maintain our exposures to our microbial partners, we will need to continue to combat pathogens, and to understand and conserve the tools we have to control them. Many microbial pathogens have a remarkable capacity for rapid evolution because they have large population sizes, short generation times and high mutation rates. This capacity, combined with large dense human populations and rapid air travel are leading to greatly increased risk of the evolution of novel pathogens, as modeled in detail elsewhere.[118] Meanwhile we may be compromising our reliance on antibiotics and vaccines. Detailed discussion of the evolution of antibiotic resistance and prospects for circumventing it are found in the online supplement, as is an account of vaccine efficacy, and the factors that determine the evolution of vaccine-escape mutants. It is interesting to note that we pay a penalty for losing microbes that our regulatory systems expect, and that we pay another penalty when we meet microbes that cost us energy, but we pay a third penalty if our medical strategies inadvertently make the pathogens more virulent.

Conclusions

Vertebrates are ecosystems (or holobionts) that include the microbiota, and they also receive poorly understood inputs from microbial biodiversity in the natural environment. The flexibility of the microbiota contributes to life history plasticity. The adaptive immune system probably evolved to handle the complex task of "farming" the microbiota, while simultaneously stopping other organisms (i.e. pathogens) from disturbing any component of the ecosystem. Inevitably therefore, infections, whether in the gut or even in the lungs, have profound effects on the composition of the microbiota,[119, 120] and the microbiota have profound effects on the regulation of the immune system (Figure 3). The immune system, metabolism, energy harvest, growth and the gut-brain axis are tightly linked via the microbiota. Perhaps as we increase our understanding of the human ecosystem and of its evolved requirements, and develop targeted hygiene that does not exclude essential organisms, we will learn to modulate our microbial exposures in ways that reduce developmental, inflammatory and infectious disorders with less reliance on anti-inflammatory treatments, antibiotics and vaccines.

Table 1

Microorganisms, metabolism and development *

*an expanded, fully referenced version of this table is available as an online supplement

Microbial signals and organ development.[2, 54]

Short chain fatty acids (SCFA), peptidoglycans, endotoxins, polysaccharide antigen (PSA) from *Bacteroides fragilis* tryptophan metabolites, and other neurochemicals (noradrenaline, dopamine and acetylcholine) and unknown components of the microbial metabolome constitute signals that are involved in development of the gut and lymphoid system, testis, neuroendocrine system, skeleton, kidneys, cardiovascular system and brain

Microbiota, sex hormones & life history plasticity.[17, 18]

- Transfer of microbiota from adult male mice to germ-free females causes a rise in testosterone.
- The composition of the microbiota changes at puberty, pregnancy and the menopause.
- Antibiotic use changes levels of sex steroid metabolites because these are secreted into the gut conjugated to glucuronide or sulphate, and lost in the faeces unless deconjugated by microbial enzymes, which also change the ratios of metabolites
- Composition of microbiota in menopausal women correlates with levels of sex steroid metabolites relevant to breast cancer risk

Western lifestyle and diet.[21, 23, 27]

- Life-style changes (see microbiota section below) distort and limit diversity of the microbiota.
- These effects are compounded by the modern Western diet.
- Obese mothers might transfer inappropriate microbiota to the infant
- Microbiota of obese donors mediates increased energy harvest.
- Microbiota modulates insulin sensitivity and metabolism
- Microbiota influences diurnal rhythms and cyclical variation in activity of metabolic pathways
- Animal models suggest a critical window in early life for correctly setting up metabolic homeostasis

Malnutrition.[25]

- Severe acute malnutrition in infants is associated with delay in the maturation of microbiota towards the adult pattern.
- In Kwashiorkor the microbiota is grossly abnormal and causes weight loss in recipient mice. This abnormal microbiota probably explains why infants with Kwashiorkor are resistant to treatment by dietary supplements.

Burden of infection

- Vaccines and efficient treatment of infections reduce the need for and energy-intensive activity of the immune system. Thus a reduced burden of infections increases resources available for growth

Immune system development and the input of microorganisms

Microbiota.[21, 58-61]

- Caesarean deliveries, lack of breast-feeding and inappropriate hygiene limit transmission of microbiota to baby
- Abnormal microbiota, or microbiota of diminished biodiversity is associated with increased risk of chronic inflammatory disorders, including allergies, autoimmunity and (IBD)
- Intensive antibiotic use in pregnancy or infancy can also disturb the microbiota and is associated with:-
  - chronic inflammatory conditions
  - obesity and metabolic disorders

Old Infections.[49, 51, 116]

- Helminths, *H. pylori* and *M. tuberculosis* are examples of "Old Infections" with which humans co-evolved.
- The "Old infections" could persist in small hunter-gatherer groups by modulating the immune system
- They drive immunoregulatory pathways including increased DCreg and Treg, and act as Treg adjuvants.
- They may protect from chronic inflammatory disorders, including allergies, autoimmunity and IBD

Environmental organisms.[42, 62, 63, 102]

- Perinatal exposures to organisms from farms and dogs correlate with reduced risk of allergic disorders and IBD.
- These exposures drive increased Treg and accelerate maturation of neonatal Th1 response in animals and humans
- Environmental organisms do not necessarily colonise; they might also act as data input to the developing immune system of the gut and airways.
- It is suggested that these mechanisms are also involved in the health benefits of exposure to green space, and to house dust rich in microbial biodiversity

Table 2

Microorganisms, immunoregulation and psychiatric disorders *

*an expanded, *fully referenced* version of this table is available as an online supplement

Animal models.[74, 75, 121]

Germ-free animals
- Abnormal brains, hypothalamo-pituitary-adrenal axes and stress responses. The abnormality is permanent if microbiota is not restored in the early weeks of life.

Effects on behaviour of altered microbiota
- Depleting microbiota with antibiotics or changing microbiota by transfer from a different mouse strain, alters behaviour and expression of neurochemicals in the brain

Stress and microbiota interact
- The microbiota participates in the stress response which is diminished if microbiota are depleted
- Early life or perinatal stress in monkeys and rodents causes long-term changes in the microbiota and maternal prenatal stress does so in humans
- Maternal stress leads to altered microbiota in offspring, that releases metabolites causing autism-like CNS effects in mice

Inflammation
- Induction of maternal inflammation during pregnancy causes abnormal brain development in the foetus, and behavioural changes reminiscent of autism and schizophrenia
- Subthreshold prenatal inflammation and peripubertal stress synergise to cause behavioural and developmental abnormality

Probiotics
- Numerous studies showing behavioural modification by probiotics

Human epidemiology.[73-78, 80]

Raised background inflammation (CRP or IL-6) and psychiatric disorders
- A subset of depressed individuals is known to have raised background CRP.
- Raised background CRP is ***predictive*** of depression in adults examined 12 years after assay of CRP
- Raised IL-6 in children aged 9 predicts psychiatric problems 9 years after assay.
- Raised resting CRP in army recruits was ***predictive*** of susceptibility to PTSD when subsequently exposed to war zones.
- The incidence of autoimmune disorders is increased in veterans with PTSD, implying an immunoregulatory disorder.
- In the Philippines exposure to a microbially rich environment in early life correlates with lower background CRP and lack of rise in CRP in response to stressors.

Inflammation during pregnancy
- Any cause of inflammation (including infections) during pregnancy increases the risk of autism.
- Chronic inflammatory disorders are increased in the families of autistic subjects.
- Raised maternal CRP is associated with an increased risk of autism in the infant.

Human interventions.[74, 75]

Inflammatory cytokines
- Therapeutic administration of Interferon alpha causes depression-like symptoms
- A neutralising antibody to TNF had a therapeutic effect on the subset of depressed individuals with raised background CRP and markers of inflammation.

Probiotics
- Efficacy in irritable bowel syndrome, and can reduce psychological distress in volunteers
- A fermented milk product altered activity in brain regions that control central processing of emotion (fMRI)

Panel KEY POINTS

What we know

- Vertebrates, such as humans, are ecosystems.
- The microbiota and its metabolic products influence development and function of most, probably all organ systems.
- There are crucial windows during infancy when an appropriate microbiota must be in place if metabolic pathways and the immune system are to be correctly set up.
- Diet is a major factor shaping the microbiota.
- We co-evolved with the microbiota, and with organisms that could persist in small hunter-gatherer groups ("Old Infections") and organisms and their genes (by horizontal gene transfer) from the natural environment. The "Crowd Infections" are more recent.
- Microbial inputs are needed for the correct functioning of the immune system.
- Modern lifestyles reduce these microbial inputs, and this is likely to be a factor in the increases in disorders of immunoregulation (allergies, autoimmunity, inflammatory bowel disease), and diseases associated with persistent background inflammation.
- The microbiota influences metabolism and energy extraction from food and so has a role in the current increases in obesity and metabolic syndrome.
- The microbiota is critical in setting diurnal rhythms
- The microbiota influences metabolism and reabsorption of sex steroids and so modulates sex-steroid-dependent aspects of life history plasticity.
- In animal models the microbiota has profound effects on cognition and stress responses (gut-brain axis). Substantial evidence suggests that the same is true in man.

What we need to know

- A more complete and reliable knowledge of the microbiota and its relationship to disease susceptibility. How much are we currently missing?
- The role of other kingdoms in the gut such as fungi and viruses.
- Should the microbiota be regarded as an essential part of "epigenetic" inheritance?
- In addition to the microbiota, what microbial exposures are optimal for health?
- Can we identify and exploit the components of the microbial metabolome that influence human development and health?
- Can we identify and exploit immunomodulatory components of "Old Infections" such as helminths that are now essentially absent from high-income urban populations?
- Does loss of environmental microbial biodiversity due to agrochemicals and monoculture compromise human health by reducing the health benefits of green space?
- Can we modulate the microbiota so as to combat obesity and metabolic syndrome?
- Can such strategies compensate for inappropriate diet?
- Do reduced loads of infection lead to redirection of energy resources towards growth?
- Can we modulate the microbiota so as to combat the chronic inflammatory disorders, and the psychiatric disorders associated with chronic inflammation?
- What strategies do we need to cope with the increasing threat of new Crowd infections?
- Can we protect the efficacy of drugs and vaccines from the evolution of resistance?
- In view of the many biological roles of the microbiota, what are the benefits and dangers of faecal microbiota transplants? How should donors be selected?
- What is the future for probiotics and prebiotics?

Contributors
All authors wrote sections of this report, provided feedback on drafts, and approved the final version.

Declaration of interests
GR, BL, AM and MM-N have no competing interests. FB is a founder and shareholder of Metabogen AB. The authors are responsible for the views expressed in this paper, and they do not necessarily represent the views or policies of the institutions with which they are affiliated.

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Figure legends

Figure 1

The position of *Homo sapiens* in geological time. **A.** Earth's history as a calendar month. The first several weeks of this month were entirely microbial. Only in the last four days do animals and plants enter the microbe-dominated biosphere, and only in the last 30 minutes of the last day do humans appear. **B.** The microbial signature on the human genome.[6]

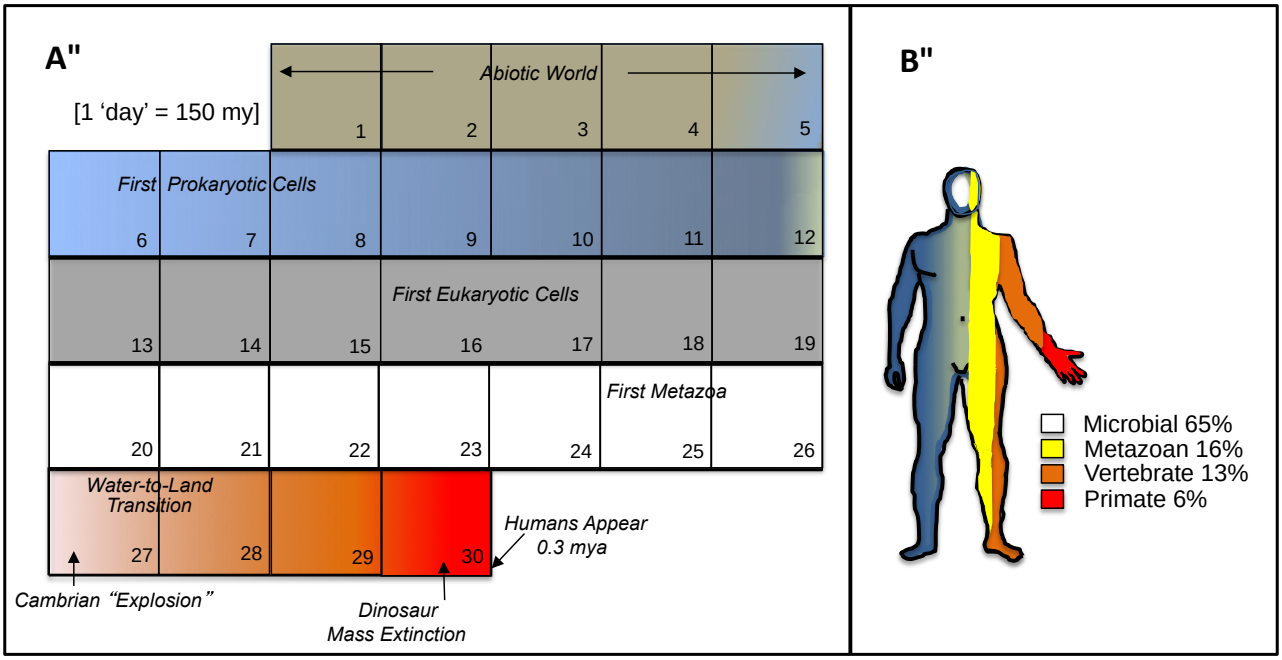


Figure 2

A simplified illustration of the development of the adult human gut microbiota. In the adult this is dominated by two phyla: Bacteroidetes (Bacteroides) and Firmicutes (Clostridium, Faecalibacterium, Eubacterium), which replace the early dominance of Actinobacteria (Bifidobacterium) and Proteobacteria (Escherichia). The windows of opportunity for the correct setting up of the immune system, metabolic system, gut-brain axis and stress responses may occur during the periods of complex change between birth and adulthood. These crucial windows are documented in animal models[21] but not yet in humans.

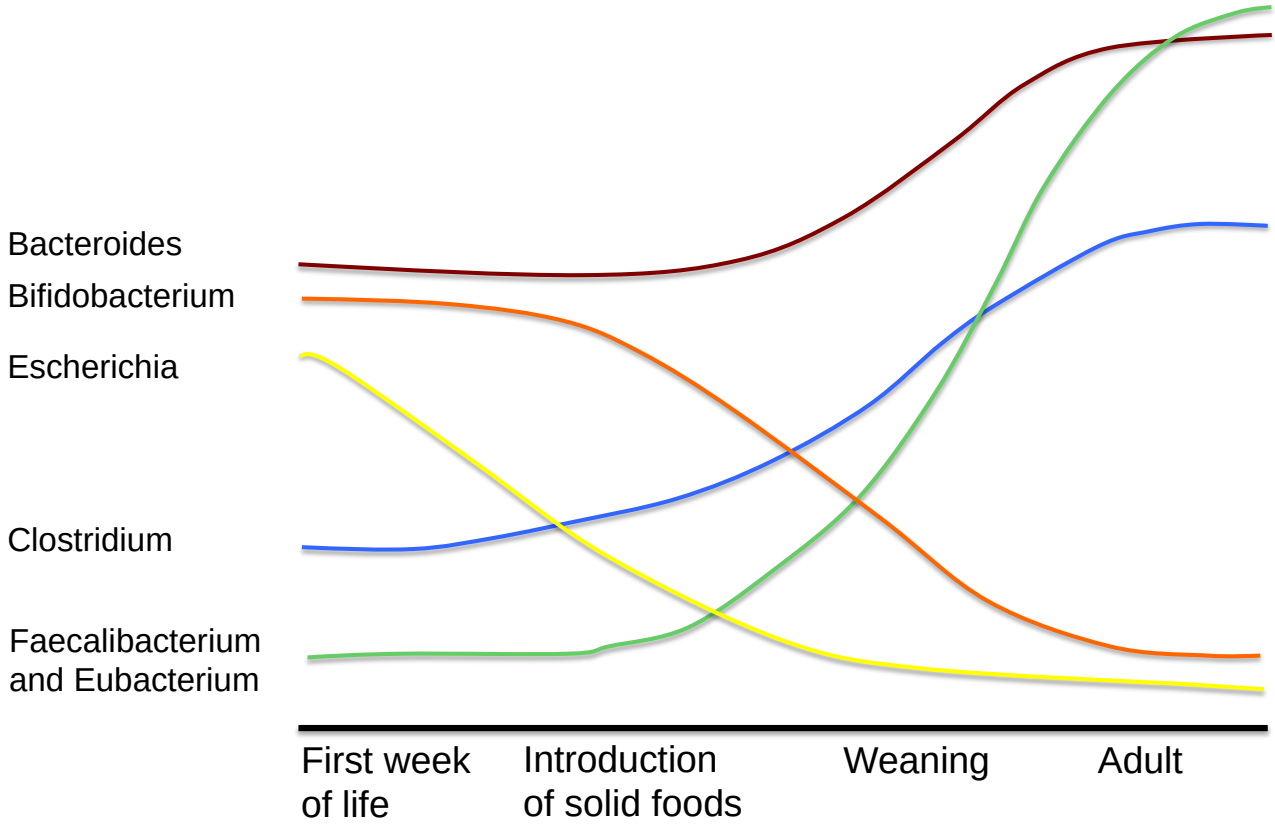
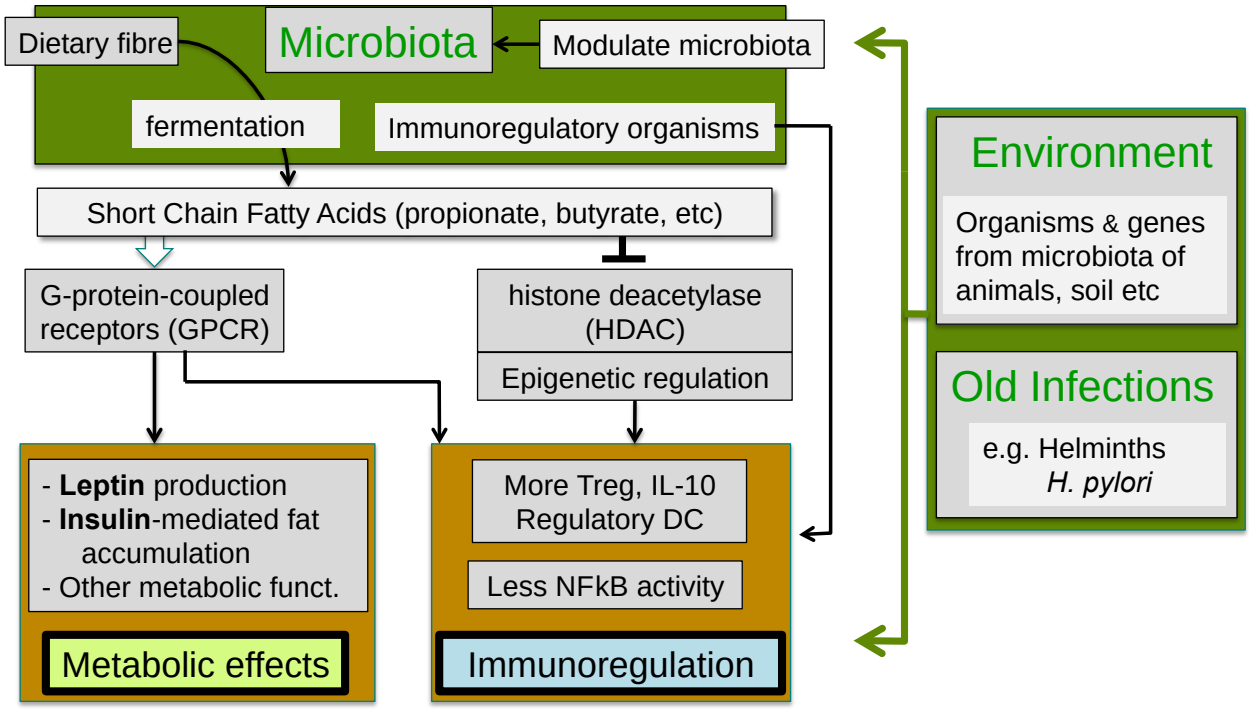


Figure 3

Some of the major pathways involved in immune and metabolic regulation by organisms with which humans co-evolved. Various members of the gut microbiota drive expansion of effector and regulatory T cell populations. An example of an "immunoregulatory organism" defined in mouse models would be *Bacteroides fragilis* which releases a polysaccharide antigen that expands Treg populations. Short chain fatty acids have anti-inflammatory effects and drive epigenetic regulation of the immune system. Helminths can modify the microbiota, drive IL-10 release, alter dendritic cell function and expand Treg populations The contribution of organisms from the natural environment is largely unknown and undocumented, though strongly suggested by epidemiological associations. The Old Infections are largely eliminated by modern medicine, while trans-generational transfer and subsequent maintenance of the microbiota are compromised by modern lifestyles, diets and antibiotics. See main text for details and references.



(Figure 4 has been removed in order to comply with length restrictions)