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How do we benefit from the microorganisms that live within us?

The human body is host to a huge array of micro-organisms, consisting of trillions of bacteria, viruses, fungi, protozoa and other tiny organisms. These organisms are known as microbes and collectively are referred to as the human microbiota. The microbes outnumber human cells ten to one, and inhabit many sites in the human body; the majority of these microbes are primarily bacterial and live in the gut. The human microbiome is the genetic material these microbes harbour [1]. The number of genes in all the microbes in one person's microbiome is 200 times the number of genes in the human genome. Our own genes amount to about 23,000, the genes of the microbial origin can range between 2 to 3 million, however because of their small size the microorganisms make up only about 1 to 3 percent of the body's mass.

Initially very little was known about the complex and dynamic role of the human microbiota in human health and disease, this was in part due to limitations of in vitro microbiological cultivation techniques. It is only in recent years that advances in molecular technology such as polymerase chain reaction (PCR), next generation sequencing (NGS), 16S ribosomal RNA (rRNA) fingerprinting and DNA profiling have revealed the extraordinary diversity of microorganisms and their genetic and metabolic repertoire [2 3]. Organisms can now be identified and their complex physiological roles and interactions are beginning to be understood.

The Human Microbiome Project (HMP) was initiated by the National Institute of Health in 2007 with the aim of identifying and categorising the microbial population in a cohort of healthy humans [5]. They have demonstrated each person is host to more than 500 different microbial species, with every individual person having a unique combination of microbes. Further work using the microbiological data obtained from the HMP and other multinational groups, including the European Union's Metagenomics of the Human Intestinal Tract (MetaHIT) have expanded this work to map the microbes inhabiting humans [6]. Microbes that colonise humans live in a symbiotic relationship that can be commensal, that is they co-exist without harming the host, whilst others have a mutualistic relationship which is beneficial to each other [7 8].

The initiation and development of the human microbiome

The development of the foetus is thought to occur in a sterile environment although recent developments have found bacteria in the placenta, and prenatal exposure to microbes may be a part of in-utero development [2]. The microbial colonisation of the newborn human intestine begins at birth and the infant's gut microbiota have significant implications for normal development as they play a central role in infant nutrition, affecting growth, energy metabolism [9] and the development of the immune system [10 11].

Babies born naturally are exposed to the normal maternal vaginal flora including microbes such as Lactobacillus and Prevotella, the Lactobacilli are the foundation of the baby's microbial population. The gastrointestinal tract is first colonised by facultative anaerobes, this encourages the growth of strict anaerobes, such as Bifidobacterium, Bacteroides and Clostridium. The Bifidobacterium are usually the main organism in early life and they are considered to be the most beneficial for infants [12].

Breast milk contains carbohydrates called oligosaccharides that babies cannot digest, however specific bacteria such as Bifidobacterium infantis can break down the sugars in breast milk and utilise this carbohydrate. Bifidobacterium also have been proved to play an important role in the stimulation of growth of other beneficial bacterial species, by optimising the gut environment [13]. As infants develop they acquire more microbes from their more complex diet and from the environment, family and close contacts. By the age of three the child has acquired its own unique individual profile of microbes whilst at the same time the young child is developing its immune, metabolic, and neurological processes. It is thought that gut microbiota provide signals and stimuli that enhance the development and function of the immune system [14]. Babies born by caesarean section are not exposed

to the normal vaginal flora, but are colonised by bacteria found on the mother's skin and other sources, by bacteria such as Staphylococcus, Corynebacterium and Propionibacterium, but not the mother's Lactobacilli. It is recognised that the mode of delivery has a significant effect on the development of the beneficial gut microbe Bifidobacterium in neonates with significantly higher levels and a more diverse population of the beneficial Bifidobacterium in vaginally delivered babies [12] compared with babies born by caesarean section. Women are also often given antibiotics at the time of delivery and this can alter both the mother's microbial profile and change the developing infant's gut microbiota. This is of concern as infants born by caesarean section or exposed to antibiotics are at risk of developing metabolic, inflammatory and immunological diseases due to disruption of normal gut microbiota at a critical developmental time [15].

The gastrointestinal tract microbiota

The gastrointestinal microbiota is the complex community of microbes living in the gastrointestinal tract, they are important in mediating host defence, immune development and nutritional state. In the stomach and small intestine, relatively few species of bacteria are generally present. The colon, in contrast, has the most bacteria and may be classified into six major families and numerous sub-groups, with nearly 3,500 species identified so far. Nearly a third of the gut microbes are from the Bacteroides family with also plentiful Lactobacilli and Bifidobacteria. Twin studies have shown that, although there is a heritable component to gut microbiota, environmental factors related to diet, drugs and geographical location are larger determinants of the gut microbiota composition [16 17].
The oral cavity is a nutrient rich environment where microbes can flourish. Some streptococci and other oral microbes guard against opportunistic bacteria.
The acidic stomach contents inhibit most microbial proliferation, however the acidic-tolerant Helicobacter pylori and also some other bacteria such as Prevotella can reside in this hostile environment. H. Pylori is regarded as a pathogen as it is associated with peptic ulcer disease and gastric cancer, the overall evidence strongly supports the benefits of eradication of H. pylori in symptomatic patients [18]. Concern has been expressed over a potential negative outcome associated with H. pylori eradication with the risk of provoking oesophageal diseases. It has been suggested that colonisation with a particular strain of H. Pylori known as Cag-positive appears to be protective against more proximal diseases of the gastrointestinal tract including gastro-oesophageal reflux, associated oesophagitis and oesophageal cancer, the incidence of which is increasing [19 20]. It has also been proposed that childhood colonisation with H. pylori is associated with reduced risks of asthma, allergic rhinitis and allergy [21 22].
The gastrointestinal microbiota protects against pathogenic invasion. This defence acts through three mechanisms: a) the direct inhibition of pathogen growth by microbiota-derived substances, b) nutrient depletion by microbiota growth and c) microbiota-induced stimulation of immune responses [23]. Most food is digested and absorbed in the small intestine. Residual food that passes into the large intestine is mostly indigestible. The bacterial fermentation of non-digestible substrates such as dietary fibre and the endogenous intestinal mucus transforms complex carbohydrates into short-chain fatty acids (SCFA) and gases [24].
SCFA are fatty acids with fewer than 6 carbon atoms. These SCFA fulfil a plethora of roles and are critical to our health. The concentration of these SCFA varies between individuals and may relate to microbial population, diet and intestinal transit time. The major SCFAs produced are acetate, propionate and butyrate.
Butyrate is the main energy source for human colonocytes, the cells that line the colonic wall, without this energy source the colonocytes can die. Butyrate can activate intestinal gluconeogenesis, having beneficial glucose and energy homeostasis [25]. Butyrate also has anti-inflammatory properties due to its ability to inhibit synthesis of cytokines and eliminating sodium urate. It further enhances the defensive features of the gut by activating mucin secretion and promoting colonic motility. This modulation of intestinal inflammation is beneficial in terms of gut maintenance, reducing the risk of inflammatory bowel disease and protecting against colorectal cancer [26]. Propionate is transferred to

the liver, where it regulates gluconeogenesis and satiety signalling through interactions with the gut fatty acid receptors [25].
Acetate is the most abundant SCFA and an essential metabolite for the growth of bacteria, it is absorbed and is used in lipid biosynthesis, and also may play a role in central appetite regulation [27].
Gut microbial enzymes contribute to bile acid metabolism generating unconjugated and secondary bile acids. Bile acid derivatives are emerging as important signals that are involved in weight control, cholesterol regulation and fat storage.
The gut microbiota diversity and metabolic function are thought to play an important role in the development of obesity and related metabolic disorders. Excess SCFA can provide up to 10% of our daily calorific needs [25]. Abundance of the microbe Akkermansia muciniphila, a mucin-degrading bacterium, is associated with a healthier metabolic status with greater improvement in glucose homeostasis, blood lipids and body fat composition [28 29].
Gut microbes are also involved in vitamin synthesis, especially the essential nutrient vitamin B12. The enzymes required for B12 synthesis are possessed by gut bacteria but not by plants or animals [30]. Several bacteria that are common in the colon (Bacteroides, Bifidobacterium, and Enterococcus) are known to synthesize other vitamins. Thiamine, folate, biotin, riboflavin, and panthothenic acid are water-soluble vitamins that are plentiful in the diet, but they are also synthesized by gut bacteria. It has been estimated that up to half of the daily Vitamin K requirement is provided by gut bacteria [31].
Gut bacteria are integral to the production of some neurotransmitters that interact directly with the brain, and these can also act via the vagus nerve. Bifidobacterium produces tryptophan, the precursor of serotonin, this neurotransmitter is involved in sleep, appetite, memory and the release of gastrointestinal secretions. Other microbes are involved in the production of dopamine, acetylcholine, gamma-aminobutyric acid and butyrate all of which are neuroactive chemicals, which may have a role in cognition, mood, appetite, sleep, and motivation [32].
The gut microbiome has the capability to perform a wide range of metabolic reactions on drugs and their metabolites. This can be advantageous and allow drug activation, the production of anti-microbial compounds and inactivation of toxins. The most important reactions involve enzymes like reductases and hydoxylases which can biotransform products. The drug sulphasalazine, prescribed in ulcerative colitis, utilises the microbial enzyme azoreductase to release the active form 5-aminosalicylic acid which has anti-inflammatory properties [2]. Microbes also affect how individuals respond to drugs, including how cancer patients respond to chemotherapy.

The respiratory tract microbiota

The upper respiratory tract contains an abundant and diverse microbiota. The lower respiratory tract, by contrast, is scantily populated with microbes. The organisms that have been identified in the lower respiratory tract include species of Bacteroides, Firmicutes and Proteobacteria. It is not clear, at this time, if these small populations of bacteria constitute a normal resident microbiota, and what their role is. These microbes may facilitate movement of air through the lung, secrete protective mucus, and fortify the pulmonary immune system.

The genital tract microbiota

Unlike the gastrointestinal tract the genital microbial flora varies significantly between men and women. In women bacteria colonise and protect the vagina. The vaginal microbiota play a significant role in preventing bacterial vaginosis, yeast infections, sexually transmitted infections, urinary tract infections and HIV infection [33 34 35 36]. The Lactobacillus species predominate in the human vagina. These microbes are mainly anaerobic and they provide a natural barrier against pathogens, through competitive exclusion. They also prevent infection by lowering the pH through lactic acid production and producing bacteriostatic and bactericidal compounds [37].

During pregnancy the vaginal flora changes, normally the lactobacilli flourish and this establishes a symbiotic microbial community, which may prevent potential pathogens from colonising and disrupting the resident microbiota [7]. Disruption of this normal low diverse microbial population may relate to complications in pregnancy. Preterm rupture of the fetal membranes, which precedes 30% of all spontaneous preterm births, is associated with a change in the vaginal microbiota with a high vaginal bacterial diversity prior to rupture [38]. This is associated with increased neonatal mortality and long-term morbidity.

Conclusion

The human microbiome is an integral component of the human body. A variety of microbes exist throughout the human body and it is clear that microbes have major implications for human health. Different parts of the body all have very different distinct communities of microbes, and each individual will have their own unique microbiota profile. Advances in technology have allowed the study of these microbes and composition at different sites.

The diversity of the microbiome with relative abundance of different species is important. During the first three years of life the gut microbiome is evolving and the foundation of a healthy gut microbiota has long term implications. The gut microbiome then stabilises but it continues to be affected by many factors including exposure to organisms, diet, drugs, pregnancy and environmental factors. The profile of organisms within the gut fluctuates during different stages of life, especially during pregnancy and birth. During old age the number and diversity of organisms declines.

The gut microbes play an important role in defence in preventing colonisation by harmful organisms. They enhance and stimulate the immune system, and may influence the host to susceptibility to immune-mediated diseases and disorders. The gut microbiota has a role in providing nutrients and detoxifying harmful compounds. The colonic microbes produce SCFA from the breakdown of carbohydrates and protein in fibre providing extra calories. These SCFA also have a diverse role and are major mediators in linking nutrition, gut microbiota, physiology and pathology. There are dual reciprocal effects between the microbiome and the host metabolism. The microbiota is both affected by the host's metabolic state as well as affecting host metabolism, in terms of energy homeostasis, fat storage, and hormonal regulation. The disturbance of the gut microbiota has been linked to many diseases, including diabetes, autism, obesity and autoimmune disease. Whereas it is advantageous to have a wide diversity of microbiota in the gut, increased bacterial diversity of the vaginal flora may be associated with disease.

Prebiotics, such as fibre inulin, and probiotics (i.e. Lactobacillus) have been advocated in order to maintain a healthy gut microbiome. With advances in medical technology and further research it may be possible that favourably altering the gut microbiota can provide new treatment options. More work is needed to obtain clinical evidence to determine how microbes are linked to human health preferably with human interventional randomised controlled trials. Microbial manipulation strategies, including human nutrition, targeted antibiotics and microbial supplementation, may provide new strategies for disease prevention and treatments.

(2434 words)

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