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Gut Flora - The Hidden Organ

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Introduction

From the prehistoric period, prebiotics and/or probiotics and their precursors have been an essential component of the human diet. Over time, medical research has proved that these molecules are essential in maintaining the gut microflora, which in turn is a positive health asset to the structure and function of the human intestinal mucosa. For example, the potential pathogens of the gut like *Escherichia coli* and *Bacillus subtilis* are kept under control by hydrogen peroxide, diacetyl and reuterin produced by this friendly commensal microflora [1] that co-evolved and has sustained through ages with human evolution. The collective metabolic activity, the complex immune system regulatory mechanism, protection from inflammatory and infectious disease process and the higher number of commensal microflora (~10 fold) than human cells have led researchers to attribute to the gut flora, the status of a hidden metabolic organ of the organism in which it exists [2] This review is intended with the objective of revisiting the long-lost importance of the gut microflora as 'an organ within an organ'.

The Diverse Human Gut Microbiota

Human immune function, metabolism, physiology and nutrition are influenced by over 100 trillion gut microbial cells [3]. Our gut harbors ~1000 bacterial spp. and contains 100-fold more genes than human genome, hence the term 'superorganism' to the gut microflora-inclusive-human [4,5]. The microbiota composition varies along the length of gut depending upon availability of oxygen, nutrients, pH etc. and also differs across lumen, mucosa, and crypt-villus axis. Thus, the digestive system of human has varying number of bacteria ranging from 10^1 per gram in stomach (this relatively low count is due to the presence of gastric acid) to 10^{11} to 10^{12} bacteria per gram in the large intestine (this high count is because of the presence of 60% of fecal mass in this segment of the GIT) [6,7]. Although in the past it was difficult to isolate and identify most of the bacteria in the gut, collective efforts of HMP Consortium [8,9], MetaHIT [5,10], and high throughput technologies like HTS, microbial culturomics, metagenomics, metatranscriptomics, metaproteomics and metabolomics have led to the description of novel 174 bacterial species of the gut [4,11-15]. Majority of human intestinal bacteria consist of Fermicute (60%), Bacteroides (20%), Actinobacterium and Enterobacteriaceae [16]. Interestingly, the gut microbiome encodes genes for supplementary metabolic pathways which are absent in the human genome. Thus, human gut health and immunity are incomplete without the contribution from microbiome.

The infant gut is sterile at birth or may contain negligible number of microbes [17]. However, the gut gets rapidly colonized with microflora shortly after birth. Although the early colonizers are predominantly enterobacteria and bifidobacteria [18], the colonization pattern varies from infant to infant depending on feeding type, mode of delivery, use of antibiotics/prebiotics/probiotics and hygiene level [19]. On comparison, significant differences in gut microbiota of European children (EU) and that of children of rural African village of Burkina Faso (BF) were observed, where the diet was high in fiber content. BF children showed unique abundance of bacteria from the genus *Prevotella* and *Xylanibacter*, known to contain a set of bacterial genes for cellulose and xylan hydrolysis, completely lacking in the EU children [20]. New colonization and hence pattern alterations continue till the first 2 years of life following which the microbiome stabilizes and remains stable in adulthood [21]. Decline of the microbiome is seen in early old age and continues through late old age (>65 years) (This explains why old age is characterized by low-grade bowel inflammation) [22,23], 16S rDNA analyzes show that adult gut microbiome has a large inter-individual microbial diversity or in other words, only a minor phylogenetic similarity between individuals. However, the core microbial population in an individual remains constant throughout his / her life [24,25].

Gut Flora - The Hidden Organ?

There are various evidences which prove the claim that the

gut flora is not merely a layer of microbes on the surface of the uni-layered gut epithelium, all ready to scavenge the undigested dietary constituents in the lumen. Rather, it is a hidden metabolic organ vital to the functioning of its housing organ, the gut. Experimental germ-free gut animals are shown to have reduced digestive enzyme activity and nutrient uptake, low muscle wall thickness, less vasculature/angiogenesis, underdeveloped enteric nervous system, high infection rate, low innate (cytokines, Peyer's patches) and adaptive (serum immunoglobulin, intraepithelial lymphocytes) immunity [26]. However, reintroduction of microflora to the GI lumen in these animals has promptly reversed the altered function of the mucosal immune system [27]. Gut microbiota also produces short-chain fatty acids (propionic acid, acetic acid, butyric acid) and helps in easy uptake of glucose even with less caloric intake. However, in an individual to sustain a normal body weight, a greater caloric intake is essential in the absence of microflora [28]. Thus, gut microbiota seems to influence weight gain and fat deposition in the host and hence influences the risk to developing obesity. Few studies have pointed at changes in microbiota composition after bariatric surgery (indicated for severe obesity), suggesting links between gut microbiota switch and metabolic improvement observed after surgery [10]. The association of specific microbial populations to lean and obese mice/human is still an ongoing debate [4] that is in want of conclusive results, but that's a different story altogether and shall not be discussed in length here.

The "Hidden Organ" Behind the Successful Host Defence System

One of the major contributions of the gut microflora is to modulate the human immune system. The human gut mucosal surface consists of 3 types of immunosensory cells viz, surface enterocytes (secrete cytokines and chemokines), M cells (luminal antigen transporters), and interstitial dendritic cells (gatekeeper-transporters to mesenteric lymph node). The microflora communicates with these immunosensory cells and decides the regulation of further immune response [2]. The microbes have molecular/pathogen associated molecular patterns/ligands (PAMP's) on their surface that interact with pattern recognition receptors (PRR'S). This molecular interaction is the major basis for differentiating between pathogenic and commensal microbiota. The immunosensory PRRs are nucleotide binding oligomerization domains (NOD) and toll-like receptors (TLRs). These PRRs provide intracellular signal to host immune cells whether to activate (pathogenic microbe) or suppress (commensal microbe) the inflammatory responses [29]. In addition, most commensal microbiomes inhibit the nuclear factor (NF)-κβ (inflammatory response inducer) [30]. Few commensal microbes are hypo-responsive to immune modulation through the mechanism of molecular mimicry [31].

Another benefit of the gut microbiota is that it synthesizes and secretes bacteriocins which are a protection for the gut from pathogenic bacteria. Bacteriocins are either narrow or broad spectrum antimicrobial peptides synthesized ribosomally [32]. Gut pathogens like *C. difficile* [19], *Campylobacter jejuni* [33], *Salmonella* spp. [34] and *Listeria monocytogenes* [35] are kept in check by these bacteriocins. Researchers are focusing on the antimicrobial property of bacteriocins as a therapeutic alternative to conventional antibiotics. In addition, commensal gut microflora like Lactobacilli and bifidobacteria produce abundant amount of acetic acid (pKa = 4.76) and lactic acid (pKa = 3.83) and keep the gut environment pH very low [16]. Such a low pH inhibits the growth of pathogenic bacteria and yeasts, however the commensal flora is resistant to these acids. The yeasts are eliminated easily in acidic condition, but pathogenic bacteria survive due to the active proton pump. However, this survival is short-lived and pathogenic bacteria are gradually eradicated from the gut because they cannot keep up with the ATP supply that is needed for the active pump [36,37].

The role of the human gut microbiome as a hidden organ is further substantiated by the manifestation of several diseases in the absence/alteration of gut flora. Several studies have shown a link between a modification of the human gut microbiota and colorectal cancer (CRC). Increasing evidence shows that gut microbiota manipulation can exert a protective effect against CRC via the production of short-chain fatty acids (SCFAs), inhibition of toxin-producing pathogens, anti-proliferative activity, reduction of aberrant crypt foci and enhanced production of anti-oxidant enzymes and anti-inflammatory responses [38]. Ulcerative colitis (UC) and Crohn's disease (CD) that constitute the inflammatory bowel disease (IBD) are classical examples for abnormal immune responses to the luminal antigen in a susceptible individual [26]. In healthy individuals, immunosensory cells recognize the commensal microflora as a 'self' with increased immune-tolerance. Further studies are warranted to decipher the complex mechanisms of negative selection/deletion, T regulatory cells or anergy involved in this process. It is to be noted that inflammatory, hypersensitivity and autoimmune diseases are becoming more common in developed countries [39]. One argument to this observation by most naturalists is that the inflammatory cells in the human body or the human body's mechanisms to defend against the microbes have been naturally designed and stabilized through generations by the evolutionary process of 'Natural selection' and 'Survival of the fittest'. However, increased human intervention on this process in terms of increased hygiene or sanitization has posed a risk of wiping off of certain microbes, probably most of them the friendly commensals. In effect, protective inflammatory responses are becoming risk factors or what our modern interventions envisage as a 'Friend' has actually turned out to be a 'Foe' or what we envisage as 'The protector' has turned out to be 'the destructor'. A support to this claim comes from a recent animal model study showing beneficial variations in the gut microbiota after feeding high-fiber

diet and acetate supplementation. This protective role of the fiber-diet prevented the development of hypertension and heart failure [40]. Interaction of the intestinal microbes with the innate immune system is a critical epigenetic factor modifying T1D predisposition [41]. Various studies on experimental mice support the hypothesis that colonization by gut microbiota impacts mammalian brain development and subsequent adult behavior by modulating the levels of adreno-corticotrophic hormone (ACTH) [42].

Also, the novel intervention of fecal microbiota transplantation (FMT) has established surprising clinical resolution, especially in the treatment of *Clostridium difficile* infection. FMT replenishes the gut microbiota which is administered in the form of encapsulated lyophilized powder. Noteworthy is the fact that while in USA alone, *C. difficile* infection epidemic affected approximately 300 deaths and 7000 infections per day [43], FMT has successfully cured about 92% of the infection [44]. In the background of a hopefully 'soon to be a past' era when broad spectrum antibiotics have caused significant amount of collateral damage, the high success rate of FMT seems to warrant the role of a harbinger of 'post-antibiotic era' to FMT. However, further research is required to explore to a greater depth, the potential application of FMT as a resurrection tool for the gut microflora.

In conclusion, the presence of friendly commensals in the gut serves a purpose, a greater one indeed, of biochemically protecting the host mucosal tissue and immunologically strengthening the host defence system against pathogens invading the lumen. Although fecal microbial transplantation seems to bring in an era of hope against the havoc caused on the gut flora by the indiscriminate use of antibiotics, one needs to keep in mind that fecal microbial transplantation is nothing different from any intervention. It is therefore only with caution that one needs to exercise its application. The spirit of the rule should be to protect the natural tendencies and natural habitat of the enteric microflora, the 'forgotten inner organ' within the gut which is itself an organ that is a doorway leading into the human body.

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