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Review Article

GUT FLORA-ROLE IN IMMUNITY AND DISEASE

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ABSTRACT

Bacteria make up most of the flora in the colon and 60% of dry mass of feces. Upon review this article stated that the relationship between gut flora and humans is not merely commensal, but rather a symbiotic relationship. Gut flora might also be an essential factor in certain pathological disorders, including multisystem organ failure, colon cancer and inflammatory bowel diseases. Nevertheless, bacteria are also useful in promotion of human health. Probiotics and prebiotics also known to have a role in prevention or treatment of some diseases. However, additional studies are needed to show that prebiotics can directly or indirectly stimulate intestinal host defenses. If this can be demonstrated prebiotics can be used as dietary supplement to stimulate a balanced effective mucosal immune system in newborns and infants.

INTRODUCTION

Gut flora consists of microorganisms that live in the digestive tracts of animals and is the largest reservoir of human flora. The digestive system is home to trillions of micro organisms colonising the gut making an amazing ecosystem all living together in harmony. A healthy adult has about 2kg of these bacteria in the gut. All these bacteria live in a highly organised micro-world with certain species predominating and controlling others. They play a number of vital roles in the body and without them we probably would not survive.

TYPES OF FLORA

Essential or beneficial flora: These bacteria are referred to as our indigenous friendly bacteria. The main members of this group are: *Bifidobacteria (Bifidobacterium bifidum), Lactobacteria (Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus rhamnosus), Propionobacteria, Peptostreptococci and Enterococci*. They are the housekeepers of the gut, without them your gut cannot be healthy. These bacteria fulfil a myriad of vital functions in the body. They provide a natural barrier and protect us against all sorts of invaders, bacteria, parasites, fungi, viruses, toxins etc. that are in our food and drink that we ingest every day. Apart from providing us with a physical barrier the beneficial bacteria produce antibiotic like substances that are anti fungal, anti viral that dissolve viruses and 'bad' bacteria. They also reduce pH near the wall of the gut making it uninhabitable for the 'bad' bacteria to colonise[1].

Opportunistic flora: This is a large group of various microbes these are: *Bacteriods, Peptococci, Staphylococci, Streptococci, Bacilli, Clostridia, Yeasts, Enterobacteria, Fuzobacteria, Eubacteria, catenobacteria*, and many others. In a healthy person their numbers are limited and are tightly controlled by the beneficial flora. Each of these microbes is capable of causing various health problems if they get out of control.

Transitional flora: These are various microbes, which we daily swallow with food and drink. When the gut is well protected by the beneficial bacteria, these microbes pass through our digestive tract without doing any harm, but if the population of the beneficial flora is damaged and not functioning well this group of microbes can cause disease.

DEVELOPMENT OF GUT FLORA IN INFANTS

The gastrointestinal tract of a normal fetus is sterile. When a germ-free baby is released

from the sterile confines of its mother's womb, it swallows a mouthful of muck. So, upon entering a world full of germs ever keen to enter a fresh new body, the bugless babe is at once no more. With no pre-existing bacteria to demand competition, bugs ingested during the birth process colonise the infant gut within days. Over the first few days of life, additional type's bacteria join the gut flora[2].

Some beneficial microbes, like bifidobacteria, receive a helping hand to become established from proteins in breast milk. As a result, after just a few weeks, this bug makes up over 90% of a breastfed baby's intestinal flora. Bifidobacteria make the baby's gut acidic which creates a barrier against infection with bugs which the child has yet to develop natural immunity, including many acid-intolerant disease-causing microbes. In contrast, the microbiota of formula-fed infants is more diverse, with high numbers of *Enterobacteriaceae, enterococci, bifidobacteria, Bacteroides, and clostridia.* After the introduction of solid food and weaning, the microflora of breast-fed infants becomes similar to that of formula-fed infants. By the second year of life, the fecal microflora resembles that of adults[3].

FUNCTIONS OF GUT FLORA

- **Carbohydrate fermentation and absorption -** The breakdown of indigestible vegetal polysaccharides (nutrient processing)
- **Metabolic function -** Production of short-chain fatty acids, syntheses of vitamins like biotin and folate, and also help in absorption of ions including magnesium, calcium and iron[4].
- **Regulation of intestinal angiogenesis -** Compared to germ-free mice, *B. thetaiotaomicron* colonized transgenic mice lacking Paneth cells established that microbial regulation of angiogenesis depends on the signaling through a bacteria-sensing epithelial cell[5].
- **Repression of pathogenic microbial growth -** Another important role of helpful gut flora is that they prevent species that would harm the host from colonizing the gut, an activity termed the "barrier effect". Harmful yeasts and bacterial species such as *Clostridium difficile* (the overgrowth of which can cause pseudomembranous colitis)[6]
- **Influence on growth and formation of organs -** The thymus gland development is dependent on intestinal flora: formula-fed infants have smaller, less productive thymuses than breastfed infants[7].
- **Intestinal homeostasis and host integrity[8] including**
    - Adaptive immunity
    - Tropic effects-development of GALT,
    - Mucosal immunity,
    - Induction of oral tolerance,
    - Diversification of the preimmune Ab repertoire[9].

TROPHIC EFFECTS

They increase growth of intestinal epithelial cells and control the proliferation and differentiation of lymphoid tissue near the gut. Bacterial cells also alter intestinal growth by changing the expression of cell surface proteins such as sodium / glucose transporters. In addition, changes they make to cells may prevent injury to the gut mucosa from occurring[10].

GALT- GUT ACCOSIATED LYMPHOID TISSUES

GALT includes both organized lymphoid compartments, consisting of PP (peyer's patch), regional lymphatics, and mesenteric lymph nodes (MLN), and dispersed lymphoid cells (T cells and B cells) in the IEL spaces and the gut LP (lamina propia).

PP - PEYER'S PATCHS: The PP regarded as main site for induction of mucosal immunity consist of a single-layer cluster of Bcell follicles, divided by T-cell-rich wedges, unevenly distributed in the wall of the small intestine. A specialized follicle-associated epithelium (FAE) overlies these clusters, forming a relatively mucus-free "dome" among the absorptive villi and their interspersed crypts. Among the cells of FAE are specialized M (microfold) cells, which serve as "afferent lymphatics" for PP, delivering antigens (Ags) and pathogens to the underlying, organized lymphoid tissue containing awaiting antigen-presenting cells[11].

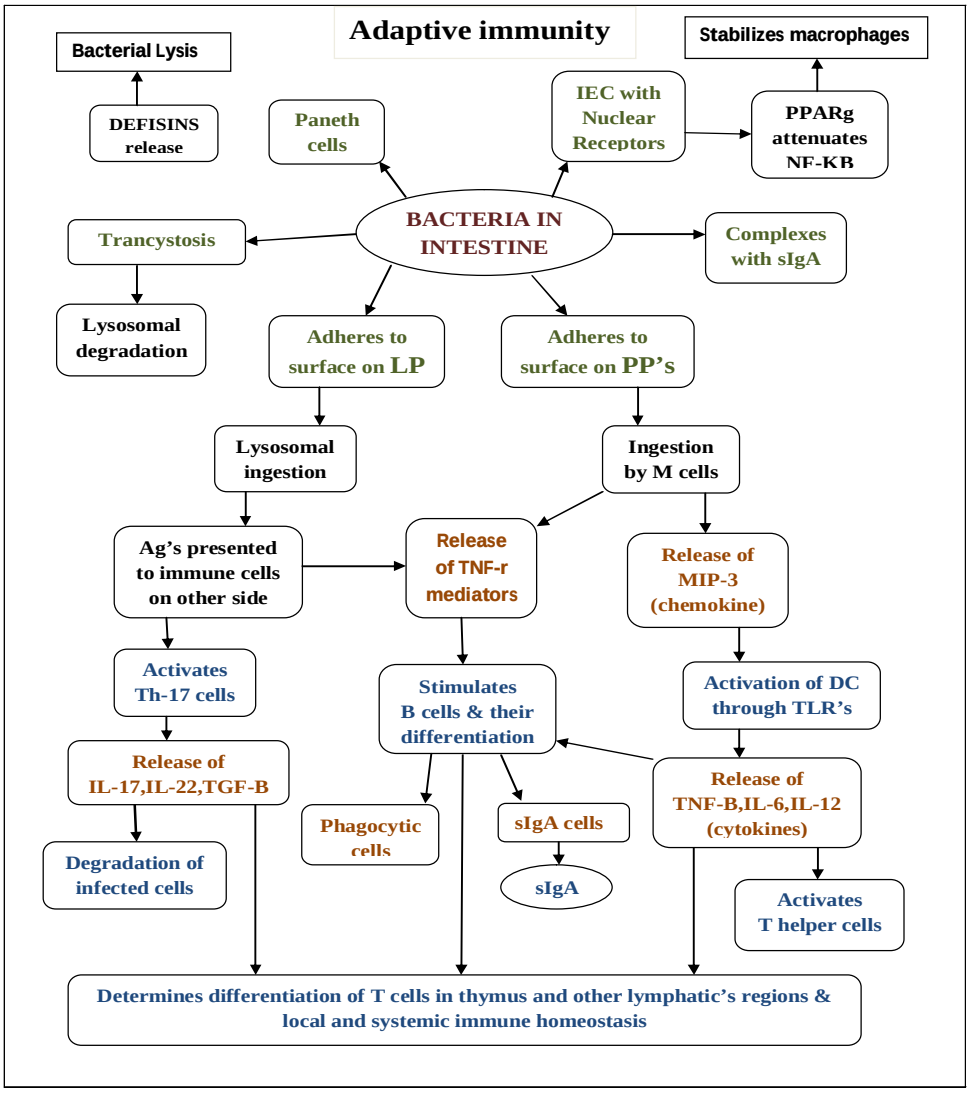
LP - LAMINA PROPRIA: The lamina propria of the small intestine at steady state contains

large numbers of two homeostatically regulated and developmentally related populations of CD4 T cells, IL-17+ helper Th17 cells and Foxp3+ regulatory T cells (Treg)[12]. The composition of the intestinal microbiota regulates the balance between Th17 and Treg cells in the lamina propria and is likely to influence intestinal immunity, tolerance, and inflammatory bowel diseases susceptibility.

DC's - DENDRITIC CELLS: DC's are activated via TLR expressed on their surface. Liu et al. observed that different subsets of DC (myeloid v. lymphoid) express different TLR, with human myeloid pre- DC1 expressing TLR2 and TLR4 and lymphoid pre-DC2 expressing high levels of TLR7 and TLR9, and Studies on the Peyer's patch, also suggest the presence of at least 4 different subsets of CD11c dendritic cells based on the expression of CD11b and CD8 surface markers.

CROSSTALK and ADAPTIVE IMMUNITY

Gut flora have a continuous and dynamic effect on the host's gut and systemic immune system. The communication between intestinal bacteria and the gut is termed microbial–epithelial 'crosstalk', which is responsible for initiation of immune responses. The various mechanisms are represented as follows



One proposed mechanism is that DC utilize their innate receptor repertoire of toll-like receptors (TLR) and C-type lectins to discriminate between microbial-associated molecular patterns (MAMP) expressed by commensal bacterial and pathogen-associated molecular patterns (PAMP)[13].

TLRs – TOLL LIKE RECEPTORS

TLR are a family of transmembrane receptors homologous to Drosophila toll proteins, characterized by extracellular domains of leucine rich repeats (LRRs) and cytoplasmic domains highly homologous to the IL-1 receptor.To date, ten members of the TLR family have been identified in mammals, with each receptor recognizing a unique set of PAMP[14].

Receptor subtype	Specific Ligand	Origin of the ligands
TLR 1	LAM/PGN	Bacteria,mycobacteria
TLR 2	Peptidoglycan, Bacterial lipopeptides	Gram positive bacteria, pathogenic bacteria
TLR 3	Ds RNA	Virus
TLR 4	LPS, commensal bacteria	Gram negative bacteria
TLR 5	Flagellin	Opportunistic bacteria
TLR 6	Diacyl lipopeptides Tollip/SIGIRP(inhibitory)	Mycoplasma
TLR 7	Synthetic compounds Loxoribine, Bropirimine	Synthetic compounds
TLR 8	Unknown	Unknown
TLR 9	cpg DNA	Bacteria (commensal)
TLR 10	Unknown	Unknown

C-type lectins on the other hand preferentially bind to carbohydrate antigens and are associated with antigen uptake, including virus, bacteria, parasites, and yeasts. C-type lectins may also be important in the migration of DC[15].

MUCOSAL IMMUNITY

SIgA - Secretary IgA

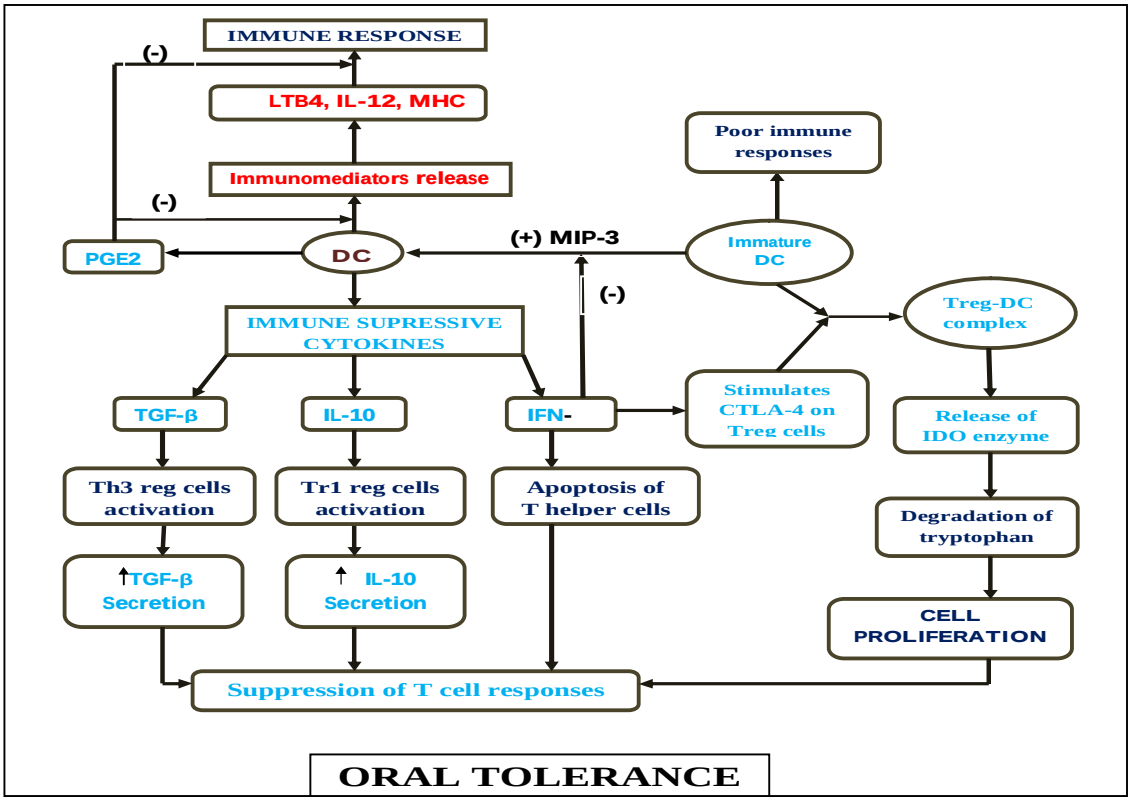
SIgA is the most abundantly produced immunoglobulin at the surface of mucous membranes in mammals. SIgA contributes to specific immunity against invading pathogenic microorganisms. As shown above, SIgA production in the gut depends on intricate mechanisms involving antigen sampling by M cells, processing by underlying antigen-presenting cells, T-cell activation, and B-cell switch in the Peyer's patch and neighboring lamina propria.

Secretory IgA is present in dimeric or polymeric form. Secretory IgA is resistant to intraluminal proteolysis and does not activate complement or inflammatory responses, which makes secretory IgA ideal for protecting mucosal surfaces. The crucial role of SIgA in maintaining bacterial homeostasis is further reflected by its contribution to microbial biofilm formation in vitro[16]. SIgA were also reported to be involved in multiple functions including bacterial binding, antibody anchoring at mucosal surfaces, and interaction with mucus .

There are differences between the upper and lower parts of the human gut-associated immune system in the isotype distribution of immunoglobulin producing cells[17]. IgA1 immunocytes predominate in the small intestine, whereas IgA2-producing cells are most frequent in the colon, the latter being more resistant to bacterial proteases.

ORAL TOLERANCE-PREVENTING ALLERGY AND INFLAMMATORY BOWEL DISEASE

Oral tolerance is required for the maintenance of intestinal homeostasis and arises following exposure of the intestinal immune system to soluble antigens[18].



ANTIBIOTICS vs PHARMABIOTICS

EFFECTS OF ANTIBIOTIC USE

Altering the numbers of gut bacteria, for example by taking broad-spectrum antibiotics, may affect the host's health and ability to digest food. Antibiotics can cause antibiotic-associated diarrhea (AAD) by irritating the bowel directly, changing the levels of gut flora, or allowing pathogenic bacteria to grow. Another harmful effect of antibiotics is the increase in numbers of antibiotic-resistant bacteria found after their use, which, when they invade the host, cause illnesses that are difficult to treat with antibiotics[19].

Gut flora composition also changes in severe illnesses, due not only to antibiotic use but also to such factors as ischemia of the gut, failure to eat, and immune compromise. Negative effects from this have led to interest in selective digestive tract decontamination (SDD), a treatment to kill only pathogenic bacteria and allow the re-establishment of healthy ones.

PHARMABIOTICS

Pharmabiotics is a generic term to encompass any form of therapeutic exploitation of the commensal flora, including the use of live probiotic bacteria, probiotic-derived biologically active metabolites, prebiotics, synbiotics or genetically modified commensal bacteria.

Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host are known as probiotics. Substances ingested to promote the growth of probiotic microbes are called prebiotics. European Commission concerted action program, coordinated by the International Life Sciences Institute, redefined probiotics as "A live microbial food ingredient that is beneficial to health". The criteria for a microorganism to be defined as probiotic include that the strain be of human origin, are safe for human use, be stable in acid and bile, and adhere to the intestinal mucosa[20]. The genera most frequently used as probiotics are *Lactobacillus* and *Bifidobacterium*.

THERAPEUTIC ROLE FOR PROBIOTICS

- **Translocation-development of adaptive immunity –** results from the crosstalk between the gut flora and IEC cells as described above.
- **Role in disease-treatment of intestinal infections -** Bacteria present in the gut doesn't allow the

pathogenic bacteria to intrude the intestinal epithelium under normal health conditions by offering a physical barrier.

- **Cancer -** *Lactobacillus* and *Bifidobacteria*, are known to prevent tumor formationby suppressing the growth factors
- **Inflammatory bowel disease -** Some suspect that IBD is due to a reduction in immune tolerance and subsequent overreaction of the host's immune system to harmful or non-harmful bacteria. IBD may be caused by the entire gut flora together or some specific types[21].

  It has been noted that though Ulcerative Colitis and Crohn's disease (two types of IBD) probably have genetic components, they are not inherited in a Mendelian fashion and are thus probably due to a complex set of factors rather than solely to a gene[22] and bacterial flora play a major role in them.

  Some suspect that inflammation in IBD is due to increased permeability of the inner lining of the colon, which may allow bacteria to invade the tissues and cause an immune reaction that leads to prolonged inflammation[23]. Tissue damage in IBD results from the immunological misperception of danger within the naturally occurring flora or due to failure of normal tolerance to pathogenic bacteria.

  Abnormal tight junctions, which are supposed to prevent permeability, have been found in cells of patients with IBD[24]. Because of the potentially harmful role of these bacteria, antibiotics are frequently prescribed to treat Crohn's disease. However, inflammation could occur first and cause the increased intestinal permeability found in diseases such as Crohn's, so the causative role of bacteria is not clear. Conventional therapies for IBD primarily target the mucosal inflammatory responses by using pharmabiotics.
- **Treatment of Colitis –** similar to bowel diseases.
- **Obesity -** The microbes occupying the human gut are in direct relation to obesity. The ratio between *Firmicutes* and *Bacteroidetes* dynamically reflects the overall weight condition of an individual, shifting towards Bacteroidetes if an obese individual loses weight[25].

CONCLUSION

It is clear that commensal flora either directly or indirectly play a major role in health and immunity, further more development of the pharma/prebiotics have show synergistic effect on development of immune defenses. However, additional studies are needed to show that prebiotics can directly or indirectly stimulate intestinal host defenses. If this can be demonstrated prebiotics can be used as dietary supplement to stimulate a balanced effective mucosal immune system in newborns and infants.

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