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Chapter 1 : Human microbiota - Wikipedia

In brief, the microbial flora affects the histologic structure of the gastrointestinal tract and the kind of substances that are released from it into the general circulation. The different parts of the digestive tract, the various microbial species that they harbor selectively, and the physiologic conditions that govern the interplay between the host and its indigenous flora constitute a highly integrated ecosystem.

Gram-positive cocci and rod-shaped bacteria are the predominant microorganisms found in the small intestine. The bacterial flora provide regulatory signals that enable the development and utility of the gut. Overgrowth of bacteria in the small intestine can lead to intestinal failure. This form of testing is also often preferable to more invasive techniques, such as biopsies. Somewhere between [9] and different species live in the gut, [10] with most estimates at about In adult microbiomes, a high prevalence of enzymes involved in fermentation, methanogenesis and the metabolism of arginine, glutamate, aspartate and lysine have been found. In contrast, in infant microbiomes the dominant enzymes are involved in cysteine metabolism and fermentation pathways. Gut microflora is mainly composed of three enterotypes: Prevotella , Bacteroides, and Ruminococcus. There is an association between the concentration of each microbial community and diet. For example, Prevotella is related to carbohydrates and simple sugars, while Bacteroides is associated with proteins, amino acids, and saturated fats. Altering the diet will result in a corresponding change in the numbers of species. As the US population has a diet richer in fats than Amerindian or Malawian populations which have a corn-rich diet, the diet is probably the main determinant of the gut bacterial composition. The fecal bacteria of children from Florence were compared to that of children from the small rural village of Boulpon in Burkina Faso. The diet of a typical child living in this village is largely lacking in fats and animal proteins and rich in polysaccharides and plant proteins. The fecal bacteria of European children were dominated by Firmicutes and showed a marked reduction in biodiversity, while the fecal bacteria of the Boulpon children was dominated by Bacteroidetes. The increased biodiversity and different composition of gut flora in African populations may aid in the digestion of normally indigestible plant polysaccharides and also may result in a reduced incidence of non-infectious colonic diseases. This effect has no genetic influence and it is consistently observed in culturally different populations. In humans, research has shown that microbial colonization may occur in the fetus [44] with one study showing Lactobacillus and Bifidobacterium species were present in placental biopsies. Various methods of microbiome restoration are being explored, typically involving exposing the infant to maternal vaginal contents, and oral probiotics. In most cases B cells need activation from T helper cells to induce class switching ; however, in another pathway, gut flora cause NF-kB signaling by intestinal epithelial cells which results in further signaling molecules being secreted. It has been shown that IgA can help diversify the gut community and helps in getting rid of bacteria that cause inflammatory responses. For example short-chain fatty acids SCFA can be produced by some gut bacteria through fermentation. Tryptophan metabolism by human gastrointestinal microbiota.

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Chapter 2 : Intestinal Microflora and Antibiotic Resistance - microbewiki

The gastrointestinal microbiota, especially that acquired during early life, influences so profoundly the morphologic and physiologic characteristics of its host that many characteristics of the.

Human timeline and Nature timeline Though widely known as flora or microflora, this is a misnomer in technical terms, since the word root flora pertains to plants, and biota refers to the total collection of organisms in a particular ecosystem. Recently, the more appropriate term microbiota is applied, though its use has not eclipsed the entrenched use and recognition of flora with regard to bacteria and other microorganisms. Both terms are being used in different literature. The problem of elucidating the human microbiome is essentially identifying the members of a microbial community which includes bacteria, eukaryotes, and viruses. The former focuses on specific known marker genes and is primarily informative taxonomically, while the latter is an entire metagenomic approach which can also be used to study the functional potential of the community. It is known that the human microbiome such as the gut microbiota is highly variable both within a single subject and among different individuals, a phenomenon which is also observed in mice. By mapping the normal microbial make-up of healthy humans using genome sequencing techniques, the researchers of the HMP have created a reference database and the boundaries of normal microbial variation in humans. From healthy U. Bacteria[edit] Populations of microbes such as bacteria and yeasts inhabit the skin and mucosal surfaces in various parts of the body. Skin and vaginal sites showed smaller diversity than the mouth and gut, these showing the greatest richness. The bacterial makeup for a given site on a body varies from person to person, not only in type, but also in abundance. Bacteria of the same species found throughout the mouth are of multiple subtypes, preferring to inhabit distinctly different locations in the mouth. Even the enterotypes in the human gut, previously thought to be well understood, are from a broad spectrum of communities with blurred taxon boundaries. Firmicutes and Bacteroidetes dominate but there are also Proteobacteria , Verrumicrobia , Actinobacteria , Fusobacteria and Cyanobacteria. If this is not removed by brushing, it hardens into calculus also called tartar. The same bacteria also secrete acids that dissolve tooth enamel , causing tooth decay. The vaginal microflora consist mostly of various lactobacillus species. It was long thought that the most common of these species was Lactobacillus acidophilus , but it has later been shown that L. Other lactobacilli found in the vagina are L. Disturbance of the vaginal flora can lead to infections such as bacterial vaginosis or candidiasis "yeast infection". Archaea[edit] Archaea are present in the human gut, but, in contrast to the enormous variety of bacteria in this organ, the numbers of archaeal species are much more limited. Mycobiota human Fungi, in particular yeasts , are present in the human gut. Human virome Viruses, especially bacterial viruses bacteriophages , colonize various body sites. These colonized sites include the skin, [32] gut, [33] lungs, [34] and oral cavity.

Chapter 3 : Microflora of the gastrointestinal tract: a review.

Savage has defined and categorized the gastrointestinal microflora into two types, autochthonous flora (indigenous flora) and allochthonous flora (transient flora). Autochthonous microorganisms colonize particular habitats, i.e., physical spaces in the GI tract, whereas allochthonous microorganisms cannot colonize particular habitats except under abnormal conditions.

The microflora of the human gastrointestinal GI tract is so extensive and integral to the proper functioning of the digestive system that it has been characterized as an additional organ of the human body 1. The intestine provides a suitable niche for many species of bacteria, as it remains at a stable temperature and is replete with bioavailable carbon, nitrogen, and solute sources of nutrition 7. The suite of microbes is acquired primarily during infancy, since the GI tract of a fetus is sterile during development. Bacteria are initially transferred to the infant during the delivery process, then continually from the immediate environment and from contact with its mother and other adults. Escherichia and Streptococcus are the first to colonize the GI tract, typically followed by Bifidobacteria, Staphylococci, Lactobacilli, Micrococci, and Propionibacteria. As the infant matures, it is continually exposed to bacteria, principally by the digestion of food, and the makeup of its intestinal microbiome changes dramatically 2, 5. The dynamic nature of the microfloral community entails shifting of community species composition over time and variation in composition among individuals. However, the predominant taxa of bacteria in the gut are fairly consistent. Firmicutes and Bacteroides are the most prevalent phyla by far; populations of Proteobacteria, Actinobacteria, Fusobacteria, and Verrucobacteria are frequently established as well 2, 6. Functions of Intestinal Microflora The functions performed by gut bacterial include regulation of intestine epithelial development, maintenance of mucosal homeostasis and repair, improved absorption of nutrients from food, and contributions to the innate immune system 1, 2, 3. The colonization of various other species of bacteria also contribute to the epithelium by causing the mucosal layer to significantly increase in depth. This growth contributes to both the successful growth and maintenence of flora colonies and the defenses against potentially pathogenic bacteria Research has indicated that the period of weaning in mice which represents a period of microfloral diversification is accompanied by the expansion of a villous capillary network that is absent in germ-free mice; also, growth of this network can be induced with the addition of B. This suggests more effective transport of nutrients in the intestines of mammals with healthy microflora 3. Digestion The metabolism of some complex polysaccharides, lipids, and other compounds is only possible in the presence of bacterial species. Many bacteria specialize in the metabolism of certain compounds, such as B. These bacteria have also been shown to differentiate gene expression to improve the efficiency of their glycan foraging behavior, which likely allows the host access to nutrients from a greater variety of food types. In general, lipids are ineffectively metabolized and stored in germ-free mice, leading to fluctuating weight. Innate Immunity The innate immune system is reinforced by the microbiome by myriad means, most of which are likely undocumented. Known responses to intestinal conditions include the stimulation of antibacterial proteins following an invasion event, triggering of inflammation after moderate injury, and maintaining protection from pathogens by interacting with toll-like receptor cells. These are discussed in section 3. These functions are all highly relevant to medicine, as a deeper understanding of how bacteria influence these systems will yield more sophisticated solutions to conditions affecting the body. An important factor to the effective functioning of the human microbiome is the movement of genetic material. Genes are exchanged both between bacteria species, via lateral gene transfer, and among bacteria and their host. The presence of documented human proteins that have homologs only in bacteria hints at the extent to which human development and function has historically been strongly influenced by bacteria 2. The transfer of genetic material among bacterial species affects human hosts in more immediate and clinically relevant ways, including, notably, influencing response to antibiotics 4. Most gut bacteria cannot be cultured due to their very particular nutritional requirements and sensitivity to oxygen. While many species in the proximal

region of the gut are facultatively aerobic, tolerance of oxygen decreases when approaching the distal region of the intesine 2. Because keeping bacterial communities intact in vitro is so challenging, previous studies may be significantly biased in their analyses of composition and function. The use of phenotypic characteristics to classify bacteria which was utilized until only recently also leads to an incomplete and oversimplified resolution of species. More modern techniques to evaluate bacterial communities and their evolutionary lineages involve whole-genome sequencing and a strong emphasis on rRNA 1, 4, 6. Cloned amplicon sequencing is common, due to its moderately high resolution and ability to clone the full length of the 16S strand. The 16S sequences are treated with primers that bind to these conserved regions and amplified with standard PCR techniques, so that the resulting clones may be identified and catalogued 8. Types of Sampling Though all of these sequencing techniques are powerful, they are inherently limited by the method of sampling. Fecal samples are commonly used to assess bacterial composition, but do not accurately represent the flora community. Mucosal tissue samples directly from the intestine are preferable, but are more invasive and expensive to obtain 1. Due to the density of the microbial system and the complex interactions among species and between bacteria and the host, many researchers consider the gut to be its own ecosystem. This perspective has influenced the analysis of the data output from these sequencing projects: The Gut Microbiome and the Defenses of the Intestine Histological image of the human large intestine, with the mucosal and submucosal layers clearly visible. From Columbia University Biology Department. Since the intestine is such an attractive habitat for microbes, it must employ many types of defenses to protect the body from invasion of pathogen microbes. Many of these defense mechanisms are intricately related to a normal population of gut microflora. Microflora inhabit the mucosal layer of the intestine, which is a gel-like substance secreted by goblet cells onto the lumen-facing surface. The invasion of exogenous bacteria, both Gram-positive and Gram-negative, stimulates the secretion of mucus, strengthening this form of defense Two pathways have been identified as ways TLRs protect microflora: Evidence that intestinal microbiota have a distinct and crucial effect on the stimulation of mucus production is presented in a study that compared goblet cells of germ-free mice to conventional mice. The size of the goblet cells were significantly augmented in conventional specimens, but more importantly the mucosal layer was up to two times as thick. The structural components of gut flora bacteria that trigger this thickening effect remain unknown Resistance to antibiotics is a necessary attribute of bacterial populations dwelling in the human gut. The epithelium of the intestine expresses a variety of antimicrobial agents as a first-line defense of the immune system. These peptides are either expressed constitutively or induced by inflammatory mediators and other messenger components In fact, expression of antimicrobial proteins can be induced by the flora themselves: Thus, in order to flourish in the human gut commensal bacteria must be recognized by toll-like receptors and other mediators as well as be resistant to these comparatively non-specific antimicrobial agents. Pathogenic bacteria are recognized by their structural attributes by means of complex pathways, then are destroyed by inflammation or the antimicrobial peptides Effects of the Use of Antibiotics on Microbe Populations The advent of broad-spectrum antibiotics has upset the delicate balance between commensal bacteria and the antimicrobial substances produced by the intestine. Antibiotics can be ingested either deliberately in prescribed medications or accidently in meat from animals treated extensively with antibiotics in industrial farm settings. Since broad-spectrum antibiotics are generally manufactured to be non-specific, vast numbers of bacteria in the gut are destroyed following administration of the drug A mg dosage of levofloaxin brand name Levaquin , a commonly prescribed broad-spectrum antibiotic. Loss of Microfloral Benefits The immediate effects of losing microflora function include, predictably, a decreased ability to metabolize certain carbohydrate and lipid structures that make up a significant portion of the diet 13 , regulation of fat storage 14 , and loss of antimicrobial structures expressed by many microflora species 2. These effects vary in duration from weeks to several months, depending on the health of the host and the extent to which flora was destroyed. Individuals vary in their response to antibiotic usage due to the variability of their bacterial colonies further obscuring studies attempting to determine makeup of the gut microbiome ; also, some taxa seem to be more vulnerable to antibiotic damage than others.

These results suggest that the spread of newly dominant species to utilize available nutrients may reduce the ability of normally distributed flora to regenerate, as well as fundamentally changing the biochemistry of the GI tract. It has also been demonstrated that Salmonella can opportunistically colonize fecal samples following treatment with ciprofloxacin, up to a threshold concentration of antibiotic â€" this suggests new vulnerabilities to pathogen attack as well Multiple treatment episodes for recurrent infections or, ironically, antibiotic-resistant pathogens may also influence the ability of gut flora to return to their pre-drug status. This could be preferable to using generic cultured bacteria, since the introduction of new bacteria could trigger an immune response. The methods of delivery each have advantages: While still in development, this method is a promising means to mitigate antibiotic damage to gut flora Personal Correspondence, Dr. Rodger Liddle, Duke University. The Gut as a Reservoir for Antibiotic Resistance A regimen of antibiotic drugs introduces an artificial selection gradient in the human body for antibiotic resistance in microflora populations. Since antibiotic resistance genes tend to be encoded on transposable elements such as plasmids, they are readily transferred among populations via lateral gene transfer. The bacteria that receive the plasmids conferring resistance are at a distinct evolutionary advantage, regardless of other benefits they provide the host. Several studies have concluded that ermB and tetQ, which provide resistance to erythromycin and tetracycline, have increased substantially both in occurrence in the gut and the number of species in which they are present. This emphasis on resistance as a fitness factor represents a shift from historical means of keeping bacterial populations in balance. Two resistance genes with no significant similarity to sequences in GenBank are not shown. The normalized fold increase of erm B compared to day 0 in community DNA extracted from fecal samples for controls Aâ€"C not receiving any treatment A and patients Dâ€"F receiving antibiotics B. Each bar graph represents the mean and standard error of the normalized expression of erm B compared to 16S. Normalization was carried out as previously been described [8]. They extracted DNA directly from bacteria from the guts of people who had not been treated with antibiotics for a year, then inserted these sequences into E. The bacteria were cultured and divided onto antibiotic-laden plates, such that each group was subjected to one of thirteen antibiotics. The researchers sequenced those bacteria that contained resistance factors to all thirteen drugs. In all, 95 new resistance inserts were identified. Phylogenetic analysis revealed the most likely origin of antibiotic resistance factors to be Bacteroides and Firmicutes; this is unsurprising considering their dominance in the gut. Of principle interest to this study was how closely related the inserts were to previous entries in GenBank, since the genetic distance between sequences might indicate rate of transfer assuming a moderately regular rate of mutation. The average similarity factors extracted from human flora and the closest known gene was These results are highly pertinent to the general system, but are not resolved to the question of exchange among indigenous and exogenous species. When they narrowed their perspective and compared resistance sequences of intestinal flora and pathogenic bacteria, they found that nearly half of the factors were identical in sequence to human pathogen genes. Though a direct means of transmission of genetic material from pathogens to human floral cells has not yet been demonstrated, these results have important implications for the human immune system and the effectiveness of antibiotics 4. If pathogens that invade the body transfer plasmids containing resistance factors to floral cells, even if they are destroyed by the immune systems the factor will remain. This may be beneficial to conserving and regenerating flora after being treated with an antibiotic regimen, but transfer occurs in both directions. If genes conferring resistance are transferred to pathogenic species, different cocktails of antibiotics at higher concentrations will be prescribed to fight off the infection, damaging the flora in novel ways. The data of Sommer, et al. Time is an essential component to the study of microflora because the regeneration or failure thereof of flora will determine how a patient will respond to a pathogen or antibiotic in the future. Rate of flora regrowth varies by individual, so the potential to refine medical techniques to be patient-specific is dependent on time studies. They found the community composition shifts radically after exposure to clarithromycin and metronidazole another common combination for H. Intriguingly, their results indicated that at after four full years since treatment, the original bacterial composition of the gut was not replenished. Of equal importance is the persistence of ermB, the resistance

factor to erythromycin. The factor had clearly remained and spread among multiple populations; the authors propose that Enterococci survived the antibiotics and distributed the factor by both asexual reproduction and lateral transfer. Conclusions The incredible diversity and richness of bacteria in the human gut is invaluable to our survival and, arguably, success as a species. Without the significant benefits to digestion and immune function conferred by bacteria, humans would be markedly less efficient and far more vulnerable to uncontrolled growth of pathogenic bacteria.

Chapter 4 : Immunity: Regulation by the Indigenous Gastrointestinal Microbiota

The indigenous gastrointestinal (GI) tract microflora has profound effects on the anatomical, physiological and immunological development of the host. The indigenous microflora stimulates the host immune system to respond more quickly to pathogen challenge and, through bacterial antagonism, inhibits colonization of the GI tract by overt exogenous pathogens.

During the birth process and rapidly thereafter, microbes from the mother and surrounding environment colonize the gastrointestinal tract of the infant until a dense, complex microbiota develops. The succession of microbes colonizing the intestinal tract is most marked in early development, during which the feeding mode shifts from breast-feeding to formula feeding to weaning to the introduction of solid food. Dynamic balances exist between the gastrointestinal microbiota, host physiology, and diet that directly influence the initial acquisition, developmental succession, and eventual stability of the gut ecosystem. In this review, the development of the intestinal microbiota is discussed in terms of initial acquisition and subsequent succession of bacteria in human infants. Intrinsic and extrinsic factors influencing succession and their health significance are discussed. The advantages of modern molecular ecology techniques that provide sensitive and specific, culture-independent evaluation of the gastrointestinal ecosystem are introduced and discussed briefly. Further advances in our understanding of developmental microbial ecology in the neonatal gastrointestinal tract are dependent on the application of these modern molecular techniques. Intestinal microbiota , acquisition , succession , breast-feeding , formula feeding , lactobacilli , bifidobacteria , obligate anaerobes INTRODUCTION The microbial community inhabiting the gastrointestinal tract is characterized by its high population density, wide diversity, and complexity of interactions. All major groups of microbes are present in the gut. Bacteria are predominant but a variety of protozoans are commonly found 1 â€” 3. Anaerobic fungi are widely distributed in the gastrointestinal tract of herbivores 4 as are yeasts 5 and bacteriophages 6. Note that these numbers were derived from fecal samples and may not accurately represent the intestinal microbiota, especially in terms of species abundance and their relative importance. Importantly, bacterial cells outnumber animal host cells by a factor of 10 and have a profound influence on immunologic, nutritional, physiologic, and protective processes in the host animal 10 , In fact, the gastrointestinal microbiota can be considered a metabolically adaptable and rapidly renewable organ of the body. The gastrointestinal tract is a specialized tube divided into various well-defined anatomical regions extending from the lips to the anus. For the purposes of this and most papers on gut microbiology, discussion is restricted to the stomach, small intestine, and large intestine as well as fecal material, because it is more readily obtained. Indigenous bacteria are not distributed randomly throughout the gastrointestinal tract but instead are found at population levels and in species distributions that are characteristic of specific regions of the tract. Acid-tolerant lactobacilli and streptococci predominate in the upper small intestine. In addition to an increasing gradient of indigenous microbes from the stomach to the colon, there are also characteristic spatial distributions of organisms within each gut compartment. At least 4 microhabitats have been described:

Chapter 5 : Gut flora - Wikipedia

Prevalence Of Bacteria In Different Parts Of The GI Tract. The prevalence of bacteria in different parts of the GI tract appears to be dependent on several factors, such as pH, peristalsis, redox potential, bacterial adhesion, bacterial cooperation, mucin secretion, nutrient availability, diet, and bacterial antagonism.

Srikanth and Beth A. This is an open access article distributed under the Creative Commons Attribution License , which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Abstract The mucosal surfaces of the gastrointestinal tract harbor a vast number of commensal microbiota that have coevolved with the host, and in addition display one of the most complex relationships with the host. This relationship affects several important aspects of the biology of the host including the synthesis of nutrients, protection against infection, and the development of the immune system. On the other hand, despite the existence of several lines of mucosal defense mechanisms, pathogenic organisms such as Shigella and Salmonella have evolved sophisticated virulence strategies for breaching these barriers. The constant challenge from these pathogens and the attempts by the host to counter them set up a dynamic equilibrium of cellular and molecular crosstalk. Even slight perturbations in this equilibrium may be detrimental to the host leading to severe bacterial infection or even autoimmune diseases like inflammatory bowel disease. Several experimental model systems, including germ-free mice and antibiotic-treated mice, have been used by various researchers to study this complex relationship. Although it is only the beginning, it promises to be an exciting era in the study of these host-microbe relationships. The biological outcome of this vast and complex population of microbes is that their genes termed the microbiome synthesize about times more proteins than the somatic cells of their host [3]. Not surprisingly, the human intestine is more densely populated with microorganisms than any other organ and is a site where they exert a strong influence on human biology. This is because the intestinal mucosa serves as the primary border between the immune system and the external environment, and in addition plays a central role in host-commensal flora interactions. Accumulating evidence indicates that the gut microbiota is instrumental in supporting energy metabolism and immune function of the host. More recent studies suggest that the commensal microbiota play an important role in the development of numerous conditions, including obesity [4 , 5], diabetes [6], nonalcoholic fatty liver disease [7], inflammatory bowel disease [8], and perhaps cancer [9]. Unfortunately, the immense complexity of gut flora together with its highly complicated interactions with intestinal epithelium makes it a recalcitrant system to study. Although largely unexplored, our gut microbiota plays an intricate and under-appreciated pivotal role for our health and well-being. In this review we will discuss new developments in the field that highlight the cellular and molecular basis of the crosstalk between the host, the commensal microbiota, and pathogenic bacteria in a healthy as well as a diseased GI tract. Role of the Microbiota in the Gastrointestinal Tract The microflora of the intestinal microenvironment as a unit provides important protective, metabolic, and trophic functions. Resident bacteria serve a central line of resistance to colonization by exogenous microbes, and thus assist in preventing the potential invasion of the intestinal mucosa by an incoming pathogen. This protective function is known as the barrier effect or colonization resistance and serves a number of important roles. For instance, adherent nonpathogenic bacteria can often prevent attachment and subsequent entry of suspected pathogens into epithelial cells, as well as compete for nutrient availability. The commensal microbiota also helps maintain GI nutrient homeostasis by administering and consuming all resources. For example, dietary nutrients are absorbed by the gut and together with various nonnutrient compounds produced by the microbiota are cometabolize by host enzymes, such as cytochrome P and conjugating enzymes in the liver [10]. The resulting metabolites that are derived from both host and microbial processes are returned to the gut by the bile for further metabolism or excretion [11]. This mutual and beneficial relationship helps to dampen unwanted overproduction of nutrients, which could potentially support intrusion of microbial competitors with a potential pathogenic outcome for the host [12]. Quite

remarkably, an absence of intestinal bacteria is associated with reduction in mucosal cell turnover, vascularity, muscle wall thickness, motility, baseline cytokine production, digestive enzyme activity, and defective cell-mediated immunity [13]. Indeed, comparative studies in germ-free and conventional animals have established that the intestinal microflora is essential for the development and function of the mucosal immune system during early life, a process that is now known to be important to overall immunity in adults. For example, it has been well established that the number of intraepithelial and lamina propria T cells is lower in germ-free animals, a feature that is reversed upon the restoration of the normal flora [14]. Likewise, levels of secretory IgA are low in the intestine of germ-free animals but are markedly increased upon intestinal colonization of the commensal bacterium, Bacteroides thetaiotamicron [15]. Furthermore, the intimate relationship between the commensal microbiota and the intestinal epithelium are involved in shaping the memory mechanisms of systemic immunity, such as oral tolerance. This was initially recognized by the discovery that the systemic response to a specific pathogen can be abrogated after ingesting the antigen; this effect continues for several months in conventionally colonized mice, whereas in germ-free mice systemic unresponsiveness persists for only a few days [16]. Therefore, the innate immune system discriminates between potential pathogens from the commensal microbiota by inducing tolerance to microbial epitopes. This, in turn, dampens responses to commonly encountered foodstuffs and other environmental antigens. Collectively, these examples help to illustrate the important concept that the commensal microbiota profoundly influence the development of the gut mucosal immune system and are essential in preventing exogenous pathogen intrusion. The intestinal microflora also makes important metabolic contributions by producing vitamin K, folate, and short-chain fatty acids a major energy source for enterocytes , and mediates the breakdown of dietary carcinogens as well [2 , 17]. Perhaps the major metabolic function of the colonic microflora is the fermentation of nondigestible carbohydrates. These nondigestible carbohydrates include large polysaccharides i. The primary metabolic endpoint of such fermentation is the generation of short-chain fatty acids acetate, proprionate, butyrate. A fundamental role of short-chain fatty acids on colonic physiology is their trophic effect on the intestinal epithelium. Therefore, short-chain fatty acids appear to play an essential role in the control of epithelial cell proliferation and differentiation in the colon. Recent studies have also shown effects of butyrate on intestinal barrier function [18]. Moreover, it has been shown that commensal bacterial can modulate gene expression in the host in order to create a sustainable environment for themselves, while at the same time prevent the growth of other competitive bacteria within the intestinal ecosystem [15]. For the host to thrive and produce more gut residents, the gut microbial ecosystem must be functionally stable over time despite the internal dynamics of the community. Constituent bacteria are expected to have a high degree of functional redundancy between species, so that the loss of one lineage does not adversely impact the homeostatic balance of the intestinal microenvironment [19]. While it is unclear how the selective pressures, microbial community dynamics, and the intestinal microenvironment shape the genome and subsequent functions of members of the gut microbiota, there are some exciting new developments in the field. For example, Gordon et al. This tenet is founded on experiments in which this team of investigators sequenced the genomes of two gut-dwelling Bacteroidetes and compared their genomes to the genomes of other bacteria that live both inside and outside of the human body. Quite remarkably, they discovered that lateral gene transfer, mobile genetic elements, and gene amplification play an important role in affecting the ability of the Bacteroidetes to vary their cell surface, sense their environment, and harvest nutrient resources present in the distal intestine [19]. Importantly, these findings lay the conceptual groundwork to suggest that adaptation to the gut ecosystem is a dynamic process that includes acquisition of genes from other microorganisms, and further underscores the significance of considering the evolution humans from the perspective of the evolution of the microbiome [19 , 20]. Restricting Pathogens and Commensal from Invading beyond the Mucosal Surface The host is protected from potentially harmful enteric microorganisms by the physical and chemical barriers created by the intestinal epithelium that are primarily comprised of absorptive villus enterocytes [21]. The apical surface of the enterocytes are highly differentiated structures consisting of rigid, closely packed

microvilli whose membranes contain stalked glycoprotein enzymes [22 , 23]. In addition, the tips of enterocyte microvilli are coated with a â€” nm thick meshwork referred to as the filamentous brush border glycocalyx [24] and is composed of highly glycosylated transmembrane mucins [25 , 26]. The intestinal epithelial barrier is also composed of enteroendocrine cells, goblet cells, and Paneth cells. Microfold M cells are also present in the follicle-associated epithelia where they represent a morphologically distinct epithelial cell type whose primary function is in the transport of macromolecules, particles, and microorganisms from the lumen to underlying lymphoid tissue [27 , 28]. Intercellular junctional complexes that are composed of tight junctions, adherens junctions, and desomosomes maintain the integrity of the epithelial barrier. The most apical components of the junctional complex are the epithelial tight junctions, which are highly regulated and serve to create a semipermeable diffusion barrier between individual cells Figure 1 a. Collectively, these features facilitate the intestinal epithelium to act as a physical barrier to prevent unwanted bacteria from gaining access to the host. A healthy intestinal epithelial surface acts as a physical and biochemical barrier with key features including the apical brush border, the mucus layer, the presence of antimicrobial peptides blue black dots in the lumen, the glycocalyx, and the epithelial tight junctions. Also seen in the illustration are numerous commensal bacteria and a dendritic cell sampling the lumen with its extended dendrites yellow. Such host pathogen interactions involve translocation of bacterial effectors green circles into the epithelial cells, membrane ruffling, bacterial endocytosis, and SCV formation. Chemoatractants are secreted by the epithelial surface that leads to PMN influx. The effect of these modifications lead to actin condensation, transcriptional activation of several genes and apoptosis. Other mechanisms that are triggered include basolateral IL8 secretion, apical Hepoxillin A synthesis, and PMN influx in the apical surface. The intestinal epithelium also provides a unique surface that is armed with a bounty of specialized cells that produce mucus, antimicrobial peptides, and antimicrobial molecules, which together form the front line of defense against pathogenic microorganisms Figure 1 a. The mucus layer is secreted by the goblet cells and this layer overlies the intestinal epithelium to create a physical blockade against offending enteric microbial pathogens. For example, it has been demonstrated that secreted mucus acts as a barrier to Yersinia enterocolitica [29], rhesus rotavirus [30], and Shigella flexneri [31]. The commensal microbiota has also been found to regulate the production of intestinal mucins, which consequently inhibits the adherence of numerous pathogenic bacteria to intestinal epithelial cells [32 â€” 34]. Paneth cells are another important cell type that are involved in intestinal defense against potential harmful pathogenic bacteria. Paneth cells also produce a number of antimicrobial molecules, including lysozyme, phospholipase A2, and angiogenin-4 reviewed in [37]. Therefore, it is inferred by numerous studies that Paneth cells are able to control the bacterial ecosystem Table 1. Angiogenin-4 is expressed mainly in the small intestine, cecum, and colon and acts on Gram-positive bacteria [49 , 50]. However, most antimicrobial peptides expressed by mammalian epithelial cells are members of peptide families that mediate nonoxidative microbial cell killing by phagocytes [50]. These amphipathic molecules interact with and lyse bacterial membranes [55]. Defensins generally possess a broad range of antimicrobial activity Table 1. In particular, human intestinal defensin-5 has been shown to kill Listeria monocytogenes, E. Additional evidence supporting a critical role for defensins in vivo was demonstrated in a study utilizing human defensin-5 transgenic mice; these mice exhibited marked resistance to oral challenge with virulent Salmonella enterica serovar Typhimurium S. LL is expressed within the epithelial cells located at the surface and upper crypts of normal human colon. Although little or no expression is seen within the deeper colonic crypts or within epithelial cells of the small intestine, studies in mice have determined these molecules to be protective against bacterial pathogens [47]. The intestinal epithelium also provides a surface where the host can sense the microbial microenvironment in order to elicit an appropriate defense response by releasing an array of signaling molecules i. These molecules then trigger the recruitment of leukocytes to initiate an early inflammatory response. Paradoxically, however, although continuously exposed to Gram-positive and Gram-negative bacteria and their products i. Exaggerated inflammatory responses in the absence of pathogenic bacteria would be otherwise deleterious [57 , 58]. Accordingly, the

normal intestinal epithelial host defenses are able to accurately interpret the complex microbial environment in order to discriminate between permanently established commensal microbes and episodic pathogens. The epithelial cells are able to sense the microenvironment within the gut by means of pattern recognition receptors PRRs that include Toll-like receptors TLRs and nucleotide-binding oligimerization domain NOD proteins [38 , 60 â€” 63]. Regulation of the expression and the specific location of TLRs and NODs in intestinal epithelial cells fosters efficient immune recognition of the commensal microflora and maintains a delicate balance; permitting a basal level of signaling events to proceed, while at the same time restraining innate immune responses. TLR5, which recognizes bacterial flagellin, has been reported to be expressed exclusively on the basolateral surfaces of the epithelial cells. This TLR is ideally positioned to detect its ligand, translocated flagellin [70]. These intracellular PRRs would not ordinarily encounter luminal commensal bacteria or those attached to the apical surface of intestinal epithelial cells but are well positioned to recognize pathogenic bacteria that actively breach the epithelial barrier. As an additional measure, commensal bacteria have the ability to induce the expression of intestinal alkaline phosphatase, which not only dephosphorylates dietary lipids but also dephosphorylates the LPS of commensal flora resulting in reduced toxicity in mammals [72]. Nonpathogenic microorganisms may also be able to selectively attenuate the NF-kB pathway as mechanism of intestinal immune tolerance. Collectively, this set of observations underscores the ability of intestinal bacterial communities to influence eukaryotic processes, and perhaps more specifically demonstrates inflammatory tolerance of the mammalian intestinal epithelia. How Pathogens Overcome the Epithelial Barrier As described above, the intestinal epithelium has evolved a rather formidable fortress to guard against microbial invasion. However, through a process of coevolution, potential harmful enteric microorganisms have evolved counter strategies to hijack the cellular molecules and signaling pathways of the host to become potentially pathogenic. As an initial step in the infection process, certain enteric pathogens target specific epithelial cell structures, including glycoproteins and glycolipids, which serve as receptors for bacterial attachment [78]; thus, enabling them to exploit the underlying signal transduction pathway. Other strategies utilized by invading enteric pathogens, such as S. This process requires the expression of a bacterial type III protein secretion system TTSS , the function of which is to deliver a set of effector proteins into the host cell [79 â€” 81]. These effector proteins co-opt host cell signal transduction cascades as a clever means of subverting normal host cell processes by triggering a marked rearrangement of the host cytoskeleton. This entry mechanism termed bacterial mediated endocytosis drives bacterial entry and facilitates the pathogen to cross the epithelial barrier as well as to induce a proinflammatory response [79 â€” 81]. The latter step in this process can be achieved by direct cytotoxic injury, intracellular migration, disruption of the epithelial tight junctions, or indirectly by inducing neutrophil infiltration.

Chapter 6 : native microbiota

INDIGENOUS FLOI~a. OF GASTROINTESTINAL TRACT TABLE 1. Digestive Flora o/NCS Mice 25 Anaerobic Coliforms and Lactobacilli Streptococci (N) Baeteroides Enterococcf.

The density and composition of the normal flora of the skin varies with anatomical locale. The high moisture content of the axilla, groin, and areas between the toes supports the activity and growth of relatively high densities of bacterial cells, but the density of bacterial populations at most other sites is fairly low, generally in s or s per square cm. Most bacteria on the skin are sequestered in sweat glands. The skin microbes found in the most superficial layers of the epidermis and the upper parts of the hair follicles are Gram-positive cocci Staphylococcus epidermidis and Micrococcus sp. These are generally nonpathogenic and considered to be commensal, although mutualistic and parasitic roles have been assigned to them. For example, staphylococci and propionibacteria produce fatty acids that inhibit the growth of fungi and yeast on the skin. But, if Propionibacterium acnes, a normal inhabitant of the skin, becomes trapped in hair follicle, it may grow rapidly and cause inflammation and acne. Sometimes potentially pathogenic Staphylococcus aureus is found on the face and hands in individuals who are nasal carriers. This is because the face and hands are likely to become inoculated with the bacteria on the nasal membranes. Such individuals may autoinoculate themselves with the pathogen or spread it to other individuals or foods. Normal Flora of the Conjunctiva A variety of bacteria may be cultivated from the normal conjunctiva, but the number of organisms is usually small. Staphylococcus epidermidis and certain coryneforms Propionibacterium acnes are dominant. Staphylococcus aureus, some streptococci, Haemophilus sp. The conjunctiva is kept moist and healthy by the continuous secretions from the lachrymal glands. Blinking wipes the conjunctiva every few seconds mechanically washing away foreign objects including bacteria. Lachrymal secretions tears also contain bactericidal substances including lysozyme. There is little or no opportunity for microorganisms to colonize the conjunctiva without special mechanisms to attach to the epithelial surfaces and some ability to withstand attack by lysozyme. Pathogens which do infect the conjunctiva e. Neisseria gonorrhoeae and Chlamydia trachomatis are thought to be able to specifically attach to the conjunctival epithelium. Newborn infants may be especially prone to bacterial attachment. Colonies of Propionibacterium acnes, found on skin and the conjunctiva. Normal Flora of the Respiratory Tract A large number of bacterial species colonize the upper respiratory tract nasopharynx. The healthy sinuses, in contrast are sterile. Sometimes pathogens such as Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae and Neisseria meningitidis colonize the pharynx. The lower respiratory tract trachea, bronchi, and pulmonary tissues is virtually free of microorganisms, mainly because of the efficient cleansing action of the ciliated epithelium which lines the tract. Any bacteria reaching the lower respiratory tract are swept upward by the action of the mucociliary blanket that lines the bronchi, to be removed subsequently by coughing, sneezing, swallowing, etc. If the respiratory tract epithelium becomes damaged, as in bronchitis or viral pneumonia, the individual may become susceptible to infection by pathogens such as H. Normal Flora of the Urogenital Tract Urine is normally sterile, and since the urinary tract is flushed with urine every few hours, microorganisms have problems gaining access and becoming established. The flora of the anterior urethra, as indicated principally by urine cultures, suggests that the area my be inhabited by a relatively consistent normal flora consisting of Staphylococcus epidermidis, Enterococcus faecalis and some alpha-hemolytic streptococci. Their numbers are not plentiful, however. In addition, some enteric bacteria e. The vagina becomes colonized soon after birth with corynebacteria, staphylococci, streptococci, E. During reproductive life, from puberty to menopause, the vaginal epithelium contains glycogen due to the actions of circulating estrogens. The lactic acid and other products of metabolism inhibit colonization by all except this lactobacillus and a select number of lactic acid bacteria. The resulting low pH of the vaginal epithelium prevents establishment by most other bacteria as well as the potentially-pathogenic yeast, Candida albicans. This is a striking example of the protective effect of the

normal bacterial flora for their human host. Normal Flora of the Oral Cavity The presence of nutrients, epithelial debris, and secretions makes the mouth a favorable habitat for a great variety of bacteria. Oral bacteria include streptococci, lactobacilli, staphylococci and corynebacteria, with a great number of anaerobes, especially bacteroides. The mouth presents a succession of different ecological situations with age, and this corresponds with changes in the composition of the normal flora. At birth, the oral cavity is composed solely of the soft tissues of the lips, cheeks, tongue and palate, which are kept moist by the secretions of the salivary glands. At birth the oral cavity is sterile but rapidly becomes colonized from the environment, particularly from the mother in the first feeding. The eruption of the teeth during the first year leads to colonization by S. These bacteria require a nondesquamating nonepithelial surface in order to colonize. They will persist as long as teeth remain. Other strains of streptococci adhere strongly to the gums and cheeks but not to the teeth. The creation of the gingival crevice area supporting structures of the teeth increases the habitat for the variety of anaerobic species found. The complexity of the oral flora continues to increase with time, and bacteroides and spirochetes colonize around puberty. Various streptococci in a biofilm in the oral cavity. The normal bacterial flora of the oral cavity clearly benefit from their host who provides nutrients and habitat. There may be benefits, as well, to the host. The normal flora occupy available colonization sites which makes it more difficult for other microorganisms nonindigenous species to become established. Also, the oral flora contribute to host nutrition through the synthesis of vitamins, and they contribute to immunity by inducing low levels of circulating and secretory antibodies that may cross react with pathogens. Finally, the oral bacteria exert microbial antagonism against nonindigenous species by production of inhibitory substances such as fatty acids, peroxides and bacteriocins. If oral bacteria can gain entrance into deeper tissues, they may cause abscesses of alveolar bone, lung, brain, or the extremities. Such infections usually contain mixtures of bacteria with Bacteroides melaninogenicus often playing a dominant role. If oral streptococci are introduced into wounds created by dental manipulation or treatment, they may adhere to heart valves and initiate subacute bacterial endocarditis. Normal Flora of the Gastrointestinal Tract The bacterial flora of the gastrointestinal GI tract of animals has been studied more extensively than that of any other site. The composition differs between various animal species, and within an animal species. In humans, there are differences in the composition of the flora which are influenced by age, diet, cultural conditions, and the use of antibiotics. The latter greatly perturbs the composition of the intestinal flora. In the upper GI tract of adult humans, the esophagus contains only the bacteria swallowed with saliva and food. Because of the high acidity of the gastric juice, very few bacteria mainly acid-tolerant lactobacilli can be cultured from the normal stomach. However, at least half the population in the United States is colonized by a pathogenic bacterium, Helicobacter pylori. Since the s, this bacterium has been known to be the cause of gastric ulcers, and it is probably a cause of gastric and duodenal cancer as well. The Australian microbiologist, Barry Marshall, received the Nobel Prize in Physiology and Medicine in , for demonstrating the relationship between Helicobacter and gastric ulcers. ASM The proximal small intestine has a relatively sparse Gram-positive flora, consisting mainly of lactobacilli and Enterococcus faecalis. This region has about - bacteria per ml of fluid. The flora of the large intestine colon is qualitatively similar to that found in feces. Coliforms become more prominent, and enterococci, clostridia and lactobacilli can be regularly found, but the predominant species are anaerobic Bacteroides and anaerobic lactic acid bacteria in the genus Bifidobacterium Bifidobacterium bifidum. These organisms may outnumber E. This is our only direct association with archaea as normal flora. The range of incidence of certain bacteria in the large intestine of humans is shown in Table 4 below. Bacteria found in the large intestine of humans.

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Chapter 7 : The Normal Bacterial Flora of Humans

The Role of the Indigenous Microbiota in Zebrafish Gastrointestinal Tract Development Karen Guillemin University of Oregon. human cells GI tract bacteria cells.

References Abstract Human beings are colonised by a beneficial ecosystem of microorganisms collectively termed the commensal microbiota or microbiome. Predominantly found at mucosal surfaces, these organisms are most abundant in the lower gastrointestinal tract. While the majority cannot be cultured outside the body, the development of molecular biological techniques e. Research has uncovered a complex interplay between the intestinal microbiome and the host immune system. Microbes are most abundant in the lower GI tract. The intestinal microbiota provides the host with vital nutrients and prevents colonisation by pathogens. Novel molecular biology techniques e. Colonization begins in the womb, continues during birth and normally reaches equilibrium by 2â€”3 years of age. Intestinal microbes can also influence systemic immunity via the production of bioactive molecules, such as pattern recognition receptor agonists e. Abnormal changes in the microbiota are associated with chronic inflammatory diseases, allergic inflammation, metabolic and neurological diseases. Science Translational Medicine 6: Avrameas S Autopolyreactivity confers a holistic role in the immune system. Scandinavian Journal of Immunology Journal of Immunology Nature Reviews Microbiology 9: Nature Reviews Microbiology 7: American Journal of Clinical Nutrition Annual Review of Physiology Glaister JR Factors affecting the lymphoid cells in the small intestinal epithelium of the mouse. International Archives of Allergy and Applied Immunology Human Microbiome Project C Structure, function and diversity of the healthy human microbiome. European Journal of Immunology Frontiers in Microbiology 7: Nature Reviews Immunology Current Opinion in Gastroenterology Human Molecular Genetics Infection and Immunity Journal of Leukocyte Biology Microbial Ecology in Health and Disease Seminars in Immunology Frontiers in Bioscience Landmark Ed. The Journal of Nutritional Biochemistry World Journal of Gastrointestinal Pathophysiology 3: Hand TW The role of the microbiota in shaping infectious immunity. Trends in Immunology

Chapter 8 : CiteSeerX â€” Indigenous, normal and autochthonous flora of the gastrointestinal tract

The indigenous microbiota is a potent source of opportunistic infections that arise when the mechanisms that normally confine the microbes to a particular site are disrupted. Anaerobic infections following bowel surgery, urinary tract infections, chronic respiratory tract infections, dental/gingival diseases, and annoying skin conditions come into this category.