Journal of Probiotics & Health
ISSN: 2329-8901

Miniello et al., J Prob Health 2017, 5:1
DOI:10.4172/2329-8901.1000162

Review Article Open Access

The Importance of Being Eubiotic

Vito Leonardo Miniello[1], Lucia Diaferio[1], Carlotta Lassandro[2] and Elvira Verduci[2*]

[1]Department of Pediatrics, Giovanni XXIII Hospital, University of Bari, Bari 70126, Italy
[2]Department of Pediatrics, San Paolo Hospital, Department of Health Science, University of Milan, Milan 20142, Italy

Abstract

The human gut microbiota plays a very important part in the host's life, being closely interconnected to its health. Upon birth, a well-balanced bacterial colonization of the infant gut has a profound impact on programming short and long term metabolic and immune homeostasis. Despite the fact that most of the causality is not yet fully understood, shift in the commensal gut microbial communities with implication to disease is often referred to as dysbiosis. Infants who tend to have a delayed and/or aberrant initial colonization with reduced microbial diversity and richness, whether induced by Caesarean section, premature delivery, or excessive use of perinatal antibiotics, could be more at risk for chronic health conditions associated with metabolic and immune disorders. Exploration of the long-term effects of this abnormal microbial number and diversity is critically needed in order to intervene early in the aberrant intestinal composition and restore numerous homeostatic systems (e.g. energy balance, glucose metabolism and immunity). Dietary manipulation of the gut microbiota through the so called 'gut microbiota biomodulators' (probiotics, prebiotics, synbiotics and postbiotics) represents a promising preventive avenue.

This review aims to highlight factors that influence the gut microbiota soon after birth and discusses the potential gut-driven pathophysiologic pathways involved in intestinal dysbiosis and the gut microbiota-modulating effects of probiotics early in life.

Keywords: Gut microbiota; Dysbiosis; Caesarean section; Obesity; Gut microbiota biomodulators; Probiotics

Abbreviations: AAP: American Academy of Paediatrics; CBR: Cannabinoid Receptors; CS: Cesarean Section; CCK: Cholecystokinin; ESPGHAN: European Society for Pediatric Gastroenterology, Hepatology and Nutrition; EAACI: European Academy of Allergy and Clinical Immunology; GLP-1: Glucagon-Like Peptide-1; GALT: Gut-Associated Lymphoid Tissue; IL: Interleukin; LPS: Lipopolysaccharide; LSAC: Longitudinal Study of Australian Children; TJs: Tight Junctions; TGF: Transforming Growth Factor; UNICEF: United Nations Children's Fund; VLBW: Very Low Birth Weight; WHO: World Health Organization; ZO-1: Zonula Occludens-1

"I have finally come to the conclusion that a good set of bowels is worth more to a man than any quantity of brains". *Josh Billings* (1818–1885)

Introduction

Human beings are born and have coevolved with environmental microorganisms. The hologenome theory of evolution proposes that natural selection acts not on the individual organism but rather on the "holobiont," which consists of the human organism together with resident microbial communities (microbiota), their metabolites and genes (microbiome) [1]. Usually the term "flora" is used to describe bacteria of human organisms while the term "microbiota", recently considered as more appropriated, refers to the whole community of microorganisms that includes not just bacteria, but also other microbes such as archaea (primitive single-celled organisms), fungi, viruses, and even some protozoans.

Immediately after birth a significant number of bacteria colonize practically every surface of the human body exposed to the external environment, including the skin, eyes, oral cavity and the respiratory, urinary, reproductive and gastrointestinal tracts (gut microbiota). The digestive tract is a complex ecosystem in which microbial communities interact with each other and with their host [2]. In 2006 the scientific community recognized the gut microbiota of healthy individual as a new, metabolically active organ.

Throughout the human lifetime, the gut microbiota is known to confer a number of health benefits relating to prevention of colonization of pathogenic microorganisms, host nutrient metabolism, xenobiotic and drug metabolism, integrity of the gut mucosal barrier and maturation of the host's innate and adaptive immune responses [3-5].

Although the composition of a 'healthy' gut microbiota remains to be elucidated, normal colonization is most likely to occur when the healthy newborn infant is born full term, by vaginal delivery and exclusively breastfed for 6 months. Beyond the microbial richness and diversity, a 'eubiotic' gut microbiota is characterized by the presence of the microbes that enhance metabolism, resilience to inflammation, resistance to autoimmunity.

Dysbiosis is considered as an alteration in microbiota community structure and/or function, capable of causing/driving a detrimental distortion of microbe-host homeostasis. One of the important discoveries in the last years is the fact that intestinal dysbiosis has a profound impact on the metabolic and immune homeostasis.

In the initial stages of life several factors influence the establishment and composition of the intestinal microbiota and shape different colonization patterns: Gestational age, delivery mode and place, infant feeding, use of antibiotics and maternal infections, among others [6].

Vaginal delivery or cesarean section may differently affect the colonization of the baby, as the infant born by cesarean section is

***Corresponding author:** Dr. Elvira Verduci, Department of Pediatrics, San Paolo Hospital, Department of Health Science, University of Milan, Milan 20142, Italy, Tel: +39-0281-844-508; E-mail: elvira.verduci@unimi.it

Received August 28, 2016; **Accepted** February 07, 2017; **Published** February 14, 2017

Citation: Miniello VL, Diaferio L, Lassandro C, Verduci E (2017) The Importance of Being Eubiotic. J Prob Health 5: 162. doi: 10.4172/2329-8901.1000162

exposed to microorganisms of maternal skin and the environment, rather than to vaginal and gastrointestinal microbiota of the mother. It has been suggested that this initial colonization pattern may impact on microbiota composition for months or even years [7,8].

Inadequate or abnormal early intestinal colonization is supposed to lead to the chronic low-grade inflammation which is a common feature of virtually all noncommunicable diseases, indicating a central role of the immune system.

In gut we trust

According to the United Nations Children's Fund (UNICEF) the time spanning roughly between conception and one's second birthday, known as the first 1000 days of life, is a unique window time of opportunity for positive impact on a child's physical and cognitive development [9,10]. One of several mechanisms by which the early environment can modify phenotype is epigenetic modification of an individual's genome. Epigenetics refers to heritable changes in gene expression not caused by changes in the DNA sequence, but by biochemical modifications of DNA which can determine whether or not genes are expressed [11]. Long-term adverse health outcomes are thought to be due to "programming", a process by which adverse stimuli during early life stages can either impair the development of a somatic structure or alter a physiological setting.

Nutrients and gut microbiota are the two most important environmental factors playing pivotal roles in epigenomic programming and are most pronounced in a narrow window of time such as pregnancy and early infancy. The gut microbiota has an important role in human metabolism and could be a significant environmental factor affecting our epigenome [12].

It has been estimated that the microbes in our bodies collectively make up to 100 trillion cells, tenfold the number of human cells and suggested that they encode 100-fold more unique genes (microbioma) than our own genome [13]. It has been proposed that 90% of the bacterial phylotypes are members of two phyla (Bacteroidetes and Firmicutes), followed by Actinobacteria and Proteobacteria [14].

In early postnatal life bacterial exposure is a stepwise process: during vaginal delivery the newborn is exposed to bacteria from the birth canal and perianal region that are important precursors for gut colonization. A well-balanced microbial colonization during the first days of life may "program" immune and metabolic homeostasis later in life [15-18].

Vaginally delivered infants are colonized by maternal vaginal and fecal bacteria, including *Lactobacillus* spp. and *Bifidobacterium* spp. [19].

The neonatal colonization pattern is markedly influenced by several perinatal environmental factors such as the mode (vaginal *vs* caesarean) and the place (home-born *vs* hospital-born) of delivery, the maternal microbiome, the number of siblings, infant feeding (breast milk *vs* infant formula), perinatal drug-based therapies (antibiotics), timing and composition of weaning and maternal infections (periodontitis, urethritis, cystitis and device-associated infections) [6,20] (Figure 1).

During prenatal life microbial exposure may influence offspring microbiota and immune system. Indeed, the "sterile womb" paradigm, the dogma that gastrointestinal tract of a normal fetus is sterile, is being challenged by increasing evidence that the human intestinal microbiota is colonized before birth [21]. The maternal basal plate of the placenta is a possible source of intrauterine colonization. Stout et al. suggested that

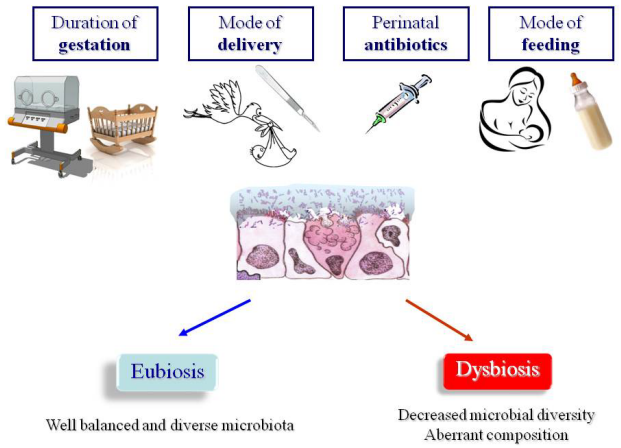

Figure 1: Perinatal environmental factors that influence neonatal colonization pattern.

the endometrial epithelium of the non-pregnant uterus may harbour occult microbes which become incorporated into the basal plate at the time of placental implantation [20].

During vaginal birth the newborn infant is exposed to a healthy bolus of maternal vaginal microorganisms and this moment represents the first and most significant phase of colonization. A more stable colonization may be reach until 4–6 years of age, when the infant is more vulnerable to infections, metabolic and immune-mediated diseases.

Biodiversity, the variability among living organisms from all sources, is closely related at both the macro- and micro-levels and concerns both environmental and commensal microbiota. This diversity manifests in differences in microbial composition not only from one human to the next but also between matching body parts, such as the right and left hands, of the same individual. The rich diversity of the microbial universe represents an ancient evolutionary beneficial process between microbial growth and host immunity [22]. Thus far, special attention has been paid to the biodiversity of commensal microbiota [23,24]. A healthy microbiota is defined by high diversity; in contrast, microbiota associated with disease (dysbiosis) is defined by lower species diversity, fewer beneficial microbes and/or the presence of pathobionts (any disease-causing microorganism). Recent studies suggest that healthy infant immune development may depend on the establishment of a diverse gut microbiota rather than the presence or absence of specific microbial strains. The biodiversity hypothesis, an extension of the hygiene hypothesis formulated in 1989 by Strachan [25], provides a link between changes in altered microbiota and disease development [26].

At the early stages of life intestinal bacteria act as pivotal challenges for the immune system and may modulate T helper (Th2)-like allergic responses by promoting Th1 responses and/or enhancing immune regulation, depending on the diversity and richness of human gut microbiome, and the genetic background of the host [27].

The instruction of the immune system to be tolerant of self, thereby preventing autoimmunity, is facilitated by the education of T cells in a specialized organ, the thymus, in which self-reactive cells are either eliminated or differentiated into tolerogenic regulatory T (Treg) cells which have immunosuppressive functions and distinct cytokine profiles [28,29]. Encounter with bacteria-derived foreign antigens in the colon seems to drive the generation of Treg cells efficiently. There

are a number of different Treg cells that can be divided into natural Treg (nTreg) cells and inducible Treg (iTreg) cells. Natural Treg cells come from the thymus, whereas iTreg cells arise in the periphery. Inducible Treg cells include interleukin (IL)-10-producing Th1 cells and transforming growth factor (TGF)-β-producing Th3. Anti-inflammatory cytokines IL-10 and TGF-β are crucial in the attenuation or containment of inflammatory process and confer suppressive effects on the immune response. The absence of a proper immunosuppressive mechanism can result in an imbalance between Th1 and Th2 cells and, in turn, Th1- or Th2-mediated inflammatory diseases.

The crosstalk between colonizing bacteria, intestinal epithelial cells and the gut-associated lymphoid tissue (GALT) has shown to have a crucial role in stimulating appropriate programming of mucosal immunity to drive tolerogenic responses and to establish immune homeostasis later in life. Notably, the host's innate and adaptive immune system may also influence the composition of gut microbiota [30].

Dysbiosis and disease

Human metabolic and immune homeostasis later in life may be influenced by a 'healthy' microbiota early in life. Indeed, early dysbiosis may be associated with the pathogenesis of intestinal and extra-intestinal disorders [31], such as obesity [32,33], type 1 and type 2 diabetes [34-39], cardiovascular disease [40], inflammatory conditions of the intestine [41] and asthma [42].

Whether early-life dysbiosis precedes and plays a role in disease pathogenesis or simply originates from the disease process itself is a question that is beginning to be answered in diseases characterised by chronic low-grade inflammation. A major determinant of the microbiota composition of newborns is the mode of delivery. Cesarean section and a lack of breast milk exposure are supposed to disrupt microbiota establishment and have been associated with increased risk for metabolic and immune-mediated disorders (autoimmunity and allergy). During natural delivery the vaginal and the fecal maternal microbiota (mainly Bacteroides and Bifidobacteria) are transferred from mother to child through the birth channel. Conversely, CS-delivered infants, deprived of contact with the maternal vaginal microbiota, experience a deficiency and a delay in colonization of Bacteroides, Bifidobacteria and Lactobacilli and a higher presence of facultative anaerobes such as Clostridium species, compared with vaginally born infants [7,18,19]. A recent pilot study demonstrated that the microbiomes of babies that were delivered vaginally or by C-section but exposed to their maternal vaginal fluids were more similar to the maternal vaginal microbiomes than to those of C-section-delivered (but unexposed) infants [43].

For nearly 30 years, the international healthcare community has considered the ideal rate for caesarean sections to be between 10% and 15% [44]. According to the World Health Organization (WHO), CS rate (percentage of births managed by CS) exceeding 15% lacks medical justification and it could be linked with adverse maternal and child health consequences [45]. Despite WHO statements, CS rates have increased by 50% or more over the last decade, with rates in the USA, UK and Australia peaking at 26.2%, 31.3% and 32.3%, respectively [46].

Numerous studies in humans and animal models have linked shifts in the gut microbiota to obesity [47]. Overweight/obesity was found more common among children delivered by CS [48]. At birth, infants delivered vaginally were slightly heavier, and there was no difference in z-score weight-for-length between the two groups. However, by 6 weeks, children born by C-section had greater standardized body mass, and this persisted until age 15, in analyses adjusted for birth weight, gender, parental body mass, sociodemographic factors, and a set of gestational factors related to obesity risk. Recently, using data from the Longitudinal Study of Australian Children (LSAC) Robson et al. showed that cesarean-born infants had a higher BMI at 8 to 9 years, although this effect could be mediated by maternal obesity [49]. Two meta-analyses confirmed that caesarean section compared with vaginal delivery is associated with greater risk of obesity in children, adolescents and adults [50,51].

Another important aspect that should be considered is the association between childhood obesity and antibiotics [52,53], the most frequently prescribed drug in children. Although antibiotics are essential for the treatment of bacterial infections, they change and alter host associated microbial communities, with rapid, deep and sometimes lasting effects, especially during childhood [54-56]. Broad-spectrum antibiotics may reduce microbiota biodiversity; alter relative proportions of bacterial species and their functional capacity [57]. In this regard it has been observed, from a large study of 74.946 children, that antibiotic treatment in the first year of life was associated with the current BMI in boys, aged 5-8, but not in girls.

C-section and early-life antibiotics deprive normal microbial colonization of the newborn gut. Such effects may highlight the importance of judicious use of antibiotics during infancy [58,59]. C-section and antibiotic use during pregnancy may alter normal maternal-offspring microbiota exchange, thereby contributing to aberrant microbial colonization of the infant gut and increased susceptibility to obesity later in life [60].

The very low birth weight (VLBW) infant is at great risk for marked dysbiosis due to multiple factors that disrupt the development of a normal gut microbiota: intestinal immaturity, inadequate colonization, frequent C-section delivery, and exposure to antibiotics in early life.

The rising incidence of childhood-onset type 1 diabetes in developed countries is likely to be a result of changes in perinatal environmental factors. The hypothesis that infants delivered by CS do not have the same exposure to maternal bacteria as infants delivered vaginally is one of the possible causal pathways.

Cardwell et al. showed the increased risk of childhood-onset type 1 diabetes in children born by CS by systematically reviewing the published literature and performing a meta-analysis with adjustment for recognized confounders [61]. This analysis demonstrated a 20% increase in the risk of childhood-onset type 1 diabetes after CS delivery that cannot be explained by known confounders (maternal age, birth weight, gestational age, birth order, maternal diabetes or breastfeeding).

Inflammatory bowel diseases, such as Crohn's disease or ulcerative colitis, can arise from the disruption of immune tolerance to the gut commensal microbiota, leading to chronic intestinal inflammation and mucosal damage in genetically predisposed hosts [62].

Allergic bronchial asthma has become a major public health burden in industrialized countries, and the incidence of this chronic inflammatory disease has been steadily growing over the last decades. Thavagnanam reported a statistically significant 20% increase in the subsequent risk of developing asthma in children born by CS [42]. The discrimination between the effect of acute and elective CS might be crucial because these events represent two completely different exposure parameters: infants delivered by elective CS do not acquire microbial colonization from the birth canal and have not been exposed to labor which is thought to promote the action of various cytokines [45]

some of which might have long-lasting effects on the immune system [63]. A recent study showed that planned cesarean delivery compared with vaginal delivery (but not compared with unscheduled cesarean delivery) was associated with a small absolute increased risk of asthma requiring hospital admission, and salbutamol inhaler prescription at age 5 years [64].

Obesity is not just obesity

The recent epidemic of childhood obesity is one of the greatest challenges facing medical professionals caring for infants and children. Its growing incidence over the last decades cannot solely be explained by genetic factors. Obesity is associated with a low-grade chronic inflammation that contributes to the development of metabolic alterations related to glucose homeostasis (glucose intolerance, type 2 diabetes and insulin resistance), dysbiosis and increased endocannabinoid (eCB) system tone [65-68].

The current evidence from prospective human studies investigating the association between infant gut microbiota and later childhood overweight is still limited. Nevertheless, recent advances in scientific research have revealed intriguing mediating factors between the gut microbiota, diet and host energy metabolism [69,70]. Although the primary cause of obesity is excess caloric intake compared with expenditure, emerging evidences show that obese and lean individuals have distinct intestinal microbiota patterns, with measurable differences in their ability to extract energy from their diet and to deposit that energy in fat [71,72].

The obesity-microbiome relationship has been the subject of many studies as the human gut microbiota is involved in the regulation of energy extraction from short chain fatty acids and indigestible polysaccharides, playing a key role in host energy metabolism and adipogenesis. From studies on lean and obese mice has been suggested that the gut microbiota influences the efficiency of energy harvest from the diet, its use and storage. Moreover, the relative composition of the gut microbiota early in life may predict later overweight or obesity [73].

Obesity was associated with an increased abundance of the phylum Firmucutes (Clostridium genus) and a decrease in the Bacteroidetes phylum, one of the most numerically abundant Gram-negative phyla in the mammalian gastro-intestinal tract [33]. Although obesity and leanness phenotypes were different at the phylum level through a change of the Bacterioidetes-to-Firmicutes ratio [74], reduced bacterial diversity and an altered representation of bacterial genes and metabolic pathways were major traits of the obese phenotype. In fact, the significant variability even in healthy individuals that has been observed makes the relevance of this ratio debatable.

Microbial richness, referred to bacterial diversity, is usually considered an indicator of a healthy status since reduced bacterial diversity has been related to metabolic and immune disorders [75-78]. A recent Danish study showed how gut commensals affect propensity to develop obesity and related conditions [75]. Results of this study [75], performed on 292 obese and non-obese individuals, showed that subjects with the lowest bacterial abundance had more abdominal fat and worst metabolic-inflammatory profile (insulin resistance, high insulin levels, increased triglycerides, decreased HDL-cholesterol, and increased C-reactive protein), compared to those with high bacterial richness. They also showed reduction in the butyrate-producing bacteria and higher levels of pathobionts such as Campylobacter, Porphyromonas, Ruminococcus and Staphylococcus. On the contrary, people with high bacterial richness showed mostly Bifidobacterium and Lactobacillus genera that determine the production of short-chain fatty acids (butyrate, lactate and propionate). These results highlighted that microbial dysbiosis may lead to low-grade inflammation and insulin resistance. Therefore, it has been suggested that subjects with low bacterial richness had an inflammation-associated microbiota and may be at increased risk of obesity-associated comorbidities. Dietary intervention could improve low bacterial gene richness and clinical phenotypes, but seems to be less efficient for inflammation variables in individuals with lower gene richness.

In humans, antibiotic use during infancy may lead to higher risk of obesity later in life, probably by reducing bacterial richness [79], as observed in animal models after repeated antibiotic use [80].

The gut is able to host commensal bacteria and molecules, absorb nutrients and inhibit the invasion of tissues by bacteria, a process known as intestinal mucosal barrier function. Soon after birth the *gut closure* takes place, decreasing gut permeability and transport of macromolecules across the intestinal barrier. Paracellular permeability across epithelial cells is regulated by tight junctions (TJs), which are the apical most junctions in epithelial cells [81]. Tight junctions are not static barriers but highly dynamic structures that are constantly being remodeled due to interactions with external signals, such as cytokines and bacterial components, originating in the lumen, epithelium and lamina propria [82]. Intestinal permeability decreases faster in breastfed babies than in formula-fed infants [83]. A host–bacterial mutualism leads to the control of gut barrier function [84]. Recent data suggest that disruption in gut microbiota composition plays a critical role in the development of obesity-associated inflammation [85].

The gut microbiota regulates the activity of the peripheral endocannabinoid system in intestinal and adipose tissue, which in turn controls gut barrier function and adipogenesis [86] (Figure 2). The widespread intercellular signalling system, consisting of cannabinoid receptors (eCBRs), endocannabinoids and enzymes involved in their synthesis and degradation, is involved in the regulation of energy balance [87]. The eCB system's salient homeostatic roles have been summarized by Di Marzo as, "relax, eat, sleep, forget, and protect" [88]. In this regard, endocannabinoid signaling is proposed to be a general hunger signal that acts at cannabinoid type 1 receptor (CB1R) to inhibit satiation [89]. Its over- activation results in chronic positive energy balance and alteration of glucose homeostasis which increase the risk of obesity. In particular, upregulation of the CB1R in the central nervous system and periphery results in overstimulation of the reward system associated with food intake, which promotes excessive food consumption and leads to visceral adiposity.

Lipopolysaccharide (LPS) is a major component of the outer membrane in Gram-negative bacteria. Gut microbiota-derived lipopolysaccharide levels were closely correlated with changes in composition where the Gram negative-to-Gram positive ratio increased during high-fat feeding [90]. It is supposed that dysbiosis is involved in increased intestinal permeability and the associated inflammation. Dysbiosis-induced disruption of the intestinal barrier causes translocation of bacterial products across the gut which in turn drives low-grade inflammation, 'metabolic endotoxemia' (increased plasma LPS levels), so called in recognition of the fact that levels are much lower than those observed in septic shock, and metabolic disorders. Intestinal microbiota regulates intestinal permeability and adipose tissue physiology through LPS-eCB system regulatory loops.

It is suggested that LPS could stimulate eCB system [91]. Cani et al. proposed that changes in the distribution and localisation of

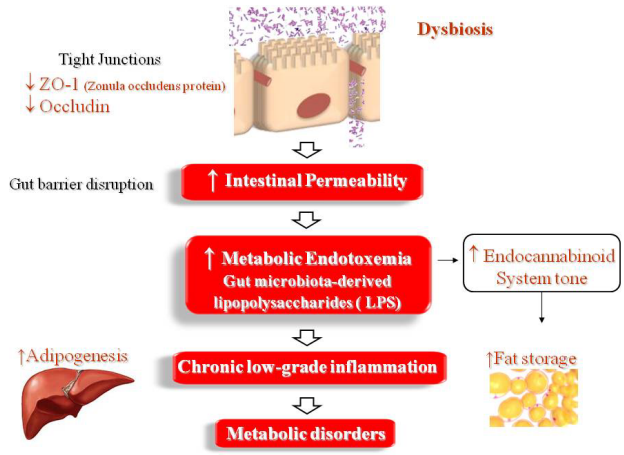

Figure 2: The link between the gut microbiota and the peripheral endocannabinoid system.

zonula occludens-1 (ZO-1) and occludin (two tight junction proteins) are associated with the increased gut permeability and metabolic endotoxemia-induced inflammation occurring in obese rodents [92].

Rationale for the use of probiotics

The establishment of a healthy gut microbiota is involved in the development of gut function, in protection against infections, in preservation of intestinal barrier function and development of a balanced immune system. When full colonization is reached, gut microbiota and underlying epithelial and lymphoid tissues established a symbiotic relationship [93].

Breastfeeding and vaginal delivery stimulate the proliferation of a rich and diverse microbiota which initially influences a switch from an intrauterine Th2 predominant to a Th1/Th2 balanced response by the activation of T-regulatory cells [94]. Gut commensals can induce Treg cells allowing the host to tolerate the massive burden of antigens presented to the gut and ensuring that innocuous antigens (food and indigenous microbiota) do not trigger excessive inflammatory immune response (tolerance).

Altered intestinal barrier function and increased intestinal epithelial permeability can be consequences of disrupted early colonization. The integrity of the epithelial barrier depends on homeostatic regulatory mechanisms, including mucosal induction of Treg cells, where commensal microbiota–host interactions play decisive roles. Early microbial colonization has been proposed as a major driver for the normal age-related maturation of both Th1 and Treg pathways that appear important in suppressing early propensity for Th2 allergic responses. Moreover, microbial abundance and diversity can induce maturation of tolerogenic dendritic cells and skew the perinatal Th2 milieu toward Th1 maturation. Notably, in white adipose tissue, which coordinates metabolism at distant tissues, Tregs contribute to the maintenance of insulin sensitivity by limiting inflammation and producing insulin-sensitizing factors such as IL-10 [95].

Emerging evidence has shown that early disruption of microbiota colonization may influence the occurrence of later diseases (microbial programming). Inadequate or abnormal early intestinal colonization (CS-delivery, prematurity, excessive use of perinatal antibiotics) lead to the breakdown in the gut homeostatic symbiosis and, in turn, to development of immunologically mediated diseases [96-98].

Increased interest in the effects of the intestinal microbiota on human health has resulted in attempts to optimize the microbial ecosystem by the so called 'gut microbiota biomodulators' [99] such as probiotics, prebiotics, synbiotics or postbiotics.

The most commonly accepted definition of probiotics was published by the World Health Organization/Food and Agricultural Organization in 2001 that stated that probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit to the host" [100]. Several properties that are thought to be important for the probiotic effect include high survival rates under acidic or bile salts condition, adherence to mucus or to epithelial cells, enzymatic activity, and antibiotic resistance or production of antimicrobial compounds.

Most probiotics taxonomically belong to two genera, Bifidobacteria and Lactobacilli known to have a wide range of human health benefits. However, Lactococcus, Streptococcus and Enterococcus species, as well as some non-pathogenic Gram-negative strains of Escherichia coli (*E. coli* Nissle 1917), and yeast strains (*Saccharomyces boulardii*) may also act as probiotics. In particular, strains belonging to Bifidobacterium and Lactobacillus are the most widely used probiotic bacteria and exert health-promoting properties, including the maintenance of the gut barrier function and the modulation of the host immune and metabolic responses [101]. Noteworthy, probiotic bacteria stimulate immune functions in a strain-specific manner [102-104].

The beneficial effect of probiotic strains is mainly on diseases involving the mucosal immune system [105]. *In vitro* and animal studies have generated most of the mechanistic rationale for the use of probiotics that act through a number of different pathways [106-109] (Table 1).

To evaluate the effect of probiotic and prebiotic supplementation in preventing allergies Finnish researchers conducted a clinical trial on more than 1200 mothers whose infants would be at high risk to develop allergies [110]. According to AAP (American Academy of Paediatrics), ESPGHAN (European Society for Pediatric Gastroenterology, Hepatology, and Nutrition) and EAACI (European Academy of Allergy and Clinical Immunology) an infant is defined as 'high risk' for developing allergic disease if there is at least one first degree relative (parent or sibling) with a documented allergic condition (atopic dermatitis, asthma, rhinitis, or food allergy). During the last month of their pregnancies, the mothers took daily doses of a probiotic mixture (*Lactobacillus rhamnosus* GG, *Lactobacillus rhamnosus* LC705, *Bifidobacterium breve* Bb99, *Propionibacterium freudenreichii* ssp. *shermanii* JS) or a placebo, and their infants were given the same probiotic mixture plus a prebiotic (GOS) or a placebo for the first 6 months of their lives. The children were followed for 5 years and evaluated for incidence of allergic diseases. Although no allergy-preventive effect was extended to age 5 years by perinatal supplementation with the probiotics and synbiotic in high-risk babies, it is noteworthy that less IgE-associated allergic disease occurred only in Caesarean-delivered children (24.3% vs. 40.5%; p=0.035). Therefore, the authors concluded that "protection was conferred only to CS babies".

The early gut microbiota is believed to maintain a state of regulated inflammation that is important in providing cross talk between intestinal microbes and the GALT [101]. Defective intestinal epithelial tight junction barrier function is implicated in a number of intestinal and systemic inflammatory conditions. Pathogenic microorganisms induce a strong host response; probiotics induce an intermediate response, whereas commensal bacteria exhibit homeostatic control

Mechanism of probiotics
Mucosal barrier function **Gut microbiota** Probiotics – Restore healthy composition – May convert a dysbiosis to a symbiosis, by balancing pathobionts (any disease-causing microorganism) with health-promoting bacteria; **Enterocytes and mucus** Probiotics • Increase TGF-β production; • Increase local IgA production; • Enhance mucus production **Tight junctions** Probiotics – Attenuate IL-1β-induced NF-κB activation – Reduce antigenic load
Immunological Action Probiotics • Modulate Innate Immunity (tolerogenic dendritic cell maturation) • Probiotics increase T regulatory cells (TGF-β-producing Th3 cells) • Probiotics increase Th1 differentiation and Th1 skewed responses • Probiotics inhibit Th2 allergic responses • Probiotics modulate of Th1/Th2 balance (↑Th1 ↓Th2)

Table 1: Mechanistic rationale for the use of probiotics.

of the response. Microbiome influences systemic inflammation through Toll-like receptor (TLR) pathways, with downstream effects on the risk of insulin resistance, obesity, and immune diseases [111]. TLR signaling is induced by commensal bacteria to produce a state of controlled inflammation that helps develop the innate immune defences and promotes pathogen recognition. One of the consequences of dysbiosis is increased gut permeability and increased microbial translocation through the mucosal barrier, leading to metabolic endotoxemia, subsequent low-grade inflammation and increased generation of proinflammatory cytokines [112,113]. Recently, Guo et al. demonstrated that secreted metabolites of *Bifidobacterium infantis* and *Lactobacillus acidophilus* protect the intestinal barrier impairment caused by the pro-inflammatory cytokine IL-1β stimulation through tight junction modulation in mature and immature enterocytes [114].

Individuals with obesity and type 2 diabetes differ from lean and healthy individuals in their abundance of certain gut microbial species and microbial gene richness. The abundance of Bifidobacterium spp. and *Akkermansia muciniphila* is consistently reduced under high-fat diet regimen [115]. Moreover, *A. muciniphila* has been inversely correlated with body weight [116] and type 1 diabetes in mice and humans [117]. Recently this mucin-degrading intestinal anaerobe bacterium has been proposed as a new functional microbe with probiotic properties.

Cholecystokinin (CCK), the most extensively studied gastrointestinal satiety hormone, was found to act as a hunger suppressant [118]. Glucagon-like peptide-1 (GLP-1) shows central effects, suppressing appetite and reducing the rate of food absorption into the blood by lowering the rate of gastric emptying. Unlike CCK and GLP-1, ghrelin does not appear to signal satiety but rather increases in the plasma in anticipation of a meal and falls immediately after the consumption of food [119]. In contrast to "adiposity signals" such as the adipose-derived hormone leptin and circulating insulin, plasma ghrelin concentrations increase in direct proportion to lean body mass. Probiotics have been shown to modify the production of gastrointestinal satiety hormones when given to rats [120].

The ability of probiotics to influence metabolism differs greatly depending on the strain in question. A recent meta-analysis analyzed randomized controlled trials and comparative clinical studies in humans and animals or experimental models assessing the effect of Lactobacillus-containing probiotics on weight [120]. The Authors found that the manipulation of the gut microbiota by *L. acidophilus*, *L. ingluviei* or *L. fermentum* results in weight gain whereas specific strains of *L. gasseri* and *L. plantarum* used as food supplements presented an anti-obesity effect.

Conclusion

Understanding the factors that regulate immune and metabolic homeostasis in health and disease may yield insight into strategies to prevent chronic low-grade inflammation and dysregulated glucose homeostasis. Prenatal and postnatal periods represent a pivotal window of opportunity to modulate metabolic and immune responses. An inadequate gut microbiota composition in early life seems to account for the deviant programming of later immunity and overall health status. In this regard, modulation of the gut microbiota composition, protection of intestinal mucosal barrier, remission of metabolic endotoxemia and relief of local and systemic inflammation may provide a novel strategy for the prevention of metabolic and immune disorders.

The potential for the positive manipulation of the gut microbiome through the introduction of probiotics is currently an intriguing area of investigation.

In infants with inadequate or abnormal early intestinal colonization (dysbiosis), whether induced by Caesarean section, premature delivery or excessive use of perinatal antibiotics, probiotics or their secretions may prevent diseases by exerting anti-inflammatory effects, improving intestinal function barrier and modulating immune responses.

Although gut microbiota biomodulators have the potential to restore the intestinal microbiota balance, further studies on the appropriate timing of interventions are required to translate these findings into preventive strategies.

References

1. Roeselers G, Ponomarenko M, Lukovac S, Wortelboer HM (2013) *Ex vivo* systems to study host-microbiota interactions in the gastrointestinal tract. Best Pract Res Clin Gastroenterol 27: 101-13.
2. Bäckhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI (2005) Host-bacterial mutualism in the human intestine. Science 307: 1915-1920.
3. Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, et al. (2015) Role of the normal gut microbiota. World J Gastroenterol 21: 8787-803.
4. Hooper LV, Littman DR, Macpherson AJ (2012) Interactions between the microbiota and the immune system. Science 336: 1268-1273.
5. O'Hara AM, Shanahan F (2006) The gut flora as a forgotten organ. EMBO Rep 7: 688-689.
6. Penders J, Thijs C, Vink C, Stelma FF, Snijders B, et al. (2006) Factors influencing the composition of the intestinal microbiota in early infancy. Pediatrics 118: 511-21.
7. Jakobsson HE, Abrahamsson TR, Jenmalm MC, Harris K, Quince C, et al. (2014) Decreased gut microbiota diversity, delayed bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section. Gut 63: 559-566.
8. Salminen S, Gibson GR, McCartney AL, Isolauri E (2004) Influence of mode of delivery on gut microbiota composition in seven year old children. Gut 53: 1388-1389.
9. Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, et al.; Lancet Nutrition Interventions Review Group; Maternal and Child Nutrition Study Group (2013) Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? Lancet 382: 452-77.
10. Lallès JP (2012) Long term effects of pre- and early postnatal nutrition and environment on the gut. J Anim Sci 90: 421-429.
11. Fraga MF (2009) Genetic and epigenetic regulation of aging. Curr Opin Immunol 21: 446-453.
12. Shenderov BA (2012) Gut indigenous microbiota and epigenetics. Microb Ecol Health Dis 23: 1-6.
13. Ley RE, Peterson DA, Gordon JI (2006) Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell 124: 837-848.
14. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, et al. (2010) A human gut microbial gene catalogue established by metagenomic sequencing. Nature 464: 59-65.
15. Rautava S, Luoto R, Salminen S, Isolauri E (2012) Microbial contact during pregnancy, intestinal colonization and human disease. Nat Rev Gastroenterol Hepatol 9: 565-567.
16. Matamoros S, Gras-Leguen C, Le Vacon F, Potel G, de La Cochetiere MF (2013) Development of intestinal microbiota in infants and its impact on health. Trends Microbiol 21: 167-173.
17. Sim K, Powel E, Shaw AG, McClure Z, Bangham M, et al. (2013) The neonatal gastrointestinal microbiota: The foundation of future health? Arch Dis Child Fetal Neonatal Ed 98: 362-364.
18. Azad MB, Konya T, Maughan H, Guttman DS, Field CJ, et al. (2013) Gut microbiota of healthy Canadian infants: Profiles by mode of delivery and infant diet at 4 months. CMAJ 185: 385-394.
19. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, et al. (2010) Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci USA 107: 11971-11975.
20. Stout MJ, Conlon B, Landeau M (2013) Identification of intracellular bacteria in the basal plate of the human placenta in term and preterm gestations. Am J Obstet Gynecol 208: 226.
21. Mshvildadze M, Neu J, Schuster J, Theriaque D, Li N, et al. (2010) Intestinal microbial ecology in premature infants assessed with non-culture-based techniques. J Pediatr 156: 20-25.
22. Dishaw LJ, Cannon JP, Litman GW, Parker W (2014) Immune-directed support of rich microbial communities in the gut has ancient roots. Dev Comp Immunol 47: 36-51.
23. Haahtela T, Holgate S, Pawankar R, Akdis CA, Benjaponpitak S, et al. (2013) WAO special committee on climate change and biodiversity. The biodiversity hypothesis and allergic disease: world allergy organization position statement. World Allergy Organ J 6: 3.
24. Butchart SH, Walpole M, Collen B, van Strien A, Scharlemann JP, et al. (2010) Global biodiversity: Indicators of recent decline. Science 6: 1164-1168.
25. Chan YK, Estaki M, Gibson DL (2013) Clinical consequences of diet-induced dysbiosis. Ann Nutr Metab 63: 28-40.
26. Hanski I, von Hertzen L, Fyhrquist N, Koskinen K, Torppa K, et al (2012) Environmental biodiversity, human microbiota and allergy are interrelated. Proc Natl Acad Sci USA 109: 8334-8339.
27. Garn H, Renz H (2007) Epidemiological and Immunological evidence for the hygiene hypothesis. Immunobiology 212: 441-452.
28. Palomares O, Martín-Fontecha M, Lauener R, Traidl-Hoffmann C, Cavkaytar O et al. (2014) Regulatory T cells and immune regulation of allergic diseases: Roles of IL-10 and TGF-β. Genes Immun 15: 511-520.
29. Josefowicz SZ, Rudensky A (2009) Control of regulatory T cell lineage commitment and maintenance. Immunity 30: 616-625.
30. Zhang H, Sparks JB, Karyala SV, Settlage R, Luo XM (2015) Host adaptive immunity alters gut microbiota. ISME J 9: 770-781.
31. Carding S, Verbeke K, Vipond DT, Corfe BM, Owen LJ (2015) Dysbiosis of the gut microbiota in disease. Microb Ecol Health Dis 26: 26191.
32. Koleva PT, Bridgman SL, Kozyrskyj AL (2015) The infant gut microbiome: Evidence for obesity risk and dietary intervention. Nutrients 7: 2237-2260.
33. Ley RE, Turnbaugh PJ, Klein S, Gordon JI (2006) Microbial ecology: Human gut microbes associated with obesity. Nature 444: 1022-1023.
34. Mejia-Leon ME, Petrosino JF, Ajami NJ, Domínguez-Bello MG, de la Barca AM (2014) Fecal microbiota imbalance in Mexican children with type 1 diabetes. Sci Rep 4: 3814-3823.
35. Baothman OA, Zamzami MA, Taher I, Abubaker J, Abu-Farha M (2016) The role of gut microbiota in the development of obesity and diabetes. Lipids Health Dis 15: 108.
36. Brown CT, Davis-Richardson AG, Giongo A, Gano KA, Crabb DB, et al. (2011) Gut microbiome metagenomics analysis suggests a functional model for the development of autoimmunity for type 1 diabetes. PLoS ONE 6: e25792.

37. Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, (2010) Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS ONE 5: e9085.

38. Markle JG, Frank DN, Mortin-Toth S, Robertson CE, Feazel LM, et al. (2013) Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. Science 339: 1084-1088.

39. de Goffau MC, Luopajärvi K, Knip M, Ilonen J, Ruohtula T, et al. (2013) Fecal microbiota composition differs between children with β-cell autoimmunity and those without. Diabetes 62: 1238-1244.

40. Senthong V, Wang Z, Li XS, Fan Y, Wu Y, et al. (2016) Intestinal microbiota-generated metabolite trimethylamine-N-oxide and 5 year mortality risk in stable coronary artery disease: The contributory role of intestinal microbiota in a COURAGE-like patient cohort. J Am Heart Assoc 5: e002816.

41. Malmborg P, Bahmanyar S, Grahnquist L, Hildebrand H, Montgomery S (2012) Cesarean section and the risk of pediatric Crohn's disease. Inflamm Bowel Dis 18: 703-708.

42. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR (2008) A meta-analysis of the association between Caesarean section and childhood asthma. Clin Exp Allergy 38: 629-633.

43. Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, Cox LM, Amir A, et al. (2016) Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. Nat Med 22: 250-253.

44. Gibbons L, Belizán J M, Lauer JA, et al. (2010) The global numbers and costs of additionally needed and unnecessary caesarean sections performed per year: Overuse as a barrier to universal coverage. World Health Report.

45. Betrán AP, Merialdi M, Lauer JA, Bing-Shun W, Thomas J, et al. (2007) Rates of caesarean section: analysis of global, regional and national estimates. Paediatr Perinat Epidemiol 21: 98-113.

46. Osterman MJ, Martin JA (2013) Changes in cesarean delivery rates by gestational age: United States, 1996-2011. NCHS Data Brief 124: 1-8.

47. Al-Ghalith GA, Vangay P, Knights D (2015) The guts of obesity: progress and challenges in linking gut microbes to obesity. Discov Med 19: 81-88.

48. Blustein J, Attina T, Liu M, Ryan AM, Cox LM, et al. (2013) Association of caesarean delivery with child adiposity from age 6 weeks to 15 years. Int J Obes 37: 900-906.

49. Robson SJ, Vally H, Abdel-Latif ME, Yu M, Westrupp E (2015) Childhood health and developmental outcomes after cesarean birth in an australian cohort. Pediatrics 136: 1285-1293.

50. Darmasseelane K, Hyde MJ, Santhakumaran S, Gale C, Modi N (2014) Mode of delivery and offspring body mass index, overweight and obesity in adult life: A systematic review and meta-analysis. PLoS ONE 9: e87896.

51. Li HT, Zhou YB, Liu JM (2013) The impact of cesarean section on offspring overweight and obesity: A systematic review and meta-analysis. Int J Obes 37: 893-899.

52. Azad MB, Bridgman SL, Becker AB, Kozyrskyj AL (2014) Infant antibiotic exposure and the development of childhood overweight and central adiposity. Int J Obes 38: 1290-1298.

53. Trasande L, Blustein J, Liu M, Corwin E, Cox LM, et al. (2013) Infant antibiotic exposures and early-life body mass. Int J Obes 37: 16-23.

54. Bailey LC, Forrest CB, Zhang P, et al. (2014) Association of antibiotics in infancy with early childhood obesity. JAMA Pediatr 168: 1063-1069.

55. Dethlefsen L, Huse S, Sogin ML, Relman DA (2008) The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16s rRNA sequencing. PLoS Biol 6: e280.

56. Jernberg C, Lofmark S, Edlund C, Jansson JK (2010) Long-term impacts of antibiotic exposure on the human intestinal microbiota. Microbiology 156: 3216-3223.

57. Hviid A, Svanstrom H, Frisch M (2011) Antibiotic use and inflammatory bowel diseases in childhood. Gut 60: 49-54.

58. Britton RA, Young VB (2014) Role of the intestinal microbiota in resistance to colonization by Clostridium difficile. Gastroenterology 146: 1627-1553.

59. Murphy R, Stewart AW, Braithwaite I, Beasley R, Hancox RJ, et al. (2014) Antibiotic treatment during infancy and increased body mass index in boys: An international cross-sectional study. Int J Obes 38: 1115-1119.

60. Chiappini E, Mazzantini R, Miniello VL, et al. (2014) Italian Society of Preventive and Social Pediatrics Rational use of antibiotics for the management of children's respiratory tract infections in the ambulatory setting: An evidence-based consensus by the Italian Society of Preventive and Social Pediatrics. Paediatr Respir Rev 15: 231-236.

61. Mueller NT, Whyatt R, Hoepner L, Oberfield S, Dominguez-Bello MG, et al. (2015) Prenatal exposure to antibiotics, cesarean section and risk of childhood obesity. Int J Obes 39: 665-670.

62. Cardwell CR, Stene LC, Joner G, Cinek O, Svensson J, et al. (2008) Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: A meta-analysis of observational studies. Diabetologia 51: 726-735.

63. Koboziev I, Reinoso Webb C, Furr KL, Grisham MB (2014) Role of the enteric microbiota in intestinal homeostasis and inflammation. Free Radic Biol Med 68: 122-133.

64. Macaubas C, de Klerk NH, Holt BJ, Wee C, Kendall G, et al. (2003) Association between antenatal cytokine production and the development of atopy and asthma at age 6 years. Lancet 362: 1192-1197.

65. Black M, Bhattacharya S, Philip S, Norman JE, McLernon DJ (2015) Planned cesarean delivery at term and adverse outcomes in childhood health. JAMA 314: 2271-2279.

66. Olefsky JM, Glass CK (2010) Macrophages, inflammation and insulin resistance. Annu Rev Physiol 72: 219-246.

67. Shoelson SE, Goldfine AB (2009) Getting away from glucose: Fanning the flames of obesity-induced inflammation. Nat Med 15: 373-374.

68. Engeli S, Bohnke J, Feldpausch M, Gorzelniak K, Janke J, et al. (2005) Activation of the peripheral endocannabinoid system in human obesity. Diabetes 54: 2838-2843.

69. Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, et al. (2013) Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science 341: 1241214.

70. Tremaroli V, Bäckhed F (2012) Functional interactions between the gut microbiota and host metabolism. Nature 489: 242-249.

71. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, et al. (2009) A core gut microbiome in obese and lean twins. Nature 457: 480-484.

72. Pihl AF, Fonvig CE, Stjernholm T, Hansen T, Pedersen O, et al. (2016) The role of the gut microbiota in childhood obesity. Child Obes 12: 292-299.

73. Borgo F, Verduci E, Riva A, Lassandro C, Riva E, et al. (2017) Relative abundance in bacterial and fungal gut microbes in obese children: A case control study. Child Obes 13: 78-84.

74. Kalliomaki M, Collado MC, Salminen S, Isolauri E (2008) Early differences in fecal microbiota composition in children may predict overweight. Am J Clin Nutr 87: 534-538.

75. Wolf KJ, Lorenz RG (2012) Gut microbiota and obesity. Curr Obes Rep 1: 1-8.

76. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, et al. (2013) Richness of human gut microbiome correlates with metabolic markers. Nature 500: 541-546.

77. Wang Y, Hoenig JD, Malin KJ, Qamar S, Petrof EO, et al. (2009) 16S rRNA gene based analysis of fecal microbiota from preterm infants with and without necrotizing enterocolitis. ISME J 3: 944-954.

78. Bisgaard H, Li N, Bonnelykke K, Chawes BL, Skov T, et al. (2011) Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. J Allergy Clin Immunol 128: 646-652.

79. Cani PD (2013) Gut microbiota and obesity: Lessons from the microbiome. Brief Funct Genomics 12: 381-387.

80. Ajslev TA, Andersen CS, Gamborg M, Sørensen TI, Jess T (2011) Childhood overweight after establishment of the gut microbiota: The role of delivery mode, pre-pregnancy weight and early administration of antibiotics. Int J Obes 35: 522-529.

81. Cho I, Yamanishi S, Cox L, Methé BA, Zavadil J, et al. (2012) Antibiotics in early life alter the murine colonic microbiome and adiposity. Nature 488: 621-626.

82. Castoldi A, Favero de Aguiar C, Moraes-Vieira PM, Olsen Saraiva Câmara N (2015) They must hold tight: junction proteins, microbiota and immunity in intestinal mucosa. Curr Protein Pept Sci 16: 655-671.

83. Wittkopf N, Neurath MF, Becker C (2014) Immune-epithelial crosstalk at the intestinal surface. J Gastroenterol 49: 375-387.

84. Le Huërou-Luron I, Blat S, Boudry G (2010) Breast- v. formula-feeding: Impacts on the digestive tract and immediate and long-term health effects. Nutr Res Rev 23: 23-36.

85. Cani PD (2012) Crosstalk between the gut microbiota and the endocannabinoid system: Impact on the gut barrier function and the adipose tissue. Clin Microbiol Infect 18: 50-53.

86. De La Serre CB, Ellis CL, Lee J, Hartman AL, Rutledge JC, et al. (2010) Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation. Am. J. Physiol. Gastrointest. Liver Physiol 299: 440-448.

87. Muccioli GG, Naslain D, Backhed F, Reigstad CS, Lambert DM, et al. (2010) The endocannabinoid system links gut microbiota to adipogenesis. Mol Syst Biol 6: 392.

88. Cani PD, Plovier H, Van Hul M, Geurts L, Delzenne NM, et al. (2016) Endocannabinoids--at the crossroads between the gut microbiota and host metabolism. Nat Rev Endocrinol 12: 133-143.

89. Di Marzo V (1998) 'Endocannabinoids' and other fatty acid derivatives with cannabimimetic properties: Biochemistry and possiblephysiopathological relevance. Biochim Biophys Acta. 1392: 153-175.

90. Di Patrizio NV, Igarashi M, Narayanaswami V, Murray C, Gancayco J, et al. (2015) Fasting stimulates 2-AG biosynthesis in the small intestine: Role of cholinergic pathways. Am J Physiol Regul Integr Comp Physiol. 309: 805-813.

91. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, et al. (2007) Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 56: 1761-1772.

92. Hoareau L, Buyse M, Festy F, Ravanan P, Gonthier MP, et al. (2009) Anti-inflammatory effect of palmitoylethanolamide on human adipocytes. Obesity 17: 431-438.

93. Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, et al. (2008) Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes. 57: 1470-1481.

94. Artis D (2008) Epithelial-cell recognition of commensal bacteria and maintenance of immune homeostasis in the gut. Nat Rev Immunol 8: 411-420.

95. Walker WA, Iyengar RS (2015) Breast milk, microbiota and intestinal immune homeostasis. Pediatr Res 77: 220-228.

96. Brestoff JR, Artis D (2015) Immune regulation of metabolic homeostasis in health and disease. Cell 161: 146-160.

97. Gensollen T, Iyer SS, Kasper DL, Blumberg RS (2016) How colonization by microbiota in early life shapes the immune system. Science 352: 539-544.

98. Walker A (2014) Intestinal colonization and programming of the intestinal immune response. J Clin Gastroenterol 48: S8-11.

99. Arboleya S, Sánchez B, Solís G, Fernández N, Suárez M, et al. (2016) Impact of prematurity and perinatal antibiotics on the developing intestinal microbiota: A Functional Inference Study. Int J Mol Sci 17: 649.

100. Miniello VL, Colasanto A, Diaferio L, et al. (2015) Gut microbiota biomodulators: when the stork comes by the scalpel. Clin Chim Acta 451: 88-96.

101. Food and Agriculture Organization/World Health Organization (2001). Report of a Joint FAO/WHO expert consultation on evaluation of health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria.

102. Weng M, Walker WA (2013) The role of gut microbiota in programming the immune phenotype. J Dev Orig Health Dis 4: 203-214.

103. Rask C, Adlerberth I, Berggren A, Ahrén IL, Wold AE (2013) Differential effect on cell-mediated immunity in human volunteers after intake of different lactobacilli. Clin Exp Immunol 172: 321-332.

104. Dong H, Rowland I, Tuohy KM, Thomas LV, Yaqoob P (2010) Selective effects of *Lactobacillus casei* Shirota on T cell activation, natural killer cell activity and cytokine production. Clin Exp Immunol 161: 378-388.

105. Sheih YH, Chiang BL, Wang LH, Liao CK, Gill HS (2001) Systemic immunity-enhancing effects in healthy subjects following dietary consumption of the lactic acid bacterium *Lactobacillus rhamnosus* HN001. J Am Coll Nutr 20: S149-156.

106. Kristensen K, Henriksen L (2016) Cesarean section and disease associated with immune function. J Allergy Clin Immunol 137: 587-90.

107. Prescott SL, Björkstén B (2007) Probiotics for the prevention or treatment of allergic diseases. J Allergy Clin Immunol 120: 255-262.

108. Gill HS, Rutherfurd KJ, Cross ML, Gopal PK (2001) Enhancement of immunity in the elderly by dietary supplementation with the probiotic *Bifidobacterium lactis* HN019. Am J Clin Nutr 74: 833-883.

109. Yang F, Wang A, Zeng X, Hou C, Liu H, et al. (2015) Lactobacillus reuteri I5007 modulates tight junction protein expression in IPEC-J2 cells with LPS stimulation and in newborn piglets under normal conditions. BMC Microbiol 15: 32.

110. Patel RM, Myers LS, Kurundkar AR, Maheshwari A, Nusrat A (2012) Probiotic bacteria induce maturation of intestinal claudin 3 expression and barrier function. Am J Pathol 180: 626-635.

111. Kuitunen M, Kukkonen K, Juntunen-Backman K, Korpela R, Poussa T, et al. (2009) Probiotics prevent IgE-associated allergy until age 5 years in Cesarean-delivered children but not in the total cohort. Allergy Clin Immunol 123: 335-341.

112. Kaplan JL, Shi HN, Walker WA (2011) The role of microbes in developmental immunologic programming. Pediatr Res 69: 465-472.

113. Yang PJ, Yang WS, Nien HC, Chen CN, Lee PH, et al. (2016) Duodenojejunal bypass leads to altered Gut microbiota and strengthened epithelial barriers in rats. Obes Surg 26: 1576-1583.

114. Andreasen AS, Krabbe KS, Krogh-Madsen R, Taudorf S, Pedersen BK, et al. (2008) Human endotoxemia as a model of systemic inflammation. Curr Med Chem 15: 1697-1705.

115. Guo S, Gillingham T, Guo Y, Meng D, Zhu W, et al. (2016) Secretions of *Bifidobacterium infantis* and *Lactobacillus acidophilus* protect intestinal epithelial barrier function. J Pediatr Gastroenterol Nutr, p: 65.

116. Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, et al. (2013) Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. Proc Natl Acad Sci USA 110: 9066-9071.

117. Gómez-Gallego C, Pohl S, Salminen S, De Vos WM, Kneifel W (2016) *Akkermansia muciniphila*: A novel functional microbe with probiotic properties. Benef Microbes 13: 1-14.

118. Hansen CH, Krych L, Nielsen DS, Vogensen FK, Hansen LH, et al. (2012) Early life treatment with vancomycin propagates *Akkermansia muciniphila* and reduces diabetes incidence in the NOD mouse. Diabetologia 55: 2285-2294.

119. Strader AD, Woods SC (2005) Gastrointestinal hormones and food intake. Gastroenterology128: 175-191.

120. Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, et al. (2001) A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes 50: 1714-1719.