Gut microbes - Early immunity and health

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ABSTRACT

Introduction: Microbes in the human gut impact holistic health. Modifiable events can steer immunity through commensal microbial action. This protects from acute diseases and lays foundation for enduring health benefits. Timely modulation of immune development by correct feeding choices negate consequences of microbial dysequilibrium.

Materials and Methods: Review and critical analysis of relevant literature integrated to the core understanding of facets of microbial existence in the gut , their roles in early immunity , and impact on health were done. Known deficiencies in newborn immunity integrated to the actions of microbes in human milk permitted some conclusions to be drawn through logical extrapolations.

Results: Deficiencies in early immunity can, at least partially, be surmounted by an optimal gut microbial milieu provided for by human milk which also enhances gut immunity and holistic health.

Limitations: This is a narrative review and articles chosen were subjectively analysed for suitability according to relevance, however, analysis by statistical methods was not done.

Conclusions: There are clear pathways linking gut microbes, intestinal epithelia, microbial metabolites and early immune maturation. The immature immune system is guided towards proper development and maturation by breastmilk factors and milk microbes for immediate and enduring holistic health. Utilising this knowledge, research must be energised on possible mutualistic benefits of gut microbes to counter the current health challenges. The counselling of breastfeeding must not overlook the unique microbial environment endowed by the mother as a gift of health.

KEYWORDS:
gut, feeding , microbes, mucosal , immunity

INTRODUCTION

Contemporary scientific information indicates that microbial seeding of the gut during the first few years of life is an opportunity for early "programming" of immune responses with support that natural feeding can lay foundation for optimal modulation of microbes to provide the infant holistic health.[1]

Culture based assessments, molecular biology and genomic data indicate that gut microbes show remarkable heterogeneity among individuals.[2] Despite this, certain constant variables influence gut health and can provide important advantages.

A state of 'eubiosis', is coexistence of diverse microorganisms, together with oral tolerance to commensal bacteria and innocuous antigens.[3] This is quite different from the state of 'dysbiosis' which essentially refers to microbial imbalances ,scenarios that alter microbial communities due to changes in the nature and quantity of the gut microbial composition.[4] Dysbiosis increases susceptibility to a number of diseases.[5]

On early events in immune development,[5,6] while the intrauterine milieu is now known to be no longer completely germ-free, the comparatively low exposure to antigenic stimulation and the relatively quiescent intrauterine immune environment, do not stimulate the production of robust immune factors in the foetus,[5] a state that favours foetal in - utero survival.

At birth, the newborn has some immune capacity, but this is immature and not fully functional.[6] The development of early gut microbiota[7] helps optimal immune maturation in the face of muted immunity in the newborn.[8] It is driven and modulated by substances in early feeding, of which breastfeeding supports selective microbial colonization for positive health and neurocognition.[1,9]

This article focuses on how newborn immunity is impacted by gut microbial action. It integrates early immunity and microbial effects, mainly those passed on from the nursing mother to her infant. This is rather crucial because gut colonization is completed within approximately three years of life and is an early event with great potential for far-reaching and holistic health impact.[9]

MATERIALS AND METHODS

This article is divided into four subtopics. In the first area of newborn immunity, literature searches used keywords such neonatal, newborn, immune, innate and adaptive. In the second subtopic, search words were gut, gastrointestinal, immune, commensals, microorganisms, barrier, intestine and epithelium. The third area used search words such as secretory immunoglobulin A (sIgA), mucosal, immunity , secretory, while in the fourth area microbes, products, metabolites and health were search words used.

With regards to experimental studies, animal experiments were important due to ethical difficulties for such studies to be conducted on human subjects, as well as because of the challenges and ethical considerations in conducting in vivo dynamic studies of breastmilk.

This article was accepted: 04 February 2021
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250 related articles were perused in accordance with the MeSH search strategy, in the PubMed, Scopus, Embase and other databases. The articles were analysed, sometimes extrapolated, and integrated. Deficiencies in one area were integrated to developments that surmount them in another.

Publications characteristics:
Original articles, systematic reviews, meta-analyses, narrative reviews, experimental studies, prospective studies, retrospective studies and case reports were included.

Excluded were letters to editor and publications in foreign language. Unpublished papers were also excluded. A total of 45 articles were chosen.

Topic characteristics:
The articles that satisfied the following inclusion criteria on topics reviewed included newborn immunity, infant immunity, gut barrier maturity, sIgA, mucosal immunity and microbial products.

Excluded were articles that focused only on adolescent and adult immunity and on maturation of mucosal surfaces other than that of the gut and respiratory tract. Animal experiments that were felt to be unsuitable for extrapolation to humans based on pathophysiology were excluded

RESULTS

Immunity of the newborn

Issues in the immature immunity of the newborn involves various arms of immunity. Innate and adaptive immune responses of the newborn have a number of recognised differences compared to the immunity in adults.[10] The newborn system must develop the ability for defences, tissue repair, wound healing, cancer cells surveillance,[10] and must learn to coexist through immune tolerance with commensal gut microbes.

The role of gut microbes in the evolution of immunity by induction of useful responses and by guiding host immune maturity, are now recognised.[1] In health, the mature immune system is in symbiosis with the host and with diverse microbes.[11] The developing immune system is exposed to commensals during passage through the birth canal and together with other variables, steer immune development.[1]

Effective mucosal barriers are necessary to defend against pathogen entry at all mucosal surfaces, most specifically, in the gut and respiratory tract. Innate responses, barrier immaturities of newborn gut epithelium with incompletely developed chemical barriers increase risks of diseases.[8,10] Defective barriers involve composition and glycosylation of the vital mucous layer; and microbial modulation of early defenses[12], are explored here.

Serum concentrations and biological activity of almost all circulating immune substances in the newborn are lower than in adults. Cord blood contains fewer specific dendritic cells for T cell presentation, affecting development of adaptive and innate immune responses, and the links between the two.[10] There are restricted responses of interferon production for adequate viral defences and natural killer cells do not respond briskly to interleukin -2 (IL-2) and interleukin -15 (IL-15), as they would, in the older child or adult.[10]

Adaptive B cell responses are not fully effective either. B cell maturity , antibody formation and antibody class switching are of particular consequence to the preterm infant.[14,15,16] T cell functions are impaired, although they may still remain responsive, because of defective cytokine production particularly in relation to Th1 cytokines that support cell mediated immune responses, hence affecting a spectrum of T cell reactions[14,15,16,17,18,19]

In the fetus and the newborn, T cell responses are skewed towards Th2 immunity,encouraging immune tolerance, decreased recognition of allo-antigen and generally, weaker responses to most foreign antigens.[10] However, the newborn has some capacity for T cell recognition of antigens relevant to MHC molecules with potentials for interleukins to link innate to adaptive immunity.[10]

A newborn faces many novel immune challenges. Antibody responses to specific vaccines such as the polysaccharide protein conjugate vaccines require T cell interaction. However, the repertoire of neonatal B cells are not equipped with sufficient co-receptors, necessary for this, impairing such important responses.[10]

Despite such deficiencies, neonatal immunity may have some elements of responsiveness.[18] Neonatal T cells are broadly reactive with potential to rapidly evolve immune cell types for prompt protection against pathogens, and tolerance to self-antigens.[18] If this is so, responsive immunity could well be advantageously modulated by specific modifiable variables with inherent immune potential, such as exclusive breastfeeding.

Cell mediated immunity in the adult controls immune responses mainly through regulatory T cells (Treg) and Th1 cells and enhances humoral and allergic responses through Th2 cells.[19] This is not the case in early life, where T cells are polarised to dominant Th2 responses under most conditions, impairing cytokine production and regulation. T cells also respond by a number of ways to the antigen in order to balance protection and the closely associated immune-mediated tissue destruction.[20]

There are intrinsic differences in the newborn, culminating in weaker B cell antibody responses as a result of greater numbers of immature cells and unclear verdict on function of individual B cell subsets.[14] As a consequence, immunoglobulins in circulation are low in quantity, except for immunoglobulin G (IgG) passed by transplacental transfer. Immunoglobulin A (IgA) is almost undetectable and Immunoglobulin M (IgM) levels are low but increase with antigen exposure. Neonatal B cells can produce Immunoglobulin E (IgE) in the presence of cytokines, but with cytokine production affected, IgE levels are limited, and relative immaturity of yet other immunoglobulin subclasses could persist even up to 10 years of age.[14,15,16]

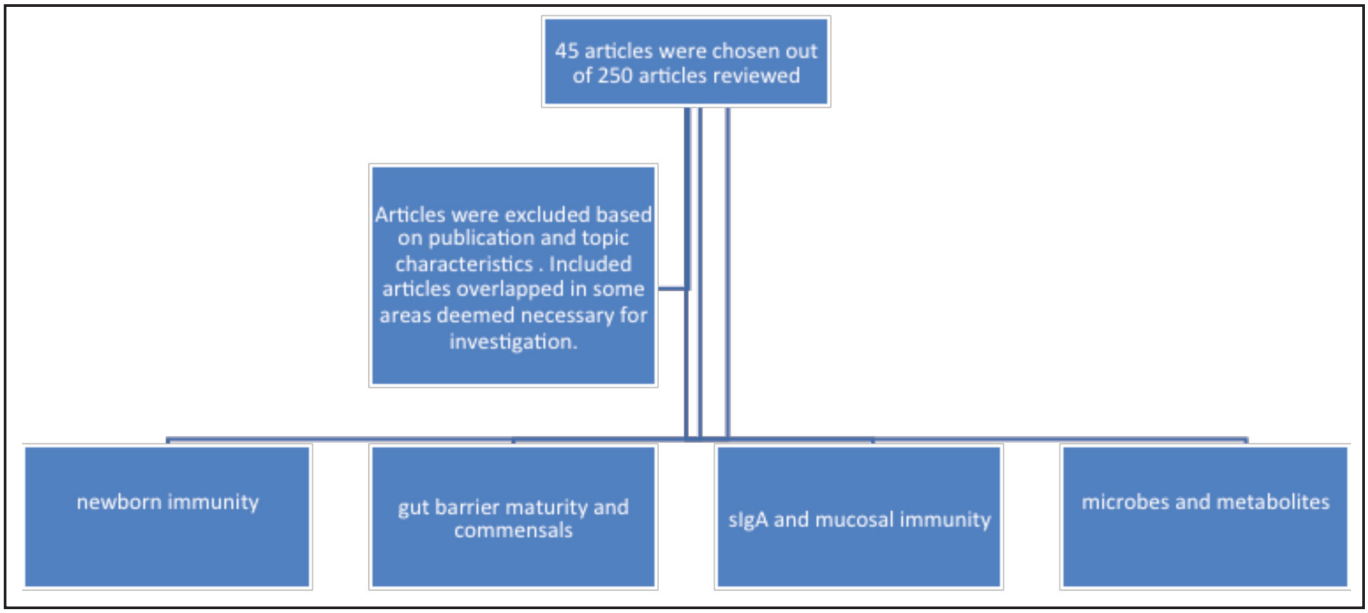

Fig. 1: Choosing articles by inclusion and exclusion characteristics.

Neonatal B cells show severely impaired class-switching, a biological mechanism that alters B cell production from one type to another, generating different antibody classes. This deficiency is most striking with IgG and IgA responses and these are linked to increased expression profiles of specific micro-ribonucliec acids (miRNA). Such responses emphasise intrinsic qualitative deficits in neonatal B cell immunity.[14]

IgA class switching after B cell activation, is crucial for effective immunity. Different affinities of sIgA maintain mucosal homeostasis and sIgA responses independent of T cells resemble innate immunity, with broad antigen specificity. T cell dependent (TD) responses, in contrast, are more specific adaptive responses, elicited by many mucosal pathogens and vaccines.[21]

Impaired innate immunity, adaptive immunity and immature gut epithelial barriers, weak Th1 and antibody responses, predispose to infection risks in the neonate, stressing emphasis on ways to enhance immunity in this crucial period.

A greater role for gut microbes in immunity

The importance of the role of gut microbes in health and disease is emphasised and microbes offer quite a different concept to early life predisposition to allergies and diseases in later life.

Most gut microbes are either innocuous or beneficial to the host. Despite marked microbial variation in individuals, three groups or enterotypes exist, the Bacteroides, Prevotella, and Ruminococcus, further identifiable by genera.[4]

The nexus that determines the development and responses of the immune system and immune mediated diseases have been considered in relation to the Th1/Th2 paradigm as well as the hygiene hypothesis.[22,23]

The hygiene hypothesis argues that patterns of microbial exposure in early life are crucial determinants of the prevalence and severity of allergic diseases in later life.[19,22,23] Early life infection exposures drive immunological responses towards a balanced cytokine profile whereas fewer intercurrent infections in the modern environment skew immunological reactions to reduce their capacity for protection against allergies.[19,24] The extended hypothesis, on the other hand, proposes that commensal intestinal microbiota, healthy host microbial interactions together with immunomodulatory and immunosuppressive responses may all be of greater importance compared to infection exposure alone, in order to stimulate immunity.[25]

Frequent infections , while probably usefully stimulating the immune system and protecting from allergies also potentially interfere with growth and development whereas commensal microbial nurture and their immunomodulation may be enhanced by behaviour patterns and safe health practices. Immunity modulated by intestinal microbes may thus be an essential tool against modern diseases.

Gut commensals , barrier maturity and immunity

From birth, many gut commensal microorganisms provide a useful "living" shield of protection against pathogens, drive metabolism needed as energy in the young and confer some important nutrients, while breaking down toxins and drugs.[9]

Microbes enter the infant's gut through various routes[26,27] and influence it as a prime organ of immune maturity. Microbes in breastmilk may be a mother's early priceless vaccination from her very own microbiota found in her mammary gland or in her gut via the entero-mammary route or the oro-mammary route. Exogenous sources such as retrograde intramammary milk inoculation through the infant's mouth or by milk contamination through the use of breast pumps,[26,27] highlight that different feeding methods impact milk microbial composition. Additionally, the mammary gland itself may autonomously regulate immune and microbial environments.[28]

Irrespective of the origin of microbes, exclusive breastfeeding provides a sustained microbial flow to the infant's gut and stabilises immature gut micro-communities.

A spectrum of bacteria such as staphylococci, streptococci, bifidobacteria and lactic acid bacteria are found in the breastfed infant. This process is sequential and orderly, where the gut may first be colonised by predominantly facultative anaerobes such as enterobacteria, coliforms and lactobacilli, then by anaerobes such as Bifidobacterium, Bacteroides, Clostridium and Eubacterium.[29] It is also notable that gut microbial colonisation is rich in signals that extend beyond the gut, influencing vital organ systems.[30,31]

Intestinal immunity depends on its barrier integrity for homeostasis and disease prevention. Epithelial translocation of pathogenic microbes or their products from the gut lumen into the systemic circulation can spread diseases.[4] Microbes influence immature epithelial barriers through their actions[9] and products. Substances such as short chain fatty acid (SCFA) augment intestinal barriers and stimulate mucus and antimicrobial peptides.[32] In this way, microbes support barrier integrity, and enhance mucus, strengthening innate immunity.

Preterm infants less than 33 weeks gestation monitored for intestinal permeability and faecal microbiota show improved intestinal permeability and barrier maturation correlating with significant increases in microbial diversity, particularly, members of the Clostridiales and Bifidobacterium. Early exclusive breastmilk feeding, shorter duration of antibiotic exposure and early microbial gut colonisation by members of the Clostridiales improved intestinal barrier function in this cohort.[33]

Intestinal barrier integrity activates intestinal immunity and this is critical to the preterm infant. Intestinal microbes within the gut lumen, in proximity to immune cells and the epithelial barrier, modulate immunity.[34] A link between commensal bacteria and optimal development of gut-associated lymphoid tissues (GALT), a part of the mucosa associated lymphoid tissues (MALT), "unifying" mucosal sites in immune responses to antigens, may clarify this role.[35] They activate immune cells of the innate and adaptive system such as macrophages, neutrophils, innate lymphoid cells 3 (ILC3), B and T cells, to produce antimicrobial factors.[4]

In the immature systems commensals guide the development of immunity. A typical molecule of commensal bacteria is bacterial polysaccharide (PSA) important for maturating the immune system by modulating T cells , Th1/Th2 imbalances and guiding lymphoid organogenesis. PSA presented by dendritic cells , the specialised sentinel cells of immunity, activates CD4+ T cells for cytokine production.[36] Integrating, it is appreciated that commensal activity can surmount some features of newborn immune immaturity.

The cells in the gut mucosa are unique , balancing pathogen responses and modulating immune tolerance towards commensal microbes. Instead of a proinflammatory milieu as occurs against pathogens, specialised intestinal cells namely the dendritic cells (DCs) at mucosal surfaces stimulate tolerance-inducing reactions, moderated responses without the unnecessary side effects of inflammation , when they encounter commensal bacterial antigens.[37]

In the gut, antigen presenting cells, (APCs) express low levels of toll-like receptors (TLRs) and microbe-associated molecular patterns (MAMPs) expressed on commensals do not trigger inflammatory reactions. Such responses not only foster microbial tolerance but may also importantly contribute to host development and health.[36]

Additionally, commensal bacteria themselves help create a tolerant immune environment. By stimulation of pattern-recognition receptors (PRR) present in intestinal epithelial cells (IEC), such as Toll-like receptor (TLR) and other receptors, by commensal bacteria, there is production of thymic stromal lymphopoietin (TSLP), for immune proliferation and modulation of host- microbial interactions.[4]

Angiogenesis is fundamental to intestinal epithelial growth and development. Commensal microbes also have impact on blood vessel development[34,35] contributing to a robust mosaic of villus capillaries in the intestinal wall.[37,38] This is corroborated by the comparisons of germ-free and colonized rodents where indigenous microbes that colonize mucosal surfaces regulate the underlying microvasculature by signaling mechanisms.[38]

The microbiota cross talk with macrophages produces regulatory molecules for intestinal homeostasis. Transforming growth factor-beta (TGF-β) is an important immune regulatory cytokine produced abundantly by IEC in the intestines for a degree of immune tolerance in the gut which help nurture commensal microbes and an intestinal milieu that can potentially prevent the growth of pathogenic microbes, through a process of commensal microbial selection deemed necessary for optimal immune development and health.[4]

Regarding adaptive immune response, the intestinal lamina propria contains T cells that stimulate T regulatory (Treg) cells which express the transcription factor forkhead box P3 (Foxp3), a transcriptional regulator in development.[39] Microbe-induced Treg cells also prevent inflammation through immune mechanisms.[40]

Gut microbial profiles influence the immune maturation of the gut , but the immune equilibrium by cytokines induced by microbes and their individual contribution to the immune balance is yet unfolding and not completely elucidated.[40,41,42] The human symbiont *Bacteroides fragilis* encourages the formation of Treg cells and suppresses proinflammatory immune responses.[40] Such responses are mediated by specific T cell subsets such as the T-helper 17 (Th17) cell, a T helper cell that produces a highly inflammatory cytokine with role in pathogenesis of immune mediated diseases,[41] whereas colonization by segmented filament bacteria (SFB) induces Th1, Th2, Th17, and Treg cells and this balance contributes to maturation of gut immunity.[42]

Breastmilk also provides factors with indirect supportive roles towards commensal growth in the gut. Human milk oligosaccharides, (HMOs) which mostly escape digestion play multiple roles , they help fortify intestinal barriers , can act as decoy receptors for pathogens and enhance innate and adaptive immunity. Some HMOs are prebiotics , providing metabolic substrate for specific commensal microbes.[1]

sIgA

A tight -knit association exits between microbes , the lining of epithelial cells of the gut and the underlying mucosal immune system (MALT), of which sIgA is key. Homeostasis at gut mucosal surfaces ensures cooperation between the three and induces production of sIgA.[34,35,36]

Specific microbes that colonise the intestine shortly after birth induce the generation of IgA antibodies of which there are two types, IgA 1and IgA 2.[43] Through mechanisms involving a proliferation-inducing ligand (APRIL), bacteria trigger IgA(2) class switching[43] This seems to be an important function of mucosal immunity, as IgA2 is more resistant to bacterial digestion[43], and such microbial actions could overcome some of the inherent deficiencies of newborn immunity. IgA, produced by lamina propria B cells is secreted into the intestinal lumen, where it is able to perform "immune exclusion",[35] a process of entrapment, agglutinating and clearance of pathogens , as well as influence gut microbiota composition and function.[4,40]

The unique structural components of the sIgA molecule and its dynamics in the mucous contribute to potent mucosal immune action.[44] In its multimeric form it is transported across mucosal surfaces and secretions by a polymeric Ig receptor (pIgR), in epithelial cells. During the synthesis of pIgR, a conformational change occurs in the molecule so that a covalent bond between polymeric IgA (pIgA) and pIgR is formed. The pIgR, which transports pIgA, also contributes to a very important part of the molecule, the secretory component (SC). SC not only protects sIgA from proteolysis resisting digestion by intestinal juices, but also contributes towards intestinal homeostasis, directly interacting with intestinal bacteria, possibly via binding them.[44]

Additionally, through T cell independent mechanisms, bidirectional responses between commensal gut microbes and host , induce the production of low affinities of sIgA,[43,44] whereas through T dependent mechanisms , high affinity sIgA defend against pathogens.[44] The suggestion that despite immaturity, neonatal T cells are capable of responsive action,[18] maybe pertinent here. Early exposure to commensals could train the immune system for a more modulated T cell development.

Microbes, products and links

There is wide individual diversity of commensal gut microbes that regulate epithelial development and guide innate immunity. A study of an impressive number of prokaryotic ribosomal RNA gene sequences from the gut of healthy subjects indicate that bacterial sequences corresponded to uncultivated species and varying novel microorganisms between subjects.[45]

Distant microbial links are supported by evidence such as of liver disease associated with gut dysbiosis, gut toxins affecting renal function and gut microbiomes influencing progression of atherosclerosis and congestive heart failure.[30,31]

CONCLUSION

Newborn immature immunity can be influenced by modifiable events such as feeding choices. Microbes in breastmilk, at least partially, help to overcome this immaturity and to guide early immunity through immune factors and biological links to positively modify the health fabric. Developing this, research on novel microbial communities can continue to be effective tools for health intervention, both at the individual level as well as at the community.

Exploring microbial balances, conferred by the wisdom in natural feeding, as in this article, is a good place to begin.

FUNDING

No funding needed

REFERENCES

1. van den Elsen LWJ, Garssen J, Burcelin R . Verhasselt V. Shaping the Gut Microbiota by Breastfeeding: The Gateway to Allergy Prevention? Front Pediatr 2019; 7: 47.
2. Yan Y, Nguyen LH , Franzosa EA , Huttenhower C Strain-level epidemiology of microbial communities and the human microbiome Genome Med 2020; 12: 71.
3. Walker WA. Initial Intestinal Colonization in the Human Infant and Immune Homeostasis Contribution of the Intestinal Microbiota to Human Health and Disease. Ann Nutr Metab 2013; 63: 8-15.
4. Silva MJ, Carneiro MB, dos Anjos Pultz B, Pereira Silva D, Lopes ME, dos Santos LM. The multifaceted role of commensal microbiota in homeostasis and gastrointestinal diseases. J Immunol Res 2015; 2015: 321241.
5. Renz H, Brandtzaeg P , Hornef M. The impact of perinatal immune development on mucosal homeostasis and chronic inflammation. Nat Rev Immunol 2011; 12 (1): 9-23.
6. Levy O Innate immunity of the newborn: basic mechanisms and clinical correlates Nat Rev Immunol 2007; 7(5): 379-90.
7. Turroni F, Milani C, Duranti S, Lugli GA , Bernasconi S, Margolles A, et al The infant gut microbiome as a microbial organ influencing host well-being Ital J Pediatr 2020; 46(1): 16.
8. Yu JC, Khodadadi H, Malik A, Davidson B, Salles ESL, Bhatia J et al Innate Immunity of Neonates and Infants Front Immunol. 2018; 9: 1759.
9. Yang I, Corwin EJ, Brennan PA , Murphy JR, Dunlop A The Infant Microbiome: Implications for Infant Health and Neurocognitive Development Nurs Res. 2016; 65(1): 76-88.
10. Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age Proc Biol Sci. 2015: 282(1821): 20143085.
11. Belkaid Y, Hand T. Role of the Microbiota in Immunity and inflammation Cell. 2014; 157(1): 121-41.
12. Deplancke B, Gaskins HR Microbial modulation of innate defense: goblet cells and the intestinal mucus layer Am J Clin Nutr 2001; 73(6): 1131S-1141S.
13. Sampah MES , Hackam DJ Dysregulated Mucosal Immunity and Associated Pathogeneses in Preterm Neonates Front Immunol. 2020; 11: 899.

14. Glaesener S, Jaenke C, Habener A, Geffers R, Hagendorff P, Witzlau K, et al. Decreased production of class-switched antibodies in neonatal B cells is associated with increased expression of miR-181b. PLoS ONE 2018; 13(2): e0192230.
15. Pastorelli G, Rousset F, Pene J, Peronne C, Roncarolo G, Tovo PA et al Cord blood B cells are mature in their capacity to switch to IgE-producing cells in response to interleukin-4 in vitro. Clinical and Experimental Immunology 1990; 82: 114-119.
16. Aksu G, Genel F, Koturoglu G, Kurugol Z, Kutukculer N, Serum immunoglobulin (IgG, IgM, IgA) and IgG subclass concentrations in healthy children: a study using nephelometric technique. The Turkish Journal of Pediatrics 2006; 48: 19-24.
17. Martin R, Nauta AJ, Amor KB, Knippels LMJ, Knol J, Garssen J Early life: gut microbiota and immune development in infancy Benef. Microbes 2010; 1(4): 367-82.
18. Rudd BD Neonatal T Cells: A Reinterpretation Annu. Rev. Immunol 2020; 38: 229-247.
19. Romagnani S. Coming back to a missing immune deviation as the main explanatory mechanism for the hygiene hypothesis. J. Allergy Clin. Immunol. 2007; 119: 1511-3.
20. Mayya V , Dustin ML What Scales the T Cell Response? Trends Immunol 2016; 37(8): 513-22.
21. Bunker JJ, Bendelac A Immunity. IgA responses to microbiota Immunity. 2018; 49(2): 211-24.
22. McLachlan SM. Graves' disease: The Th1/Th2 paradigm versus the "hygiene" hypothesis and defective immune regulation. Thyroid 2003; 13: 127-8.
23. Strachan DP, Hay fever, hygiene, and household size. Br. Med. J. 1989; 299: 1259-60.
24. Brandtzaeg P. Food allergy: separating the science from the mythology. Nat. Rev. Gastroenterol. 2010; 7: 380-400, erratum: 478.
25. Samuli R, Olli R, Arthur O, Seppo S, Erika I. The Hygiene Hypothesis of Atopic Disease-An Extended Version J. Pediatr. Gastroenterol. 2004; 38(4): 378-88.
26. Rodriguez, JM. The origin of human milk bacteria: is there a bacterial entero-mammary pathway during late pregnancy and lactation? Adv. Nutr. 2014; 5: 779-84.
27. Moossavi S, Azad MB Origins of human milk microbiota: new evidence and arising questions Gut Microbes Gut Microbes. 2020; 12(1): 1667722.
28. Niimi K, Usami K, Fujita Y, Abe M, Furukawa M, Suyama Y, et al Development of immune and microbial environments is independently regulated in the mammary gland Mucosal Immunol 2018; 11: 643-53.
29. Houghteling PD, Walker WA, M.D. Why is initial bacterial colonization of the intestine important to the infant's and child's health?J Pediatr Gastroenterol Nutr. 2015 ; 60(3): 294–307.
30. Konturek PC , Harsch IA , Konturek K, Schink M, Konturek T, Neurath MF, et al The Gut-Kidney Axis: Putative Interconnections Between Gastrointestinal and Renal Disorders Front Endocrinol (Lausanne). 2018; 9: 553.
31. Forkosh E, Ilan Y The heart-gut axis: new target for atherosclerosis and congestive heart failure therapy Open Heart. 2019; 6(1): e000993.
32. Kamada N , Seo SU, Chen GY, Núñez G Role of the gut microbiota in immunity and inflammatory disease. Nature Reviews Immunology. 2013; 13(5): 321-35 .
33. Ma B, McComb E, Gajer P, Yang H, Humphrys M, Wonodi ACO, et al Microbial Biomarkers of Intestinal Barrier Maturation in Preterm Infants Front Microbiol. 2018; 9: 2755.
34. Hooper LV, Wong M H, Thelin A, Hansson L, Falk PC, Gordon J I Molecular analysis of commensal host-microbial relationships in the intestine. Science 2001; 291: 881-4.
35. Corthésy B Multi-Faceted Functions of Secretory IgA at Mucosal Surfaces Front Immunol. 2013; 4: 185.
36. Mazmanian SK, Liu CH, Tzianabos AO Kasper DL An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. Cell 2005; 122: 107-18.
37. Hooper LV, 2004. Bacterial contributions to mammalian gut development. Trends in Microbiology 2004; 12: 129-34.
38. Stappenbeck TS, Hooper LV. Gordon JI, 2002. Developmental regulation of intestinal angiogenesis by indigenous microbes via Paneth cells. Proc Natl Acad Sci U S A 2002; 99: 15451-5.
39. Li L, Boussiotis VA The role of IL-17-producing Foxp3+ CD4+ T cells in inflammatory bowel disease and colon cancer. Clin. Immunol. 2013; 148(2): 246-53.
40. Round JL., Mazmanian S. K. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. PNAS 2010; 107(27): 12204-9.
41. Tesmer LA,Lundy SK, Sarkar S, Fox DA Th 17 cells in human disease Immunol Rev. 2008; 223: 87-113.
42. Routhiau VG, Rakotobe S , Lécuyer E, Mulder I, Lan A , Bridonneau C et al The key role of segmented filamentous bacteria in the coordinated maturation of gut helper T cell responses. Immunity. 2009; 31(4): 677-689.
43. He B, Xu W, Santini PA, Polydorides AD, Chiu A, Estrella J, et al Intestinal bacteria trigger T cell-independent immunoglobulin A(2) class switching by inducing epithelial-cell secretion of the cytokine APRIL Immunity 2007; 26(6): 812-26.
44. Li Y, Jin L, Chen T.The Effects of Secretory IgA in the Mucosal Immune Systems. Biomed Res Int. 2020; 2020: 2032057.
45. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M et al Diversity of the Human Intestinal Microbial Flora Science. 2005; 308(5728): 1635-8.