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Review - Human and Animal Health

Gut: Key Element on Immune System Regulation

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HIGHLIGHTS

- Intestinal mucosa is the greatest area for antigen contact and immune system regulation.
- Gut-associated lymphoid tissue allows to immune tolerance
- Epigenetic factors, life-style and food intake impacts the intestinal microbiota and thus regulate the immune response.

Abstract: The gut is the main organ that mediates the contact between antigens with our organism, controlling the immune response against environmental factors, such as microbiota and food. Innate lymphoid cells participate in the gut-associated lymphoid tissue (GALT) maturation during the prenatal and early postnatal periods. After birth, breast milk provides the essential elements for the continuity of development of this tissue, leading to structural changes and healthy microbiota installation. The microbiota participates in the organogenesis of the GALT, as in the formation of intestinal villi, stimulating the proliferation of stem cells and maintaining the integrity of epithelial barrier. Foods are also involved in maturation of the GALT, where the protein source depletion reduced the number of resident

lymphocytes. This unique microenvironment present in the intestinal lamina propria (LP) and mesenteric lymph nodes (mLN) induce tolerance to innocuous antigens from the diet, known as Oral Tolerance. Antigens sampled by intestinal epithelium cells are transferred to specialized dendritic cells, residing in the LP, which migrate to the mesenteric lymph nodes where they participate in the induction of regulatory T cells (Treg). Understanding these phenomena may establish the intestinal mucosa as a tool in therapy of inflammatory bowel diseases and immunological disorders.

Keywords: Immunology; Gut; Peripheral Tolerance.

INTRODUCTION

The relationship between immune function and the gut is paramount, starting in early embryologic development with hematopoietic stem cells being produced by the fetal liver around the seventh week of development, just two weeks after the invagination of the liver from the foregut [1]. At the end of gestation, hematopoietic stem cells migrate to bone marrow where B cell development occurs, as T cell development takes place in the thymus [2].

The greatest contact of a mammal organism with antigenic material occurs in the intestinal mucosa. With approximately 300 m² area, the intestinal mucosa receives around 30 Kg of proteins per year, which 130-190 g are daily absorbed. Intestinal microbiota stands as an additional source of antigenic stimulation, as it is composed by 1012 microorganisms per gram of stool [3, 4, 5]. Despite all antigenic stimulation, the organization of the gut-associated lymphoid tissue (GALT) allows a microenvironment propitious to immune tolerance. The immunological tolerance developed against food antigens is known as oral tolerance, characterized as a local and systemic suppression of immune response after challenge with antigen [5]. Unlike tolerance to food antigens, tolerance to intestinal microbiota does not prevent systemic immune response [6]. The interactions between epithelial cells, stromal cells, cells from innate and adaptive immune response interplay in promoting immune tolerance to innocuous antigens as well as protective immune response against pathogens [7].

The present work aims to critically evaluate the role of the gut as the main organ responsible for immune system regulation, considering developmental aspects, as the role of breastfeeding, diet antigens and intestinal microbiota in the GALT development and function.

Gut associated lymphoid tissue

By its function and structure, the GALT can be classified in two distinct groups: the organized GALT, composed by Peyer's Patch and mesenteric lymph nodes (induction sites) and the diffuse GALT, composed by the intestinal lamina propria and intraepithelial lymphocytes (effector sites). Peyer's patch are constituted by a great number of B cells, T cells, macrophages and dendritic cells, organized as B cells follicles with intermediate areas of T cells. Peyer's patch follicular epithelium presents M cells; modified enterocytes specialized in the capture of small soluble antigens to whole microorganisms [8, 9] Figure 1.

Mesenteric lymph nodes (mLN) are the biggest lymph nodes in the immune system [10]. Its development is different from the Peyer's patch and other peripheral lymph nodes, as it's not affected by the lack of tumor necrosis factor (TNF) and its respective receptor (TNFR). Dendritic cells CD103+ and stromal cells from mLN are capable of converting vitamin A obtained from diet to retinoic acid (RA), essential in the synthesis of gut-homing molecules as α4β7 integrin and chemokine receptor 9 (CCR9) as in the generation of regulatory T cells. The higher levels of retinoic acid in the mLN favor the maintenance of tolerance in the gut [6].

Innate lymphoid cells (ILC) are crucial in the development of GALT during the prenatal. All subtypes of ILC rely on the expression of retinoic acid orphan receptor (RORγt), as the knockout of the gene responsible for RORγt expression resulted in complete absence of any GALT structure. However, mice deficient in recombination activating gene (RAG), which do not have B and T cells, developed structures similar to isolated lymphoid follicles (ILF) [7]. Thus, it is observed the ancient evolutionary origin and genetically predetermined function of ILCs. In postnatal period, ILCs respond quickly to microorganisms present in the gut, producing IL-22, IL-17 or IL-13. ILCs are not only essential in organogenesis, but they also can directly modify adaptive immune response via cell-cell interaction [7].

Lamina propria (LP) is a layer of connective tissue, located between the epithelial tissue and the muscularis mucosae, composed by myeloid and lymphoid cells [8]. The large number of T cells, dendritic cells (DCs) and macrophages found on LP allows the efficient processing and presenting of commensal antigens and food proteins [11]. Among the leucocytes present in LP, the macrophages are in greater abundance. By its high phagocytic activity, they are constantly controlling microorganism burden, as they also secrete anti-inflammatory cytokines such as IL-10 [10]. Recently, an especial population of myeloid intestinal cells CX3CR1highCD11b+CD11c+ was identified. Named Mregs, these macrophages are distributed all over the LP, being unable to promote T cell differentiation, besides inhibiting Th1/Th17 proliferation in an IL-10/stat3 mechanism. The administration of wild-type Mreg to mice deficient in stat3 improved intestinal inflammation, indicating that Mreg dysfunction might play a role in inflammatory bowel diseases [12]. IgA secreting plasmocytes represent 30 to 40% of mononuclear cells in healthy LP [8]. Regulatory B cells (Bregs) CD1dhigh regulate adaptive immune response by secreting IL-10, inhibiting activation of myeloid intestinal cells [12]. T cells present in LP are most CD4+ (60-70%), where 10% express CD25. T CD4+ plays an important role in immune system regulation to food antigens. Cytokines like IL-10 and transforming growth factor β (TGF-β) secreted by these cells helps in the suppression of Th1/Th2/Th17 immune response [5].

Another important component of the GATL is the intraepithelial lymphocytes (IEL). These cells are usually found in the frequency of one IEL to ten epithelial cells in the small intestine of mice and one to each five absorptive cells in human jejunum, decreasing along the bowel [8, 5]. IELs functions are not completely understood, but some works point that they help maintaining the integrity of intestinal epithelial barriers, respond to infectious agents and participate in tissue renewal [8, 5]. Almost all IELs are CD3+, where most are CD8+. IEL CD8+ expresses the T cell receptor (TCR) αβ and γδ, whereas CD8+γδ are in higher frequency in intestinal epithelium than in LP and peripheral blood. Independently of

its phenotype, all intestinal IEL express αEβ7 integrin (CD103+), ligand of E-Cadherin. This interaction, in addition to facilitating the anchoring of IEL to intestinal epithelium, they can ensure the functionality of the same. IELs might be involved in oral tolerance, as its depletion is associated to oral tolerance impairment [13].

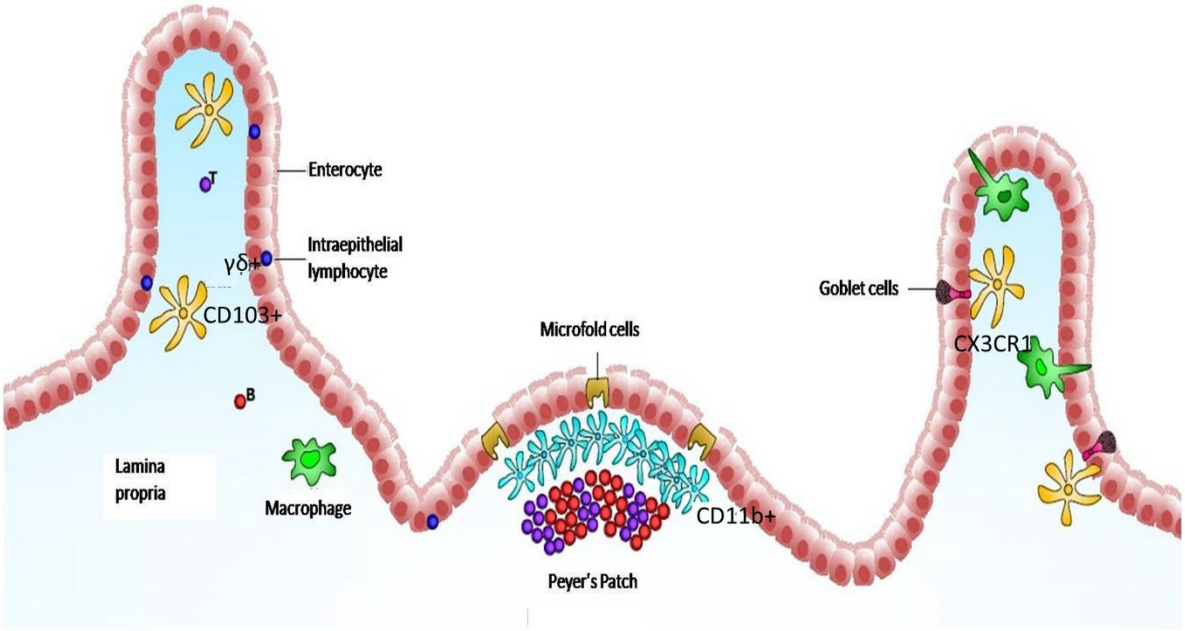

Figure 1. Schematic representation of gut associated lymphoid tissue. Dendritic cells CD103+ sample antigens from intestinal lumen and migrate to mesenteric lymph nodes, where they drive T regulatory cells differentiation. Goblet cells and CX3CR1high macrophages mediate the capture of soluble antigens. Peyer's patch is mainly responsible for inducing immune response against microorganisms as well as maintaining peripheral tolerance.

Breastmilk and immune programing

Breast milk is the ideal form of human nutrition during the first months of living, constituting as a strong source of nutrients in the first year of the child [14]. Besides promoting the essential nutrients for organism development, the breastmilk plays a crucial role in the maturation of newborn's immune system. It is attributed to this function the diversity of active immunological substances present in the milk, allowing the newborn to make the appropriate transition between the sterile environment, found in the mother's womb, to the external environment. In this dynamic process, the immune system has to adapt to potentially harmful antigens as well as innocuous antigens [15].

Several studies show the impact of breastfeeding in allergic diseases, autoimmune diseases, metabolic diseases and protecting the infant against infections and comorbidities. In a systemic review [16], evaluate breastfeeding and the risk of developing Crohn's disease and ulcerative colitis, showing that breastfeeding until six months might be associated with reduced risk in developing intestinal inflammatory disease. In a study evaluating the effects of breastmilk in developing bronchial asthma during childhood, was suggested a strong protector effect in families with the historical atopic disease [17]. Exclusive breastfeeding

during the first three months was associated with a lower incidence of atopic dermatitis in childhood. While there's conflict in data about breastfeeding and obesity [18, 19]. Moreover, breastfeeding was associated with a reduction in the incidence of Diabetes Mellitus type II, with lower glucose and plasmatic insulin concentration during childhood and adulthood [20].

The benefits that breastmilk provides are well comprehended when it is observed the multiplicity of components that the infant receives [21, 22, 14]. Oligosaccharides from breastmilk stimulates the growth of bifidobacterium and lactobacillus, building a healthy microbiota in the gut [23]. Aminoacids such as arginine, glutamine and threonine affects mechanical, hormonal and neuroendocrine functions in the gastrointestinal tract (TGI) [24]. They increase cellular migration by mechanisms evolving nitric oxide (NO), increase protein synthesis, reduce intestinal permeability, increase enterocytes and lymphocytes survivability and antioxidant capability of cells. Medium chain triglycerides (MCT) and polyunsaturated fat acids (PUFA) are also involved in structural function and immunoregulation in the gut. MCTs promote an increase in intestinal structure and are also antimicrobial, while PUFAs enrich enterocyte membrane with phospholipids, reduce mast cell degranulation, increase glucose uptake via GLUT-2 and sodium-dependent glucose transporter (SGLT-1) and reduce the denudation of villi [24]. The breastmilk has abundant growth factors, with broad spectrum of effects on TGI, on vascular development and on nervous and endocrine system [22]. Epidermal growth factor (EGF) is critical in maturation and intestinal mucosa repair. It is two thousand times more present in colostrum than later in lactation. EGF is resistant to acid pH and degradation to digestive enzymes, where it stimulates enterocytes growth and proliferation. The immaturity of early gut extends to the enteric nervous system, which relies on brain-derived neurotrophic factor (BDNF) and glia-derived neurotrophic factor (GDNF) for its development [21]. Both are detected in breast milk three months after birth [22]. Vascular endothelial growth factor (VEGF) and erythropoietin are also in higher levels in colostrum, reducing gradually along lactation. They are related to angiogenesis and increase in red cells in the newborn, respectively [26].

Not only soluble factors, the breastmilk is also rich in a great variety of cells, including macrophages, stem cells and lymphocytes [27], effector and anti-inflammatory cytokines [28], chemokines [22] and immunoglobulin (IgA, IgG and IgM) [29]. All these immune system components provided by mother are essential for healthy development and maturation of TGI and GALT of newborn. Monocytes from peripheral blood migrate to the milk through mammary epithelial, where they differentiate to non-phlogistic macrophages. Macrophages then differentiate to dendritic cells that stimulate infant T cells [30]. The profile of anti-inflammatory and effector cytokines on breastmilk varies according to the mother's [28]. TGF-β is the main cytokine present on breastmilk, where the isoform TGF-β2 prevails. TGF-β participates in thymus development and T cells homeostasis on peripheral lymphoid tissues [31], preventing allergic diseases and promoting regulatory T cell generation (FoxP3+ and LAP+) [5]. Granulocyte colony stimulation factor (G-CSF) is presented on breastmilk, but it is not absorbed on intestinal surface. It's effects are observed on structural development of gut, where it increases intestinal villi, crypt depth and stimulate epithelial cell proliferation [32, 22]. Pro-inflammatory cytokines like TNF-α, IL-6, IL-8 and IFN-γ are also present in breastmilk, however in lower concentration than suppressor cytoklines,

decreasing along lactation. Higher levels of pro-inflammatory cytokines were observed in preeclampsia [33] and mastitis [34]. In the colostrum of allergic mothers, IFN-γ presents reduced while Th2 cytokines like IL-4 and IL-13 are increased [35]. In a previous study analyzing the profile of cytokines of newborn was evaluated between infants fed with breastmilk and infant fed with infant formula. TNF-α and IL-2 were found significantly increased in the serum of newborn fed with infant formula, whereas TGF-β levels were decreased, compared with breastmilk fed infant [14]. Immunoglobulin found on breastmilk reflects the history of mother's immune system, as in the encounter and exposure to antigens, to the profile of immune response triggered after exposure. The newborn, yet with an immature immunological system, relies heavily on maternal immunoglobulin for protection against pathogens [29]. sIgA is the predominant class of antibody secreted on breastmilk, followed by sIgM and IgG. Plasmocytes derived from GALT migrate to mammary gland, transporting sIgA and sIgM via polymeric immunoglobulin receptor (pIgR) and IgG by neonatal Fc receptor (FcRN). Due to the origin of plasmocytes, the repertoire of antibodies passed to the newborn is targeted to antigens that might be found in the gut [29]. Secretory IgA and IgM exert they effects by immunological exclusion and anti-inflammatory activity [36]. sIgA reduced antigenic burden through binding to microorganisms, peptides as other macromolecules, reducing the rate of particles binding the intestinal epithelium and entering intestinal LP [37]. It is possible to observe that breastfeeding, besides being essential for newborn development, it provides components required for immune system maturation and promotes an anti-inflammatory profile that is kept during childhood, contributing to oral tolerance induction and preventing the development of allergic and inflammatory bowel diseases.

Food and immune system

Recently, more importance has been directed in the understanding of mechanisms performed by food in development and regulation of immune response, as well as its impact on microbiota [15]. Mice free from protein source, treated with equivalent quantities of aminoacids, displayed poor GALT development, result in lower quantities of intraepithelial lymphocytes, lower levels of sIgA and reduction on serum levels of IgA and IgG. The immune predominant profile of cytokines was Th2, similar to mice not breastfed [38]. The later introduction of potential allergenic food was associated with a higher risk in developing allergies in infants. The way how immune system reacts in these situations is not completely cleared, but evidence suggest that food antigens participates on immune system maturation and homeostasis [39]. Exploring the concept of systemic biology, it has been observed the interplay between the immune system, intestinal epithelium, and microbiota [40]. In the absence of B cells or IgA and in the presence of microbiota, intestinal epithelium activates mechanisms that promote an increase in IFN-γ expression and simultaneously suppress metabolically functions related to Gata4. This change impairs lipid absorption and consequently reduced lipid deposit [40]. These data may explain the long-term relationship between immunodeficiency and impaired lipid absorption.

Prebiotics are non-digestible foods that stimulate the growth of a select group of microorganisms in the gut [41]. The administration on inulin in IL-10 knockout mice increased the intestinal villi and crypt depth in the proximal colon. Despite IL-10-/- mice

naturally developing enterocolitis, mice treated with inulin did not show weight decrease or signs of intestinal inflammation [42]. The administration of prebiotics in obese hyperphagic mice ob/ob promoted an increase in cells producing GLP-1 and GLP-2, regulating the activation of endocannabinoid system in the gut and in the adipose tissue. These effects contribute to the reduction of intestinal permeability, reducing the entrance of antigens to the intestinal LP [43].

Oral tolerance

Oral tolerance is the state of local and systemic anergy, induced by the oral administration of innocuous antigens, such as food proteins [6]. Since the early decades of last century, it has been shown that the ingestion of immunogenic proteins is capable of reducing specific immunological reactions after immunization [44]. The phenomena of oral tolerance were extensively shown in rodents, by using recombinant proteins, cellular antigens and haptens [45, 46]. In contrast to low pH and the presence of proteolytic enzymes in the superior TGI, some immunogenic components are resistant to degradation and enter intestinal lumen. Oral administrated antigens were detected in intestinal epithelium and LP few minutes later administration [47]. In another study, it was visualized CD11c+ charged with antigens in LP after 30 to 60 minutes of oral administration [48].

The antigenic nature determines how DCs samples foreign particles from intestinal lumen to LP Figure 2A. Molecules with low molecular weight such as haptens and polypeptides can cross directly the epithelium by diffusion through pores or by tight junctions that connect epithelium cells [6]. Molecular complexes can undergo transcytosis through enterocytes that express the major histocompatibility complex II (MHC II), delivering antigens to DCs via exosomes [37]. Exosomes are formed when endosomes containing partially degraded proteins fuse to MHC II compartments [49]. Also, human enterocytes express FcRn, which helps the recirculation of IgG bound to intestinal antigens [49]. The retro-transport of IgA bound with virus/bacteria through M cells is beneficial in the induction and protective immune response, but the retro-transport of intact peptides of gliadin via ectopic expression of IgA receptor (CD71) on enterocytes contributed to abnormal activation of T cells, characterized in coeliac disease (CD) [37].

Macrophages, enterocytes and dendritic cells secrete TGF-β, that in the absence of IL-6, participates in the generation of regulatory T cells (Treg) FoxP3+. TGF-β signaling induces and maintains the expression of forkhead box P3 transcriptional factor in CD4+CD25+Tregs, besides suppressing effector T cells in vitro and in vivo [50]. The main population of dendritic cells involved in Treg generation expresses the αEβ7 integrin (CD103). These cells migrate from intestinal LP to mesenteric lymph nodes, promoting Treg differentiation and inducing the expression of gut-homing molecules [51, 52] Figure 2B. DCs CD103+ properties are related to its expression of retinal-dehydrogenase (RALDH2), converting vitamin A to retinoic acid [53]. RA alone is sufficient in inducting the gut-homing molecules CCR9 and α4β7 integrin on T cells, beyond acting as a cofactor in the conversion of naiveCD4+ to Tregs mediated by TGF-β 6. mLN stromal cells also participate in RA synthesis by expressing RALDH1, RALDH2 and RALDH3. This microenvironment rich in RA is indispensable for oral tolerance induction, as shown by mice that lack vitamin A from diet

displayed a reduced number of DCs CD103+, that behave like Langerhan's cells [54, 55]. Tregs generated on mLN return to intestinal LP via CCR9 and α4β7 integrin where they proliferate de novo by IL-10 action, secreted by DCs CD11b+. Tregs can stimulate DCs CD11b+ to produce IL-27, which increases IL-10 production by type I regulatory T cells (Tr1) [56]. Tregs can reach peripheral blood by exiting mLN through peripheral lymph nodes, following thoracic duct [10]. One of the explanations for the systemic effects of oral tolerance was demonstrated in a previous study, where Tregs derived from mLN induce Indolamine 2,3 deoxygenase (IDO) expression on spleen-derived DCs [57].

Tregs can mediate immune suppression by a set of different mechanisms. Tregs can inhibit effector T cells through the production of suppressor adenosine or direct transfer of cAMP to these cells [58]. Tregs also inhibit the production of pro-inflammatory cytokines in effector T cells by inhibiting Ca2+ signaling and so NFAT and NF-KB expression [59]. Besides the production of suppressive cytokines like IL-10, IL-35 and TGF-β, Tregs suppress effector T cells by competing in consuming IL-2 [60]. Indirectly, Tregs affect T effector generation by inhibition the expression of co-stimulatory molecules (CD80/CD86) on activated DCs [60].

Besides induced CD4+CD25+FoxP3+Tregs, other classes of regulatory cells are activated after oral administration of innocuous antigen. These, include natural Tregs derived from thymus, IL-10 dependent Tr1 cells, T helper 3 (Th3) LAP+ TGF-β dependent cells, CD8+Tregs and B regulatory cells (Bregs) [5, 61]. Tr1 cells participate on oral tolerance by secreting high levels of IL-10 and inducing apoptosis in APCs via granzyme B. They express CD49b and lymphocyte activating gene 3 (LAG-3) [62]. Th3 cells are distinct by presenting a pro-peptide bound by non-covalent on the amino-terminal domain of TGF-β, forming a latent complex of TGF-β (LAP). Th3 cells remain on the peripheral immune compartment, being activated via TCR stimulation driven by intestinal antigens [61]. The phenotypes of Bregs are similar to Tregs; Br1 cells express mainly IL-10, Br3 cells express TGF-β and BrFoxP3+ express both cytokines. Bregs can be activated by toll-like receptors, being activated early than Tregs and disappearing when Tregs are functional [61]. CD8+Tregs are involved in the production of IgA by local plasmocytes, which are important in reducing the antigenic burden on intestinal lumen. Despite being involved on oral tolerance, works point that they are not essential for oral tolerance induction with low antigen doses [63].

Some T cells recognizing self-antigens with high affinity are capable of expressing FoxP3 and become naturally occurring T regs (nTreg) in positive selection in the thymus [64]. This concept was challenged by the demonstration that non-self antigens constitute the main source of peptides recognized by TCRs expressed on nTregs [65]. Although had been demonstrated that induction of oral tolerance in the absence of nTregs [66], others have point that Thymus-derived Tregs constitute the main population of Tregs in all lymphoid organs, where the TCR repertoire is highly influenced by microbiota [67]. There is also evidence suggesting that nTregs and not iTregs are the main responsible for mediating tolerance to commensal antigens [68]. Despite the phenomena of tolerance being commonly described as a state of anergy and inhibition, mice tolerant to ovalbumin (OVA)

presented higher frequency of immunoglobulin-secreting cells (ISC) in the spleen and bone marrow, where ISCs from spleen express preferentially IgA and IgM [68].

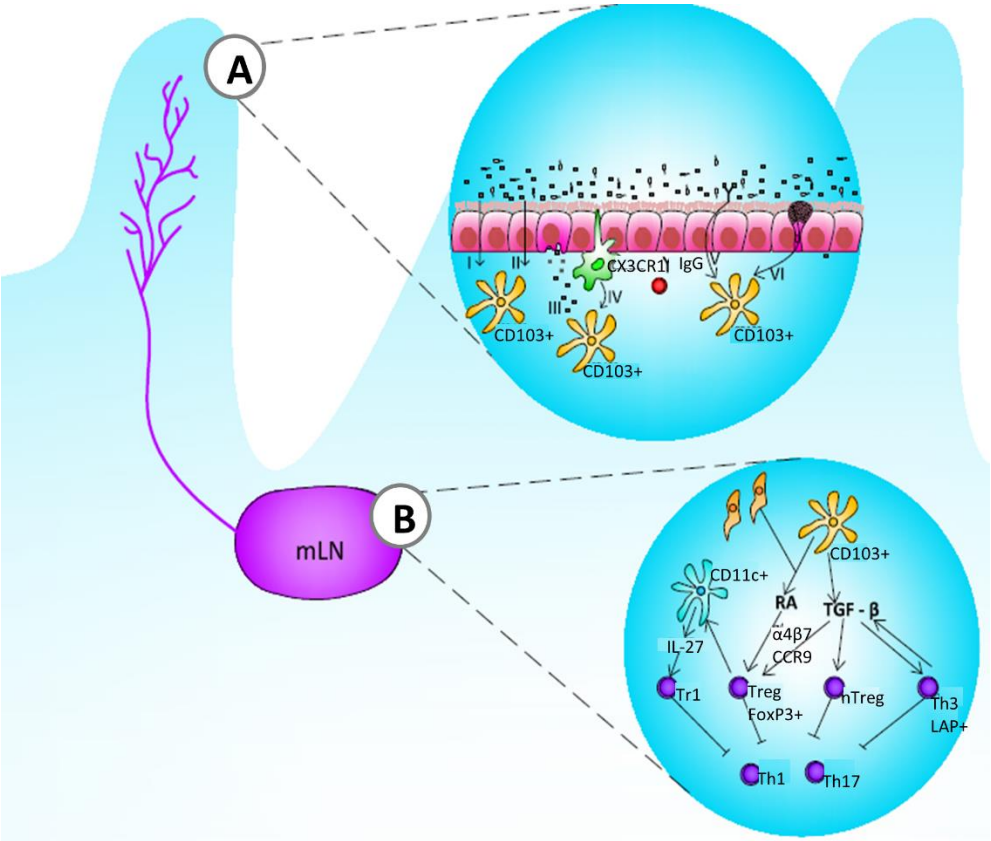

Figure 2. Mechanism of antigen capture and generation of regulatory T cells. DCs 103+ perform a fundamental role in the presentation of antigens and induction of tolerance. (A) DCs can acquire soluble antigens that crossed the tight junctions between epithelial cells (I) or via transcellular (II). Exosomes containing MHC class II processed antigens are captured by DCs (III). CX3CR1high macrophages capture luminal antigens through cellular extensions (IV). IgG secreted by plasmocytes can be retro-transported via neonatal Fc receptor (FcRn) to intestinal lamina propria (V). Goblet cells also mediate antigen sample from intestinal lumen to LP (VI). (B) DCs CD103+ migrate to mesenteric lymph nodes (mLN) where they drive Treg generation. Retinoic acid secreted by DCs and mLN stromal cells induce the synthesis of gut-homing molecules CCR9 and α4β7 integrin. TGF-β generates and maintains the phenotype of Th3, iTregFoxP3+ and nTregs. Tregs FoxP3+ cells stimulates CD11c+ cells to secrete IL-27, responsible for inducing proliferation of IL-10 cells (Tr1). Tregs generally inhibit the activation of Th1/Th2/Th17 cells, promoting a tolerogenic microenvironment in intestinal lamina propria and mesenteric lymph nodes.

Intestinal microbiota and immune system

The establishment and maintenance of beneficial relations between the host and microbiota are undoubtedly important for the host's health [69]. The gut has approximately 500 to 1000 species of bacteria that belong to a few known bacterial phyla [70]. The basic concept of self and non-self in immunology assumes that microorganisms, being non-self to our organism, would be eliminated by the immune system or otherwise would cause infectious disease. With the perception that we live in a world dominated by microorganisms,

which human benefits, the superorganism theory classifies microbiota as “self” to us [71]. Microorganisms might be evolved in the arising of adaptive immunity. Despite all the effort, it was not found the phylogenetic relation between RAG1 and RAG2 with other molecules in ancestor lineages. It is suggested that these genes might have been acquired by horizontal transmission, from the genome of a microorganism to a jawed ancestor [72]. Corroborating with this hypothesis, speculated if adaptive immunity on jawed vertebrates evolved in a way to preserve the beneficial relationships with microorganisms [73].

Human microbiota composition is sensible to a broad number of environmental factors, lifestyle, usage of antibiotics, diet and hygiene habits. Hyperimmunity immunodeficiency can also modify the intestinal microbiota composition, and so metabolic syndrome and chronic inflammation [69]. Microbiota plays a fundamental role in TGI organogenesis, especially in the GALT. The main impact of intestinal microbiota are visualized in the formation of intestinal villi, crypt depths, proliferation of local stem cells, increase in vases density and improving epithelial integrity [69]. Germ free mice, besides presenting lower epithelial barrier integrity, the local vasculature is less complex and Peyer’s patch as mesenteric lymph nodes are immature [69]. On the immune system aspect, polysaccharide A from Bacteroides fragilis can enhance Tregs proliferation. In contrast, segmented filamentary bacteria induces the proliferation of Th17 cells, maintaining the equilibrium between effector and suppressive immune response in the GALT [74, 11]. In a study was observed that the administration of probiotic Lactobacillus acidophilus and Bifidobacterium infantis can prevent necrosis caused on enterocolitis [75]. Bifidobacterium are reduced in elderly populations (>65 years), where the administration of Bifidobacterium as a probiotic increased the frequency of stool and reduced the intestinal inflammatory environment [41]. However, clinic relevant evidence of usage of probiotics on inflammatory bowel disease (IBD), irritable bowel syndrome, constipation and allergy are weak or inexistent. The most well suited evidence gathered about probiotics are the reduction in diarrhea duration caused by gastroenteritis and in the prevention of diarrhea caused by antibiotics usage [76].

CONCLUSION

The present work concluded that development and maturation of gut rely on diverse factors: Innate lymphoid cells, breastmilk and microbiota provide the structural and functional development of GALT, where in the absence of these elements the tissue homeostasis is impaired. Dietary proteins stimulates the normal functioning of immune system, as animals lacking protein source displayed lower levels of plasmatic immunoglobulin and poor developed GALT. The unique microenvironment present on intestinal lamina propria and mesenteric lymph nodes promotes the induction of oral tolerance to antigens captured on intestinal lumen, a mechanism that might represent a strong strategy in the treatment of allergic and autoimmune diseases.

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