adjacent to the lymph node anlagen induced CXC13 expression in stromal organizer cells and consequently led to the initial clustering of lymphoid tissue inducer cells (31). Therefore, RA has diverse functions in the regulation of versatile immunological events including cell trafficking, differentiation, cytokine production, and lymphoid organogenesis.

The various roles of RA in the mucosal immune system, especially regulating cell trafficking into the intestine, enable us to consider clinical applications of this metabolite. In general, parenteral immunization fails to achieve efficient antigen-specific immune responses in the intestine because it does not induce the necessary gut-homing molecules for the migration of antigen-sensitized immune cells into the intestine. A recent study demonstrated that the addition of RA at the time of subcutaneous vaccination increased the accumulation of antigen-specific T cells and IgA-producing PCs in the intestine and concurrently induced protective immunity against intestinal pathogens (e.g., *Salmonella*) (32). These findings suggest that exogenous RA treatment might be used to stimulate the production of gut-migrating T_{reg} cells for the control of intestinal inflammation and allergy. Additional investigation into the immune functions of RA is warranted to advance potential clinical applications of this vitamin A metabolite.

MEMBERS OF THE VITAMIN B FAMILY CONTROL CELL METABOLISM AND ACTS AS LIGANDS IN THE REGULATION OF INTESTINAL IMMUNITY

Initially thought to be a single vitamin, vitamin B currently is recognized as a family comprising eight different members. All B vitamins are water-soluble, and they are involved in various pathways of cell metabolism. Among the B vitamins, vitamin B6 is essential for metabolism of nucleic acids, amino acids, and lipids and thus influences cell growth. Consequently, vitamin B6 deficiency leads to various impairments of immunity, such as lymphoid atrophy and reduced numbers of lymphocytes (33); conversely, vitamin B6 supplementation bolsters these weakened immune responses (34). A previous study suggested the involvement of the lipid mediator sphingosine 1-phosphate (S1P) in vitamin-B6-mediated immune regulation. S1P has been shown to regulate cell trafficking, especially cell egress from organized lymphoid tissues in both systemic (e.g., thymus, bone marrow, and lymph nodes) and mucosal (e.g., intestine) compartments [reviewed in Refs. (35, 36)]. The cell trafficking is determined by the S1P gradient that is achieved through the coordinated production of S1P and its degradation, which is mediated by S1P lyase and S1P phosphohydrolase (35). S1P lyase requires vitamin B6 as a co-factor for the degradation of S1P (37), and the administration of a vitamin B6 antagonist impair S1P lyase activity and thus create an inappropriate S1P gradient. These defects lead to impaired trafficking of lymphocytes from lymphoid tissues and consequently reduced numbers of lymphocytes in the periphery (38, 39).

Like vitamin B6, vitamin B9 (that is, folate or folic acid) is essential for nucleic acid and protein synthesis (40), and inadequate levels of vitamin B9 dramatically alter the immune response. Previous studies suggested that vitamin B9 deficiency inhibits the activity of $CD8^+$ T cells and NK cells; in turn, this inhibition is associated with decreased resistance to infections (41).

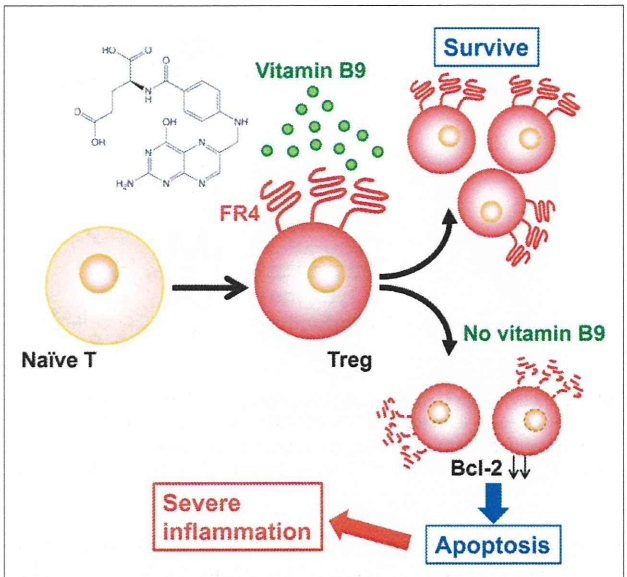

FIGURE 2 | Vitamin B9 is required for the survival of regulatory T cells and subsequent maintenance of immunologic homeostasis in the intestine. Once naïve T cells differentiate into regulatory T (T_{reg}) cells, they express folate receptor 4 (FR4), and require vitamin B9 for their survival. The absence of sufficient amounts of vitamin B9 induces the apoptosis of T_{reg} cells, with decreased expression of Bcl-2 and subsequent increased intestinal inflammation.

Folate receptor 4, a vitamin B9 receptor, is highly expressed on the surfaces of T_{reg} cells (42), implying a specific function of this vitamin in these cells. In particular, our recent study revealed that vitamin B9 is crucial in the maintenance of T_{reg} cells (43). In the absence of vitamin B9, naïve T cells can differentiate into T_{reg} cells, but differentiated T_{reg} cells fail to survive owing to the decreased expression of anti-apoptotic molecules (e.g., Bcl-2) (**Figure 2**). As a result, mice maintained on a vitamin-B9-deficient diet have decreased numbers of intestinal T_{reg} cells (43). As a result, the impaired survival of T_{reg} cells in these mice leads to their increased susceptibility to intestinal inflammation (**Figure 2**) (44).

A recent study demonstrated an additional function of the vitamin B family in the control of immune responses via mucosa-associated invariant T (MAIT) cells. MAIT cells are unconventional T cells that express a semi-invariant αβ T cell receptor that is restricted by the MHC class I-related molecule MR1; these cells are mostly found in the intestine, liver, and lung (45). Because MAIT cells can react rapidly to bacterial infections (e.g., *Escherichia coli, Klebsiella pneumoniae,* and *Mycoplasma tuberculosis*), it was supposed that the antigen presented to MR1 was bacteria-derived molecules. However, a recent study clarified that, in fact, bacterially produced metabolites of vitamin B9 and vitamin B2 bound to MR1 are presented as antigen to MAIT cells (46). Furthermore, like vitamin B2 derivatives, the vitamin B9 metabolite 6-formyl

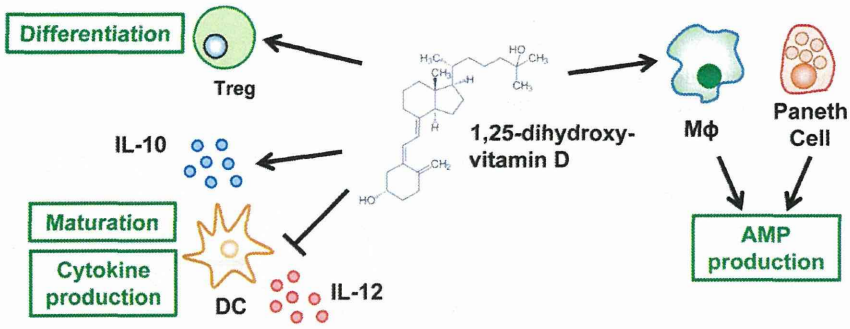

FIGURE 3 | Vitamin D mediates innate and acquired immunity. The active form of vitamin D, it metabolite 1,25-dihydroxyvitamin D, inhibits the maturation of dendritic cells (DCs) and their production of IL-12 but simultaneously promotes their production of IL-10. In addition, T cells respond directly to 1,25-dihydroxyvitamin D for their preferential differentiation into T_{reg} cells. As a component of innate immunity, 1,25-dihydroxyvitamin D promotes the production of anti-microbial peptides (AMP) by macrophages and Paneth cells.

pterin binds to MR1 but, unlike vitamin B2 derivatives, fails to activate MAIT cells (46). These findings suggest that, depending on their metabolism by commensal bacteria and presentation by MR1, members of the vitamin B family can act either as positive or negative regulatory ligands for MAIT cells.

VITAMIN D IS AN INHIBITOR OF IMMUNE RESPONSES

In its typical role of maintaining optimal concentrations of serum calcium, vitamin D is essential to a healthy mineralized skeleton (47). In addition to its effects on calcium and bone metabolism, vitamin D – especially its metabolite 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] – is an important regulator of the immune system, and its deficiency is linked to aberrant immune responses, including intestinal inflammation (48). Regarding a possible mechanism linking vitamin D and intestinal inflammation, $1,25(OH)_2D$ may be important in the creation of an immunologic regulatory or suppressor environment. For example, $1,25(OH)_2D$ inhibits the maturation of DCs and the production of their effector cytokine, IL-12, and simultaneously promotes the production of their inhibitory cytokine, IL-10, thus regulating T cell function and development (**Figure 3**) (49). In addition, T cells directly respond to $1,25(OH)_2D$, with preferential differentiation into T_{reg} cells (**Figure 3**) (50).

Furthermore, vitamin D enhances innate immunity (**Figure 3**). More than 25 years have passed since the anti-microbial function of $1,25(OH)_2D$ against *Mycobacterium tuberculosis* in human monocytes was reported (51). Subsequent studies have revealed the molecular and cellular mechanisms underlying this anti-microbial activity. Once they are activated through Toll-like receptors, macrophages–monocytes express CYP27B1, a key enzyme in the synthesis of $1,25(OH)_2D$ (52), and the vitamin D receptor (VDR) (53). These changes lead to intracrine synthesis of $1,25(OH)_2D$, which enhances the gene expression mediated by vitamin D and the VDR axis. VDR-mediated genes include the anti-microbial molecules cathelicidin (LL-37) and β-defensin 2 (54). Similar $1,25(OH)_2D$-induced production of these anti-microbial molecules occurs in epithelial cells (55) and Paneth cells (56). In addition, $1,25(OH)_2D$ stabilizes tight-junction structures between epithelial cells in the intestinal tract (57). Together, these diverse functions of vitamin D contribute to the creation of the first line of defense against pathogens without the induction of aberrant inflammatory responses.

CONCLUSION

Clinical evidence has long indicated that inadequate vitamin intake disrupts host immunity, thus predisposing humans to infectious and inflammatory diseases. Accumulating evidence has revealed the molecular and cellular mechanisms underlying myriad functions of vitamins in innate and acquired immune responses. These findings clarify the beneficial roles of vitamins in the maintenance of immunologic homeostasis and inform the design of vitamin analogs as pharmacologic agents for the generation and maintenance of a healthy immune condition. The complex functions of vitamins in the regulation of the immune system merit continued investigation, and these research efforts likely will enable scientists to refine our understanding of the mechanisms underlying the immunologic roles of various vitamins and to advance the development of vitamin-dependent therapeutic agents for the control of infectious and immune diseases.

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Immune regulation and monitoring at the epithelial surface of the intestine

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The intestinal enterocytes and other epithelial cells create physical barriers, including tight junctions and mucus layers. These cells also actively transport antibodies across the epithelium and simultaneously produce antimicrobial peptides and enzymes. These functions maintain intestinal homeostasis by allowing the selective absorption of nutrients and simultaneously preventing pathogenic infections. Recent evidence has revealed that both host-derived factors (e.g., cytokines) and gut environmental factors (e.g., commensal bacteria, dietary materials, and their metabolites) regulate the physical and immunological functions of the epithelium. Understanding the interactions between host cells and these environmental factors should help us to develop new strategies to prevent and treat immune diseases of the intestine.

The surface of the gastrointestinal tract is covered by a single layer of epithelium that separates the outside world from interstitial tissues. The intestinal epithelium is mainly composed of absorptive enterocytes (ECs) but also includes enteroendocrine, goblet, and Paneth cells [1]. Cross-communication among these cells enables the selective absorption of nutrients while simultaneously preventing the penetration of antigens and pathogens. The defense against pathogenic materials is at least partly achieved by the physical barriers of the epithelium, which include tight junctions and mucus layers. A large number of pathogens disrupt these barriers to access deeper tissues for dissemination [2,3]. The barriers also contribute to the establishment and maintenance of mucosal homeostasis. Indeed, a leaky intestinal barrier is one of the characteristics of chronic intestinal inflammatory diseases, such as inflammatory bowel disease and celiac disease [4,5].

Intestinal tissues also show intense immunological activity, and ECs contribute to the intestinal immune system by transporting and processing antibodies and associated antigens, by producing immunologically functional molecules, and by interacting with immunocompetent cells in the intestine [6]. Accumulating evidence has revealed that both host-derived factors (e.g. cytokines) and gut environmental factors (e.g. commensal bacteria, dietary materials, and their metabolites) engage in molecular crosstalk with the intestinal epithelium and affect intestinal barrier function and immune responses [7,8]. In this review, we focus on the immunological functions of ECs in the intestine and their regulation by commensal bacteria and dietary materials.

Physical barriers at the intestinal epithelium

Tight junctions

ECs provide a physical barrier to prevent the paracellular transport of luminal antigens and pathogens. Tight junctions are multifunctional complexes that are crucial for the maintenance of barrier integrity because they form a seal between adjacent ECs [9]. The tight junction regulates the absorption of nutrients, ions, and water while preventing the entry of pathogens into the host.

Tight junctions are composed of numerous interacting cellular proteins, including claudin, occludin, and zonula occludens (ZO) proteins (Fig. 1). Claudin and occludin are transmembrane proteins that seal the paracellular space between adjacent ECs. Among

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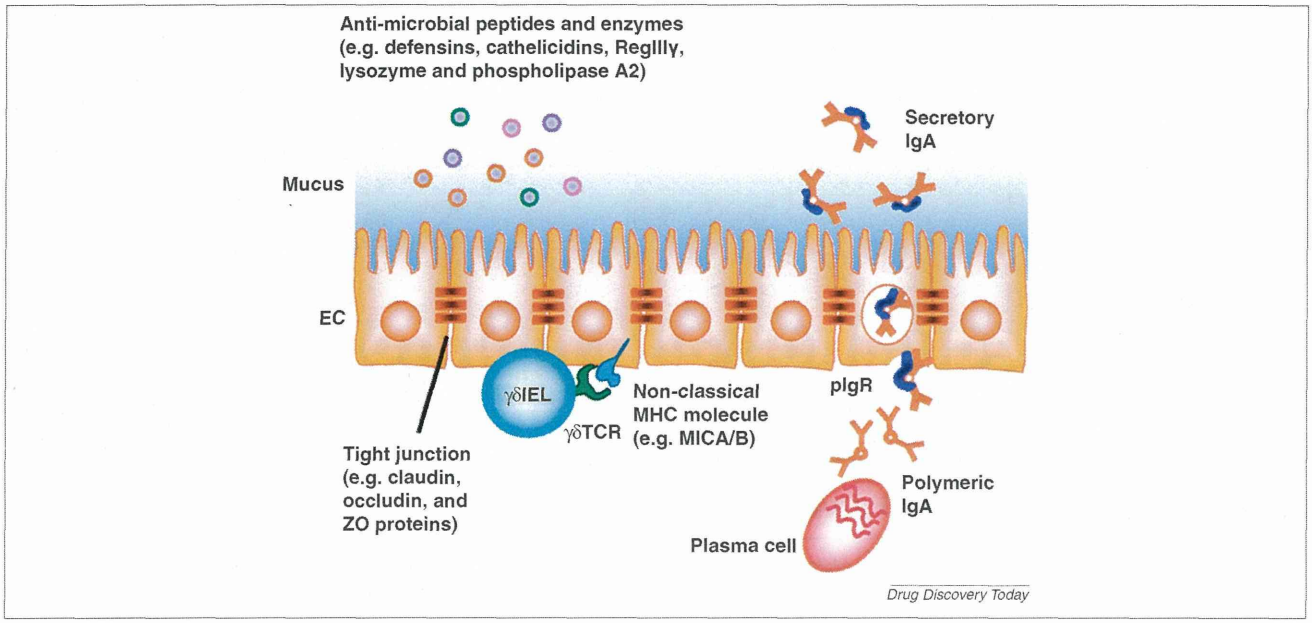

FIGURE 1

Physical and immunological barriers mediated by ECs. ECs (including Paneth cells) produce several molecules that create physical barriers in the intestine. They also produce antimicrobial peptides and enzymes, such as defensins, cathelicidins, RegIIIγ, lysozyme, and phospholipase A2 to kill the bacteria and establish a mucus layer to prevent bacterial attachment to the ECs. Tight junctions among ECs prevent bacterial penetration between the cells. ECs also have immunological functions. They express polymeric immunoglobulin receptor (pIgR), which binds and transports polymeric IgA produced from plasma cells into the intestinal lumen. ECs exposed to stresses (e.g. infection or cancer) express non-classical MHC molecules (e.g. MICA/B). MICA/B acts as a ligand for γδ T cell receptors, which are uniquely expressed on intraepithelial lymphocytes (γδIELs). *Abbreviations*: EC, enterocytes; MHC, major histocompatibility complex; ZO, zonula occludens.

the various types of claudins, claudin-1, -2, -3, -4, -5, -7, -8, -12, -15, -18, -20, and -23 are expressed in the intestinal epithelium [10,11]. ZO proteins are adaptors that connect transmembrane proteins; in particular, ZO-1 interacts with the claudin proteins and with F-actin in the intestinal ECs [12,13].

The physical barriers created by ECs are at least partly regulated by the immunological stimulation provided by commensal bacteria and dietary materials. Indeed, commensal and probiotic bacteria, their metabolites, food extracts, and dietary materials (e.g. fatty acids, polysaccharides, and flavonoids) have been shown to promote intestinal barrier integrity by increasing the expression of tight junction proteins [10].

Mucus

The mucus layer has been recognized as an important component in the intestine (Fig. 1). Mucin 2 (MUC2), a large glycoprotein characterized by variable O-linked glycans, is abundantly expressed by goblet cells located in the intestinal epithelium [14]. Generally, mucus can be divided into two layers. Although both layers have similar protein composition, the outer mucus layer is loose, whereas the inner mucus layer adheres firmly to the surface of the ECs. The firm mucus in the inner layer is an efficient barrier against pathogens [15]. In addition to the physical and biological barrier function of mucus, mucus also ensures the concentration of antimicrobial peptides and IgA antibodies at the surface of ECs. As similar to tight junctions, mucus expression is regulated by commensal bacteria, and the mucus layer of germ-free mice is thicker than that of specific pathogen-free mice [15].

Production of antimicrobial molecules at the epithelium

Antimicrobial peptides

The epithelium also secretes a variety of antimicrobial peptides [e.g. defensins, cathelicidins, and RegIIIγ (Fig. 1)]. The production of these peptides is mainly mediated by ECs and Paneth cells [16]. Paneth cells reside at the base of the crypt regions of the intestine, where they constitutively produce α-defensins. This does not require bacterial stimulation, because Paneth cells produce normal amounts of α-defensin in germ-free mice [17]. By contrast, ECs require microbial stimulation for the production of β-defensins [16]. ECs also produce cathelicidin, the expression of which is regulated by short-chain fatty acids produced when polysaccharides are metabolized by fermenting bacteria [18]. Both defensins and cathelicidin are cationic small peptides that exhibit antimicrobial activity by damaging and permeabilizing the bacterial cell membrane by pore formation [19].

RegIIIγ is a C-type lectin produced by ECs and Paneth cells in the ileum, where it kills Gram-positive bacteria by binding to surface-exposed carbohydrate moieties of peptidoglycans [20]. Commensal bacteria, especially Gram-negative bacteria, induce RegIIIγ expression on ECs, and a recent study demonstrated that MyD88 intrinsically expressed on ECs controls the production of RegIIIγ, which establishes the physical separation between the microbiota and the intestinal epithelial surface [21].

Unlike RegIIIγ, which specifically targets Gram-positive bacteria, bactericidal and/or permeability-increasing protein (BPI) shows antimicrobial activity against Gram-negative bacteria. The high affinity of BPI for lipopolysaccharide (LPS) leads to the

destabilization of the outer membrane of Gram-negative bacteria and also neutralizes LPS-induced inflammation [22].

Antimicrobial enzymes

Antimicrobial activity is also mediated by bacteriolysis enzymes (e.g. secretory phospholipase A2 and lysozyme). Phospholipase A2 is a small enzyme produced by Paneth cells that degrades bacterial phospholipids and subsequently disrupts the integrity of Gram-positive and -negative bacteria [23]. Phospholipase A2 enzyme activity is normal in the intestine of germ-free rats [24], but caloric restriction increases the gene expression of lysozyme and phospholipase A2 [25]. Therefore, it is likely that nutritional conditions rather than commensal bacteria regulate the activity of these antimicrobial enzymes in the intestine. Lysozyme is produced by Paneth cells and ECs. Its bactericidal activity derives from its cleavage of the glycosidic linkage between *N*-acetylglucosamine and *N*-acetyl muramic acid of peptidoglycan. Because Gram-positive bacteria express more peptidoglycan than Gram-negative bacteria, lysozyme acts preferentially on Gram-positive bacteria.

Transport of antibodies through ECs

IgA transport mediated by polymeric immunoglobulin receptors

One function of the epithelial immune barrier is to transport antibodies across the barrier. ECs express polymeric immunoglobulin receptors (pIgR) for the transport of polymeric forms of IgA (pIgA) and IgM (pIgM) in the basal-to-apical direction in association with an extracellular proteolytic fragment of the pIgR (known as the secretory component) [26]; together, the IgA and the secretory component form secretory immunoglobulin A (S-IgA). After S-IgA is secreted into the intestinal lumen, it inhibits adherence of pathogens to host ECs in the intestine and neutralizes pathogenic toxins by binding to their biologically active sites (Fig. 1) [27]. Additionally, IgA is able to exclude antigens and pathogens from the intestinal secretions while it is transported through ECs, and it also prevents viral replication inside ECs [28,29].

In addition to the function of S-IgA in the immunosurveillance, several lines of evidence demonstrate that S-IgA has a key role in preventing the penetration and/or growth of commensal bacteria [30]. These functions of S-IgA achieve the immune responses against commensal bacteria restricted in the intestinal but not systemic immune compartments in normal mice, while IgA-deficient mice exhibited systemic IgG responses against commensal bacteria [31–33]. A recent study also demonstrated that, in the absence of IgA, commensal bacteria-derived stimulation induced the increased expression of interferon-regulated genes in the ECs for the compensatory immunosurveillance with simultaneous reduction of lipid metabolism-related Gata4-regulated genes, which resulted in the lipid malabsorption and decreased lipid deposition [34]. Thus, S-IgA mediates the regulation between ECs and commensal bacteria, which is important not only for the maintenance of immunological homeostasis but also for metabolism [34].

Neonatal Fc receptor for IgG transport

Another receptor for immunoglobulin is the neonatal Fc receptor for IgG (FcRn). Although early studies in rodents indicated that FcRn was responsible for the passive acquisition of IgG neonatally, subsequent studies indicated that FcRn is also expressed by adult human epithelium and antigen-presenting cells in the intestine and thus is not strictly limited to neonatal life [35]. Unlike pIgR mentioned above, human FcRn binds IgG and the transport pathway is bidirectional, both apical to basal and basal to apical [36]. The bidirectional transport of IgG enables retrieval of intestinal antigens in a complex with IgG into the intestinal lamina propria, where the antigen and/or IgG complexes are subsequently taken up by antigen-presenting cells to prime T cell responses [37].

Intraepithelial T lymphocytes

The epithelium also includes lymphocytes that are commonly termed intraepithelial lymphocytes (IELs) [38]. IELs reside between the basolateral surfaces of ECs, and one IEL occurs for every 4–10 ECs in the small intestine and for every 30–50 ECs in the large intestine.

Most IELs are T cells. As similar to T cells observed at other sites (e.g. spleen and intestinal lamina propria), some portions of IELs express αβ T cell receptors and act as cytotoxic T lymphocytes by recognizing antigenic peptides presented by classical major histocompatibility complex (MHC) molecules on pathogenic ECs (e.g. microbe-infected cells) and killing them by producing cytotoxic molecules (e.g. perforin and granzymes) [38]. Other IELs express the γδ T cell receptor (and are therefore known as γδIELs) and show minimal pathogen-specific activity [38,39]. The innate immune function of γδIELs enables the rapid removal of infected ECs. To recognize the infected ECs, non-classical MHC molecules, such as MHC class I chain-related protein A/B (MICA/B) in human, act as ligands for γδIELs. MICA/B is generally not expressed on ECs, but is induced by stresses such as heat shock and microbial infections. The activated γδIELs then synthesize an array of cytokines, including interleukin (IL)-2, IL-3, IL-6, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and transforming growth factor (TGF)-β, and cytotoxic molecules, such as perforin, granzyme, and Fas ligand to kill the microbe-infected ECs [38].

Epithelium senses signals from commensal bacterial in the regulation of T cell differentiation in the intestine

The immune system requires interactions with commensal bacteria for its development. Toll-like receptors (TLRs) act as sensors of commensal bacteria although they were initially discovered as pathogen recognition receptors. ECs express several kinds of TLRs and the ligands from commensal bacteria promote immunological functions of Ecs, such as IgA transport, tight junctions, and expression of antimicrobial peptides [40]. Of note, ECs have unique expression profiles and spatially restricted distribution (apical vs. basolateral) of TLRs together with unique underlying signaling pathways, which enables the prevention of deleterious inflammatory responses in the intestine [40].

Because commensal bacteria express shared molecules which act as a ligand of TLRs, it was previously thought that unspecified commensal bacteria indiscriminately induced the development of the immune system; however, accumulating evidence has demonstrated that individual species of commensal bacteria have specific roles in the determination of immunological balance by regulating T cell differentiation in the intestine [8]. ECs have an important role in this pathway.

Segmented filamentous bacteria induce the differentiation of Th17 cells

Several groups have shown that segmented filamentous bacteria (SFB) induce components of the active immune system, including IgA-producing cells, γδIELs, and IL-17-producing T (Th17) cells [41–43]. SFB colonization on ECs results in the production of serum amyloid A, which acts on intestinal dendritic cells (DCs) to enhance the production of IL-6 and IL-23 [43]. Because these two cytokines are Th17 cell-inducing cytokines, the immunological environment mediated by SFB, ECs, and DCs results in the preferential induction of Th17 cells in the intestine.

Preferential induction of Treg cells in the colon by Clostridium *clusters IV and XIVa*

Another form of crosstalk between ECs and commensal bacteria in the regulation of T cell differentiation is mediated by *Clostridium* clusters IV and XIVa (also known as the *Clostridium leptum* and *coccoides* groups) [44]. By contrast to the effects of SFB, colonization by *Clostridium* clusters IV and XIVa induces regulatory T (Treg) cells in the colon to achieve quiescent immunity. *Clostridium* clusters IV and XIVa form a thin colonizing layer on the epithelium, where they enhance the release of the active form of TGF-β by increasing the expression of matrix metalloproteinases that convert latent TGF-β into the active form. Because TGF-β is an essential cytokine for the differentiation of Treg cells from naive T cells, colonization with these *Clostridium* species converts non-Treg cells into Treg cells locally in the colon with little effect on thymus-derived Treg cells.

Dietary metabolites regulate intestinal immunity through the epithelium

Nutritional materials also influence intestinal immunity, and commensal bacteria are involved in metabolizing indigestible dietary materials into biologically active metabolites. Dietary materials (e.g. polysaccharides, vitamins, and lipids) and their metabolites contribute to the regulation of intestinal immunity (Fig. 2).

Polysaccharides

Dietary polysaccharides and endogenous mucus in the intestine are digested and metabolized into short-chain fatty acids, such as acetate, butyrate, and propanoate, by bacterial fermentation. These short-chain fatty acids are an energy source for ECs and affect immune cell functions. For example, acetate and butyrate maintain epithelial barrier function by stimulating the release of mucin and by facilitating the maintenance of epithelial integrity [45,46]. Acetate and butyrate also regulate the proliferation of ECs and their production of cytokines [47,48]. In addition, acetate modulates the immunological function of neutrophils that express G-protein-coupled receptor 43 [GPR43, also known as free fatty acid receptor 2 (FFAR2)], a receptor for the short-chain fatty acids. Neutrophils lacking GPR43 show decreased levels of phagocytic activity and lower production of reactive oxygen species, but also are more responsive to chemoattractants such as C5a and inflammatory chemokines [49]. Consistent with these findings, intestinal inflammation is exacerbated in GPR43-deficient mice.

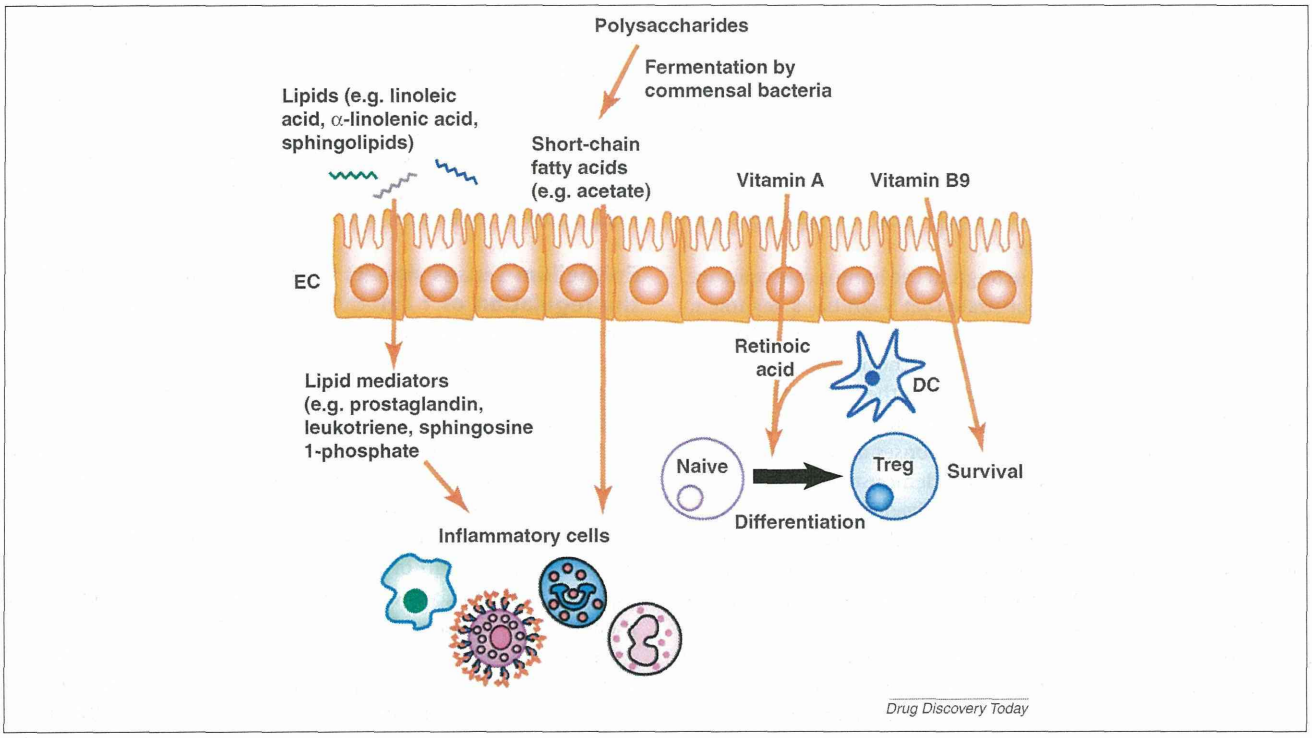

FIGURE 2

Dietary materials in the regulation of EC functions. Dietary lipids are metabolized into lipid mediators, and short-chain fatty acids are generated by fermentation of polysaccharides by commensal bacteria. These products positively or negatively regulate the functions of inflammatory cells. ECs also absorb vitamin A, and both ECs and dendritic cells (DCs) metabolize vitamin A into retinoic acid, which preferentially induces regulatory T (Treg) cells from naive T cells. The differentiated Treg cells require vitamin B9 for their survival. *Abbreviation:* EC, enterocytes.

Vitamins

Vitamins are supplied by both the diet and commensal bacteria. Several lines of evidence have shown that vitamins are involved in regulating immune responses through the epithelium. For example, retinoic acid, a metabolite of vitamin A, is involved in the preferential induction of regulatory T cells and the inhibition of Th17 cells [50]. Both ECs and DCs in the intestine are the major cell types that express retinaldehyde dehydrogenase, a key enzyme for the conversion of vitamin A into retinoic acid, suggesting that the unique gut environment mediated by ECs, DCs, and vitamin A preferentially induces Treg cells for maintaining quiescent immunity in the intestine. Because it was reported that Treg cells enhanced the differentiation of IgA^1 B cells in the intestine [51,52] and retinoic acid induced the expression of gut-homing molecules (e.g. CCR9 and α4β7 integrin) on IgA-committed B cells as well as T cells [53,54], it is likely that retinoic acid directly and indirectly enhances intestinal IgA responses.

Vitamin B9 is another important vitamin in the maintenance of Treg cells. Vitamin B9 receptor (folate receptor 4) is exclusively expressed on Treg cells and can therefore be used as a cell surface marker of Treg cells [55]. We recently showed that vitamin B9 is an essential survival factor for Treg cells [56]. Indeed, Treg cells differentiate from naive T cells but fail to survive in vitamin B9-reduced conditions. Because vitamin B9 is supplied from both the diet and commensal bacteria, and dietary vitamin B9 is predominantly absorbed by ECs in the jejunum and duodenum, depletion of dietary vitamin B9 results in the reduction of Treg cells in the small intestine.

Lipids

Dietary lipids also involved in the regulation of intestinal immune responses. The ratio of omega-3 polyunsaturated fatty acids (ω-3 PUFA) to ω-6 PUFA in the diet may determine the presence and/or levels of inflammatory conditions. Dietary linoleic acid is the parent fatty acid of ω-6 PUFA which is metabolized into proinflammatory lipid mediators, whereas ω-3 PUFA, which is derived from dietary linolenic acid, is metabolized into anti-inflammatory mediators [57]. A possible molecular mechanism is that ω-3 PUFA exert anti-inflammatory effects through binding to GPR120, which is mostly expressed by macrophages, thereby inhibiting the production of inflammatory cytokines [58].

Another lipid metabolite with important immunological function is sphingosine 1-phosphate (S1P), which regulates cell trafficking, activation, and survival. Intestinal tissues contain higher levels of sphingolipids, including S1P, than other tissues and diet could be a major source of sphingolipids in the intestine, especially sphingomyelin from meat, milk, eggs, and fish [59]. Because ECs express alkaline sphingomyelinase and ceramidase to degrade dietary sphingomyelin into ceramide and sphingosine, respectively, and also express several key enzymes in the production of S1P from ceramide and sphingosine (e.g. sphingosine kinase), it is possible that ECs produce ceramide, sphingosine, and S1P for the regulation of intestinal immune responses.

Concluding remarks

ECs in the intestine have both physical and immunological barrier functions, which are achieved by immunological communication with both immunocompetent cells and gut environmental factors (e.g. commensal bacteria, dietary materials, and their metabolites). Elucidation of the complex networks established by commensal bacteria, dietary molecules, and the host immune system will provide new insights in gut environment-based mucosal immunology and should lead to new strategies to prevent and treat infectious and immune diseases in the intestine.

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