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Vitamin A: A key coordinator of host-microbe interactions in the intestine

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Vitamin A regulates bacteria-immune crosstalk

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ABSTRACT

The human intestine is home to a dense community of microbiota that plays a key role in human health and disease. Nutrients are essential regulators of both host and microbial physiology and function as key coordinators of host-microbe interactions. Therefore, understanding the specific roles and underlying mechanisms of each nutrient in regulating the host-microbe interactions will be essential in developing new strategies for improving human health through microbiota and nutrient intervention. This review will give a basic overview of the role of vitamin A, an essential micronutrient, on human health, and highlight recent findings on the mechanisms by which it regulates the host-microbe interactions.

Introduction

The human intestine is home to trillions of resident microorganisms including bacteria, archaea, fungi, bacteriophages, and viruses. These microorganisms, collectively termed microbiota, form a complex and dynamic community along the length of the gastrointestinal tract (1). Diverse metabolic pathways of microbiota maximize the host's capacity for nutrient utilization from the diet and provide key metabolites that are essential for the host's health. However, when the microbiota escapes from its niche and invades the host tissue, an infection occurs that could induce uncontrolled inflammation and lethal sepsis (2,3). Therefore, the host is equipped with physical and immunological defense systems to prevent the invasion of microorganisms. This includes the production of mucin, multiple antimicrobial proteins such as defensins, lysozyme, Reg3 lectins, cathelicidins, and secretory immunoglobulin A. In addition, the host should develop tolerance to the commensal microbiota to prevent unnecessary inflammation, failure of which could lead to uncontrollable inflammatory diseases (4–8). Therefore, the microbiota modulates the pathogenesis, progression, and treatment of various diseases, and modulating host-microbiota interactions is an emerging therapeutic avenue for disease control and prevention.

This complex ecosystem is maintained with the interplay of nutrients, microbiota, and the host that is distinctive along the length of the intestine (1,2,9). The intestinal epithelial cells are located at the vital interface between microbiota/nutrients and the host and play a key role in the host-microbiota-nutrient interplay by functioning as a selective barrier that prevents the entry of harmful molecules while absorbing necessary nutrients (4,10). One of the most important tasks of intestinal epithelial cells is to monitor the intestinal environment (e.g., microbiota and nutrient availability) and regulate intestinal immunity accordingly. Multiple nutrients such as vitamins, amino acids, and fatty acids, and their metabolites are known to regulate epithelial and/or immune functions that are critically important for human health (11).

As nutrients are the essential regulators of the intestinal environment, bacteria, and host cells, it is important to understand how nutrients from the diet affect and regulate microbiota and different host cells. Understanding this host-microbe-nutrient interplay is central to the current efforts on microbiota and/or nutrient interventions for human health and diseases. This mini-review overviews an example of vitamin A, a relatively well-studied nutrient, and highlights the role of vitamin A in regulating the host-microbe interactions in the intestine.

Vitamin A

Vitamin A in health and diseases. Vitamin A is a fat-soluble micronutrient that is essential for human health. Vitamin A is a collective term for a group of compounds with similar biological activities to retinol. Retinol is the principal form of dietary vitamin A and there are multiple derivatives present in the body, including all *trans* retinoic acid (RA), retinaldehyde (retinal), and retinyl esters (Fig.1) (12). Vitamin A is required for multiple essential body functions, including growth, immunity, vision, and reproduction (13,14). Vitamin A deficiency (VAD) in humans causes childhood blindness, stunting, and anemia, and predisposes individuals to increased morbidity and mortality from various infections (15,16).

Vitamin A absorption and metabolism in the intestine. Multiple forms of vitamin A are present in the body (Fig. 1A). Retinol and retinyl esters are found in animal-based diets, and are absorbed through the epithelial cells in the small intestine. Retinyl esters cannot enter the enterocyte, but rather are first hydrolyzed into retinol in the lumen. The uptake of retinol is known to involve a carrier-mediated active transport at dietary concentrations, yet the specific transporters are not identified (17,18). In addition, provitamin A, called carotenoids, is mainly found in plants and converted to retinol within the enterocyte after absorption. Mechanisms involved in the uptake of carotenoids by enterocyte is well established (reviewed in (18)).

After absorption, the majority of the retinol is esterified and packaged into chylomicron

for delivery into the lymphatics (19). Liver hepatocytes uptake retinyl esters in chylomicron remnants and then transfer them into the stellate cells which are the major storage site of vitamin A in the body (20,21). It is noteworthy that enterocytes also secrete a significant amount of unesterified retinol unassociated with lipoproteins (19,22), and have distinct and specific physiological roles within the intestine. For example, a family of retinol-binding proteins, serum amyloid A (SAAs), is produced by intestinal epithelial cells and delivers retinol from the epithelium to the intestinal immune cells (Fig.1B) (23).

Molecular mechanisms of vitamin A for regulating cellular functions

Retinoic acid and RA signaling. Different forms of vitamin A have distinct roles in the body. Retinol is the primary form for transport while retinyl esters are the storage forms. Retinol is the immediate precursor of retinal and RA, two forms that have biologically active functions within the cell. Retinal is primarily required for the formation of rhodopsin thereby essential for vision (more details on the function of retinal are reviewed in (24)). Retinal also serves as an intermediate in the synthesis of RA from retinol.

RA has broader physiological importance as it functions as a ligand for the nuclear receptors, RA receptors (RAR-α, -β and -γ). RARs bind with retinoid X receptors (RXR-α, -β and -γ for) and participate in direct regulation of various gene expressions (25,26). RAR-RXR heterodimer binds to DNA sequences known as retinoic acid response elements (RARE) that are usually located on the promotor region of the target genes. Unliganded receptors bind to co-repressor molecules and repress the transcription, and the binding of RAs to the ligand-binding domain of the receptors leads to a conformational change that results in the release of co-repressors and the recruitment of co-activators (27,28) (Fig. 2). Retinoids are known to control most developmental processes through these canonical pathways. Alternatively, the RA-receptor complex can indirectly down-regulate the expression of genes with no RAREs in

their promoters by competing for the required co-activator proteins (25,29,30). Under some but not all circumstances, RA is known to activate peroxisome proliferator-activated receptor (PPAR) β/δ when it is delivered to the nucleus via a specific intracellular lipid-binding protein, FABP5, albeit its mechanism activating PPARβ/δ is not yet clear (31,32).

RA synthesis in the intestine. RA is a key regulator of intestinal immune homeostasis through various cells of the innate and adaptive immune system (33). In the intestine, epithelial cells, stromal cells, and certain immune cells including dendritic cells (DCs) and macrophages are known to produce RA (34–38). RA is produced in a two-step enzymatic process involving the conversion of retinol to retinal (by the action of the alcohol dehydrogenases, ADHs and RDHs) and subsequent conversion to RA (by retinaldehyde dehydrogenases, RALDHs) (39). A confined population of cells is equipped with the enzymes of both steps, presumably as nature's strategy for regulating the production of this highly active metabolite. Many local factors within the mucosal environment, including vitamin A itself, fatty acids, cholesterol metabolites, GM-CSF, and Toll-like receptor (TLR) ligands, can promote RA production by cells (40–46).

RA and intestinal immunity. RA has context- and concentration-dependent immunomodulatory roles. Vitamin A is critical for the functioning of various innate immune cells, including DCs, macrophages, neutrophils, and natural killer (NK) cells at the mucosal site(43,47–49). RA is also essential for imprinting innate lymphoid cells (ILCs) (50) and regulatory and effector T and B cells (36,51,52) with gut-homing specificity. The anti-inflammatory role of RA involves the production of RA by myeloid cells which are critical for promoting Foxp3 regulatory T cell differentiation (53,54) and immunoglobulin A (IgA) production (52,55). Under infectious conditions, RA signaling can induce the production of proinflammatory cytokines by DCs and promote the differentiation of effector T cells (56,57). Therefore, RA is crucial in maintaining a balance between immunogenicity and tolerance at

the intestinal barrier (Fig. 3).

Bacterial regulation of vitamin A metabolism and function

Direct metabolism of vitamin A by gut bacteria. Many studies attempted to identify bacteria that metabolize or biosynthesize vitamin A. Multiple bacteria including gut commensals have been proposed to metabolize carotenoids to retinoids (58–61). The ability of bacteria to directly metabolize retinoids was discovered relatively recently, with *Bacillus cereus* being the first example to directly convert retinal to RA or retinol using aldehyde dehydrogenase (ALDH) (62). No specific gut commensal bacteria have been identified with the activity until very recently. Recent work by Woo and colleagues showed that commensal gut microbes including segmented filamentous bacteria (SFB) express ALDH and produce RA. RA produced by bacteria promotes the host's defense against intestinal infection by activating epithelial RA signaling (63) (Fig. 3A). It remains to be determined how bacterial vitamin A metabolism is regulated and whether vitamin A metabolism *per se* regulates bacterial physiology and function in the gut.

Regulation of host vitamin A metabolism by gut bacteria. Recent studies characterized how intestinal bacteria regulate host vitamin A metabolism. Grizotte-Lake and colleagues identified that gut commensal bacteria belonging to class Clostridia repress intestinal epithelial cell expression of retinol dehydrogenase 7 (Rdh7) and suppress epithelial RA synthesis. This suppression of epithelial-intrinsic RA signaling by gut commensals prevents the expansion of pathogenic bacteria by specifically reducing IL-22-dependent antimicrobial responses (64). More recently, a specific bacterium, *Faecalibaculum rodentium*, has been shown to suppress epithelial RA signaling at the proximal small intestine, which results in the loss of a certain eosinophil population. This, in turn, promotes the proliferation and turnover of intestinal epithelium via intraepithelial lymphocyte (IEL) interferon (IFN)- γ production (65) (Fig. 3C).

In addition, it has been reported that colonization of *Bifidobacterium infantis* increases the expression of RALDH by intestinal DCs, which then imposes anti-inflammatory effects by suppressing T_H1 and T_H17 responses (66). Therefore, gut microbiota contributes to immune homeostasis by regulating host RA production in multiple ways (64–66).

Bacterial regulation of host vitamin A mobilization into immune cells. Mobilization of retinol, the primary transport form of retinoids, is a critical regulator of the function of vitamin A in the body. Being hydrophobic, retinol does not readily diffuse across aqueous environments between cellular compartments, but it rather relies on the binding proteins for mobilization. I and colleagues have recently discovered how gut microbiota regulates retinol mobilization in the intestine (23). Gut microbiota and dietary vitamin A induce the expression of a family of retinol-binding proteins, serum amyloid A (SAA) (67), by intestinal epithelial cells. Epithelial RA signaling mediated by RARβ induces epithelial cell expression of *Saa* genes in the presence of dietary vitamin A (68). Retinol is mobilized from epithelium by binding to SAAs and delivered to myeloid cells through the interaction of SAA with its receptor, LDL receptor-related protein 1 (LRP1). The SAA-mediated retinol delivery is important for some vitamin A-dependent adaptive immune responses including the intestinal homing of lymphocytes and their effector functions (23,68,69). It remains to be elucidated how different intestinal immune cells acquire retinol and/or retinoic acid through other sources and pathways (Fig. 3B).

Role of vitamin A on bacterial infection. Vitamin A is essential for the defense against bacterial infection at the mucosal site. The production of an antimicrobial protein, Resistin-like molecule α (RELMα), is induced by vitamin A in the skin, which promotes vitamin A-dependent resistance to skin infection (70). Vitamin A induces intestinal epithelial cell-intrinsic RA signaling and increases the production of interleukin (IL)-18 by epithelial cells. IL-18 induces the production of IFN-γ and promotes the shedding of infected epithelial cells, which

limits the pathogen invasion early in infection (71) (Fig. 3D). Vitamin A may also directly regulate enteric pathogens. A study showed that retinol and RA inhibit the growth of *Mycobacterium tuberculosis* in a dose-dependent manner (72). A vitamin A-deficient diet in mice has been shown to significantly change the composition of gut microbiota, partly by vitamin A directly regulating bacterial growth in the gut (73). Whether dietary vitamin A directly affects the growth of enteric pathogens remains to be elucidated.

Concluding remarks

The human intestine has a complex ecosystem consisting of nutrients, microbiota, and host cells. Gut microbiota constantly interacts with host cells and plays critical roles in the health and disease of humans. Microbiota-based interventions have great therapeutic potential as well as challenges. Nutrients are the essential regulator of both host and bacterial physiology and function as key coordinators of host-microbe interactions. Understanding the roles and underlying mechanisms of each nutrient in regulating the host-microbe interactions will be essential and require further work. Such efforts should yield deeper insight into how host cells, microbes, and nutrients interplay in the intestine and should provide new strategies for improving human health.

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CONFLICTS OF INTEREST

The author declares no conflict of interest.

FIGURE LEGENDS

Figure 1. Vitamin A absorption and metabolism. (A) Structure of vitamin A derivatives in the body. (B) Uptake, metabolism, and delivery of vitamin A. Retinol is absorbed through the intestinal epithelial cells and then converted to retinyl esters for storage. Retinyl esters are packaged into chylomicron, travels through the lymphatics, and stored in the liver. Serum retinol binding protein 4 (RBP4) delivers stored retinol to peripheral tissues and cells from the liver. Serum amyloid A (SAA) binds with retinol and delivers it from the intestinal epithelial cells to intestinal immune cells.

Figure 2. Mechanisms of gene regulation by *all trans* retinoic acid. (A) RARs complex with their RXR heterodimer partner bind to retinoic acid response elements (RARE) DNA sequences. In the absence of *at*RA, they recruit corepressors that link RAR-RXR complex to histone deacetylases (HDACs), which leads to chromatin condensation and repression of gene expression. When *at*RA binds to RARs, a conformational change occurs which releases corepressors and recruits coactivators. The coactivators interact with histone acetylases (HATs) which lead to chromatin decompaction and allow access to DNA by transcriptional machinery (27,28). (B) Example of genes that are regulated by RA (26). The genes shown have conserved RAREs (or predicted RAREs) in their promoters and the expression is regulated in a RA-dependent manner. RAR, retinoic acid receptor; RXR, rexinoid receptor; *at*RA, all *trans* retinoic acid.

Figure 3. Vitamin A is a central modulator of bacteria and immune crosstalk in the intestine. (A) SFB produce RA and promote defense against intestinal infection through epithelial RA signaling (63). (B) SFB induce expression of a retinol binding protein, SAA.

Retinol is mobilized from epithelium by binding to SAAs and delivered to myeloid cells through LRP1-mediated endocytosis. Myeloid cells may also acquire retinol and/or retinoic acid by unknown pathways. RA produced by myeloid cells is a central regulator of immune homeostasis by regulating differentiation and intestinal homing of T and B cells (23). (C) Commensal bacteria regulate RA pathways in multiple ways. *Bifidobacterium infantis* increases RALDH expression by DCs to promote anti-inflammatory responses. Clostridia species and *Faecalibaculum* suppress epithelial RA synthesis, which then reduces IL-22-dependent antimicrobial responses (64) and promotes epithelial turnover through IEL production of IFN-γ (65). (D) Epithelial RA signaling increases IL-18 production and induce cell shedding and IFN-γ production, which promotes the clearance of pathogen (71).

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Figure 1

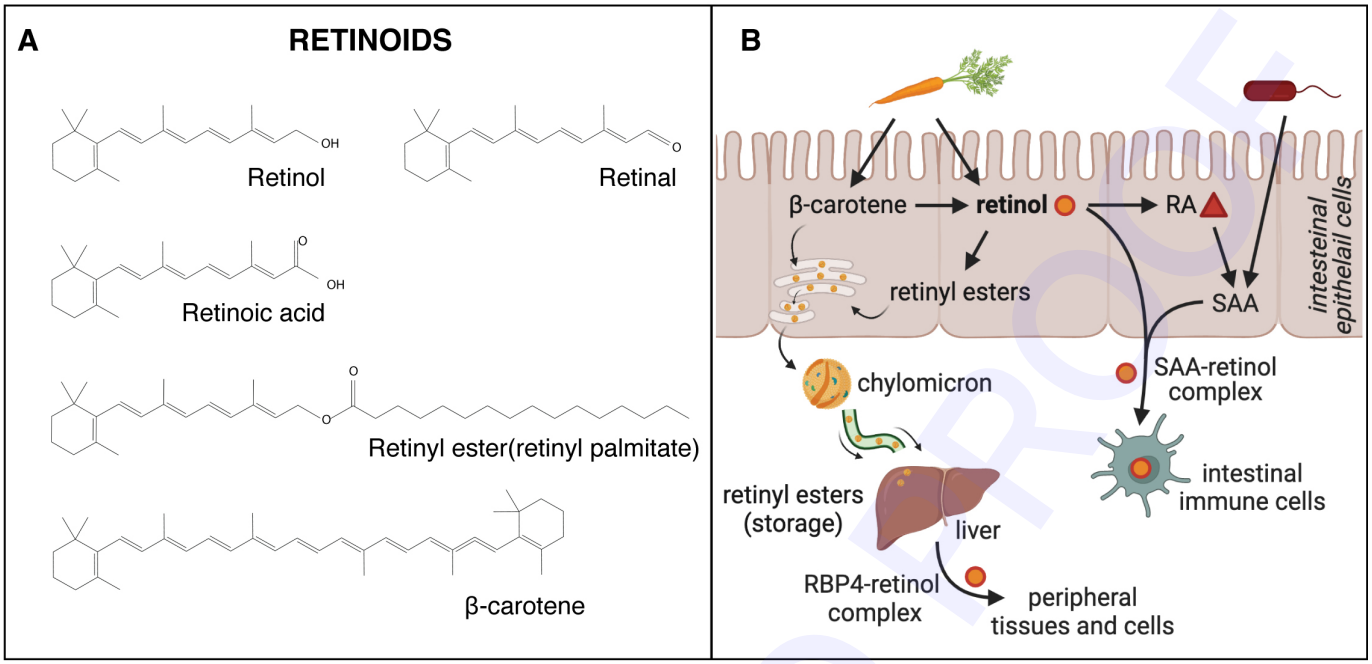
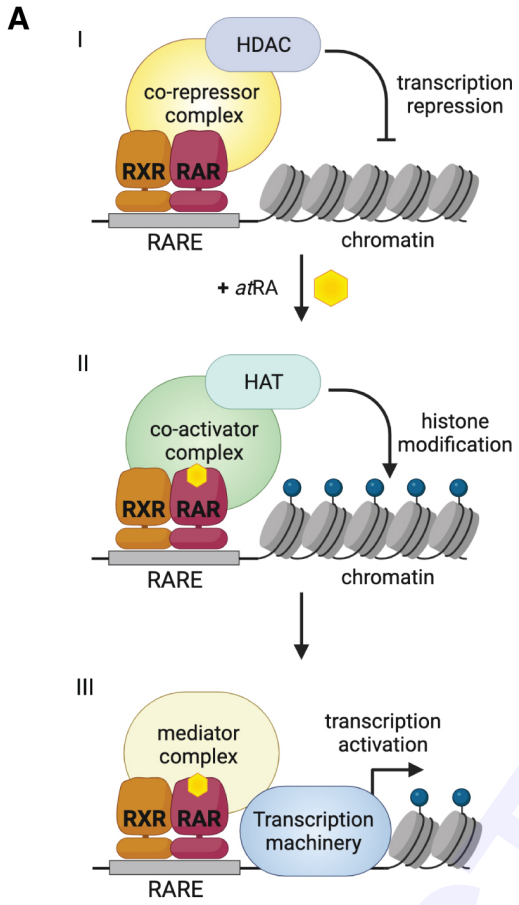


Fig. 1.

Figure 2



B

RA-regulated genes (*partial list*)	
Adh1c	Alcohol Dehydrogenase 1C
Cd38	CD38 Molecule
Cdx1	Caudal Type Homeobox 1
Cebpe	CCAAT Enhancer Binding Protein Epsilon
Crabp2	Cellular Retinoic Acid Binding Protein 2
Cryab	Crystallin Alpha B
Drd2	Dopamine Receptor D2
Egr1	Early Growth Response 1
Ets1	ETS Proto-Oncogene 1, Transcription Factor
Foxa1	Forkhead Box A1
H1F0	H1.0 Linker Histone
Hoxa1	Homeobox A1
Hoxa4	Homeobox A4
Hoxb1	Homeobox B1
Hoxb4	Homeobox B4
Hoxd4	Homeobox D4
Hsd17b1	Hydroxysteroid 17-Beta Dehydrogenase 1
Il2ra	Interleukin 2 Receptor Subunit Alpha
Pck1	Phosphoenolpyruvate Carboxykinase 1
Pit1	POU domain, class 1, transcription factor 1
Rara	Retinoic Acid Receptor Alpha
Rarb	Retinoic Acid Receptor Beta
Rarg	Retinoic Acid Receptor Gamma
Rbp1	Retinol Binding Protein 1
Sftpb	Surfactant Protein B
Tgm2	Transglutaminase 2
Ucp1	Uncoupling Protein 1

Fig. 2.

Figure 3

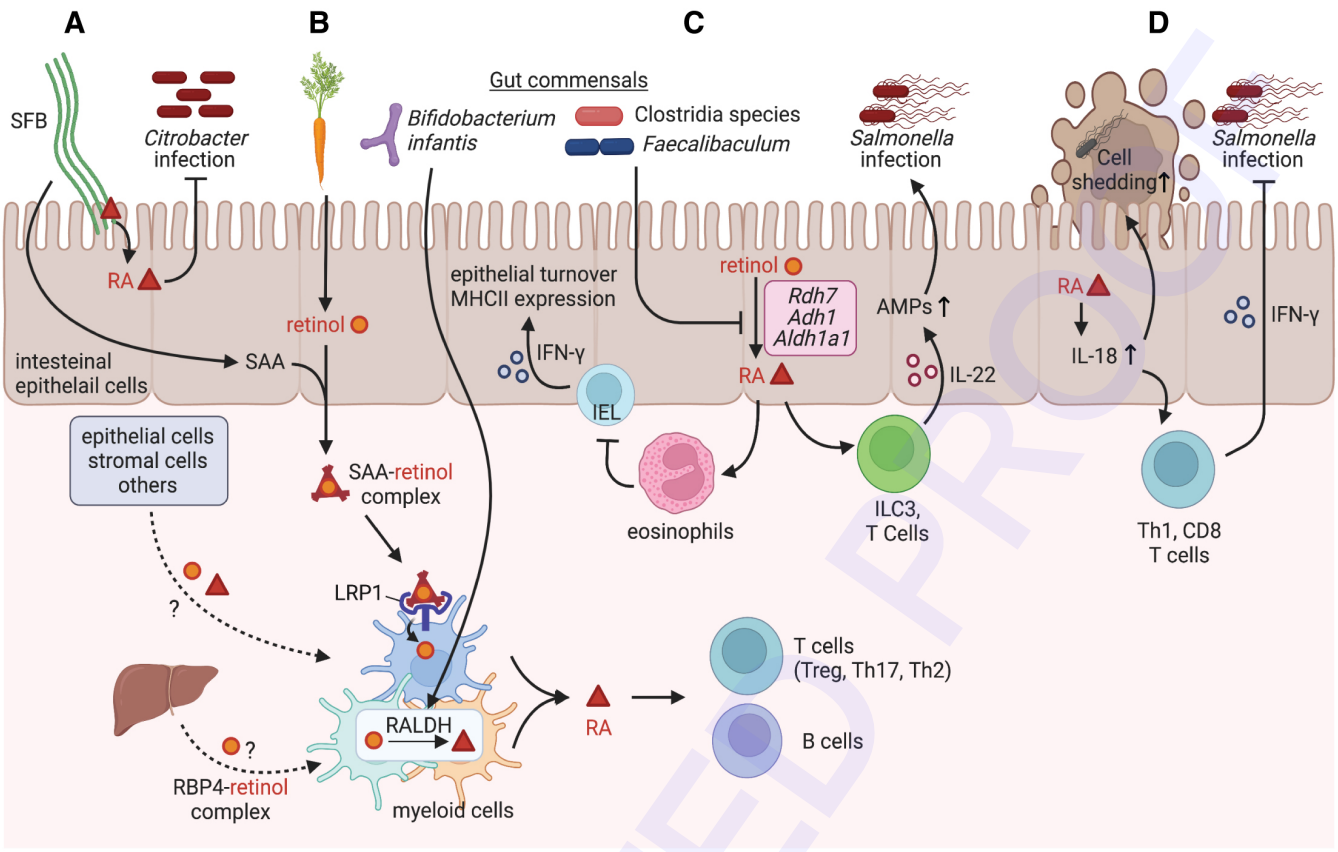


Fig. 3.