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Basic study

Understanding the role of vitamin A and its precursors in the immune system

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ABSTRACT

Vitamin A is the first defined vitamin and is also known as an anti-inflammatory micronutrient. Although the primary biological function is preservation of epithelial tissue integrity, vision and growth, vitamin A also plays a role in immune system regulation. It is known that susceptibility to infections increases in developing countries due to vitamin A deficiency. Therefore, the purpose of this review is to evaluate the role of vitamin A on the immune system in line with current studies. In this review, we focused on the immunobiological effects of vitamin A and its precursors. Vitamin A refers to retinoids and carotenoids, but both function in the body through the most active form, all trans retinoic acid. All trans retinoic acid has the highest affinity of nuclear retinoic acid receptor. Reports from in-vivo and in-vitro studies shown that the formation of retinoic acid/retinoic acid receptor complex is important in the generation of innate and adaptive immune cell response. In addition to immune cell response, vitamin A also plays an important role in mucus secretion, morphological formation and functional maturation of epithelial cells. In this way, vitamin A appears to contribute to immune development by regulating immune cell response and providing mechanistic defense. Vitamin A has received particular attention in recent years as the vitamin have been shown to have a crucial effect on the immune response. Although more randomized controlled studies are needed, data from observational human studies have shown that vitamin A is associated with infectious, inflammatory, allergic diseases and cancers.

1. Introduction

Vitamin A (Retinol) is an indispensable micronutrient for mammals as it cannot be synthesized. Vitamin A deficiency causes negative effects on growth, reproduction and counteraction of pathogens. Depending on the severity of the deficiency, various levels of biochemical and clinical symptoms are observed in the body. The most significant consequence of serious vitamin A deficiency is xerophthalmitis, in which irreversible blindness may occur. Xerophthalmia was documented in the ancient ebers papyrus in 1400 BC [1]. The fact that vitamin A deficiency caused xerophthalmitis was observed after World War I and pathological effects of vitamin A deficiency on epithelium became known [2].

Vitamin A is the first defined vitamin. Vitamin A refers to either retinol or carotenoids. Retinol or other retinoids are defined by the IUPAC-IUB Biochemical Nomenclature Joint Commission Rules, consisting of a 6-member carbon ring with 5 carbon-carbon double bonds and a side chain of 11 carbons [3]. Vitamin A contains retinol (vitamin A1) and dehydroretinol (vitamin A2) forms [4]. The chemical structure of retinol is shown as Fig. 1.

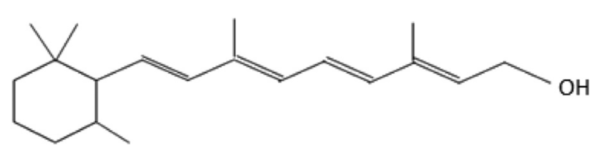

Fig. 1. Chemical structure of retinol.

In the literature, the term retinol is generally used for "all-trans retinol" because retinyl esters and retinal are derived from the basic compound, all-trans retinol. The polar end of the hydroxymethyl group of this structure is oxidized to the aldehyde group and then to the carboxylic acid group (Fig. 2). Furthermore, the hydroxyl group of retinol may also be converted to long-chain fatty acid esters such as palmitate ester for storage in the liver [3].

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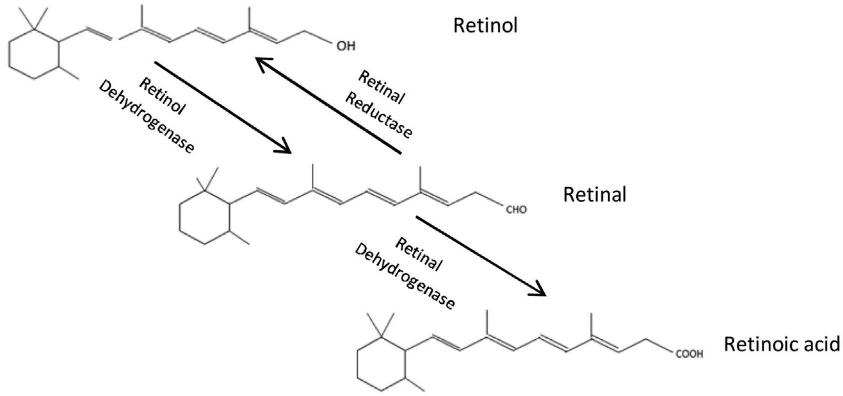

Fig. 2. Oxidation of retinol: retinol oxidizes to retinaldehyde via the actions of retinol dehydrogenases. Retinal undergoes irreversible oxidation to retinoic acid via the actions of retinal dehydrogenases or reduction catalyzed by retinal reductases to retinol. Retinoic acid is the physiologically most active form, regulating transcription of more than 500 genes.

Plants use carotenoids as a free radical scavenger to prevent side effects during photosynthesis. Vertebrates use the antioxidant properties of carotenoids by eating these plants or produce retinoids via carotenoid degrading enzymes localized in the liver and intestinal epithelium [3]. Not all carotenoids in the structure of plants are the precursors of vitamin A. Carotenoids such as lycopene or zeaxanthin are not precursors of vitamin A but ß-carotene, α-carotene and ß-cryptoxanthine are the precursors of vitamin A. ß-carotene was the most important source of vitamin A in meals [5].

Mellanby and Green (1928) reported that vitamin A could increase the anti-inflammatory response in an organism and defined it as an anti-inflammatory vitamin [6]. The anti-inflammatory effects of vitamin A were investigated more extensively in the 1980s and 1990s [7,8]. Biologically the most active form of vitamin A is retinoic acid (RA) formed by two consecutive oxidation of retinol. RA has two major derivatives; 9-cis retinoic acid (9-cis RA) and all-trans retinoic acid (ATRA) [9]. Although the primary biological function is the preservation of vision, growth, and epithelial tissue integrity, the immune regulator effect of vitamin A is also widely studied [10–12]. It is stated that approximately 250 million preschool children in developing countries have increased susceptibility to some infections due to vitamin A deficiencies. [13]. However, it is still not clear how vitamin A shows the immune regulator effect. Therefore, the goal of the review is to submit theoretical contribution to investigate vitamin A efficiency in the immune system.

2. Absorption, storage and transport to peripheral tissues

Vitamin A (Retinol) is stored mainly in the liver, kidneys and lungs between the range of 10-1000 nmol/g [14]. It is stored as unreacted retinyl ester of the body and can be mobilized as needed [15]. A specific metabolic pathway containing retinoid-binding proteins, receptor and enzymes is required to introduce vitamin A to specific tissues. In order to understand the molecular principles of absorption, storage and transportation to peripheral tissues, an understanding of the key steps in these processes is imperative.

The proximal intestine is the first part of the small intestine, via which dietary retinoids and carotenoids are absorbed [16]. Retinyl esters are hydrolyzed in the intestinal lumen or brush border membrane before absorption, and converted to retinol. Retinol can be directly absorbed via passive diffusion [17]. But in contrast to retinol, carotenoids are absorbed in a more controlled way. Absorption of carotenoids requires the scavenger receptor class-B1 (SCARB1), a receptor for high density lipoproteins which enhance the absorption of fat-soluble molecules [18]. The SCARB1 expression levels in enterocytes are controlled through the intestine-specific homeobox ISX mediated by RA [19]. In addition, ISX controls the ß,ß-carotene-15,15-dioxygenase (BCO1) (master enzyme) expression level, symmetrically disintegrating the ß-carotene chain and forming two retinal molecules [20]. Therefore, absorption of carotenoids is regulated by a negative feed-back mechanism that suppresses the intestinal SCARB1 and BCO1expression by the retinoic acid signal, which is directly linked to the retinol requirement of the organism [19].

Passive diffusion of retinol and receptor-mediated transport of carotenoids occur due to concentration difference across the enterocytes membrane. This difference in concentration must be maintained continuously and this difference is possible either by retinol binding proteins or enzymatic conversion of retinol to its metabolites. Retinol binds to specific cellular retinol binding proteins to facilitate the dissolution and cytosolic retinol. Cellular retinol binding protein 2 (CRBP2), a sub-form of these carrier proteins, is highly expressed in enterocytes and allows retinol to be transported from the cytosol to the endoplasmic reticulum to esterify [21].

Esterified retinol is transmitted to immature chylomicrons with other dietary lipids, then submitted from the enterocytes to the lymphatic canal. Roughly 70% of the chylomicrons are uptaken by the liver, which is the fundamental storage organ and is responsible for regulating the serum vitamin A. The remainder is uptaken by peripheral tissues [22]. The removal of chylomicron residues by the liver is a receptor-mediated process including a low-density lipoprotein receptor [23]. The esterified retinols are then rapidly hydrolyzed to the retinol in hepatocytes. Many enzymes assume a role in the process, such as carboxyl ester lipase, carboxyl esterase and hepatic lipase [24]. Retinol is submitted from hepatocytes to stellate cells (HSCs), which comprise 15% of liver cells and these cells undertake an essential mission in the storage and remobilization of retinol by forming retinol esters or by hydrolyzing retinol esters [25].

With the increased retinoid requirement of peripheral tissues, the signal cascade that causes the retinyl esters to be hydrolyzed and mobilized is not yet understood. However, it is known that retinyl esters should be hydrolyzed to retinol for retinoid release. Some lipases expressed in hepatic stellate cells have the ability to break the ester linkage of retinyl esters [26–28]. After hydrolyzing, retinol is returned to the hepatocytes and bound to retinol binding protein (RBP) [29]. RBP is then secreted into the bloodstream. An important point here is that most of the total retinol amount in the bloodstream is present in RBP-dependent form in cases of fasting [25]. The administration of RBP-transported retinol to some specific tissues is mediated by an RBP-receptor that is induced by retinoic

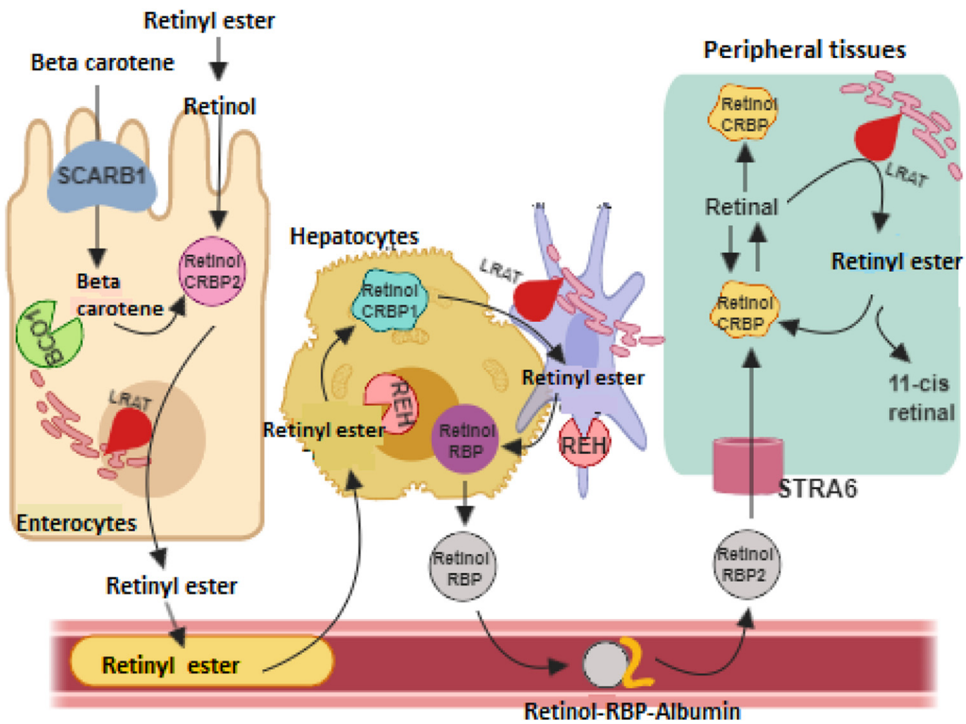

Fig. 3. Absorption, storage and transport to peripheral tissues of vitamin A: retinyl esters are hydrolyzed in the intestinal lumen or brush border membrane before absorption, and converted to retinol. Retinol can be directly absorbed via passive diffusion, while absorption of carotenoids is regulated by negative feed-back mechanism that suppresses the intestinal SCARB1 and BCO1 expression by the retinoic acid signal. Cellular retinol binding proteins (CRBPs) are expressed in some spesific tissues and allows retinol to be transported from the cytosol to the endoplasmic reticulum to esterify during storage. One of the main storage organs of retinol is the liver. Here, retinol is submitted from hepatocytes to stellate cells and these cells undertake an essential mission in the storage and remobilization of retinol by forming retinol esters or by hydrolyzing retinol esters. After retinol remobilization, the RBP-Retinol complex is secreted from hepatocytes into the bloodstream. The transportation of RBP-Retinol complex to specific tissues is mediated by an RBP-receptor that is induced by retinoic acid and called STRA6.

acid and called STRA6. This membrane receptor is expressed in many tissues associated with retinoid metabolism, except the liver and adipocytes [30]. For effective absorption of retinol via STRA6, retinol should be linked with cellular retinol-binding protein-1 (CRBP1) and lecithin retinol acyltransferase (LRAT) [31]. The absorption and storage of vitamin A, then transportation to peripheral tissues is shown as Fig. 3.

3. Retinoic acid nuclear receptors

Retinoic acid is the ligand of the nuclear retinoic acid receptor protein. The retinoic acid receptor (RAR) subgroup has three key members: RARα, RAßR and RARγ [32]. Nuclear RAR act as a ligand-activating transcription factor that regulates gene transcription in accordance with cell type [33]. ATRA is the endogenous ligand with the highest affinity of RAR [34]. A second receptor family, retinoid-x receptor (RXR), is activated by 9-cis RA. The RXR subgroup also has three main members. These are RXαR, RXRß, RXRγ [35]. RAR and RXRs generally form heterodimers and they act as ligand-dependent transcriptional factors, which bind to specific RA response elements (RAREs) in the gene promoter region. The RAREs situated in the promoters of many genes come about via variable repetition of the five nucleotide-aligned PuGG-TCA sequences [36]. A RA/RAR/RXR complex formation stimulates chromatin dissociation and alteration of transcriptional activity of RA target genes [37]. RA is also converted to oxidized metabolites by the enzymes of the CYP26 family. A lipophilic molecule, RA, can show autocrine activity in the cell in which it is synthesized and may show paracrine activity in nearby cells [38].

4. Observational and clinical studies on the immune system role of vitamin A

The role of vitamin A on the immune system has been known for many years. In 1937, Albert-Szent-Gyorgyi explained the effects of vitamin A on the immune system as follows. Vitamin A is a molecule that makes you sick if you don't eat it' [39]. Many studies have explained the mechanism of vitamin A on both innate and adaptive immune responses through certain specific pathways [40–45]. Observational and clinical studies have established that vitamin A is correlated to infectious diseases [46,47], inflammatory diseases [48,49], allergic diseases [50,51] and cancers [52,53].

The guide prepared jointly by the World Health Organization (WHO), the United Nations Children's Fund (UNICEF) and the International A Vitamin Advisory Group (IVACG), provides advice on vitamin A and measles. This guidance recommends vitamin A supplements given in dosages of 50,000 IU (15 mg) in infants under 6 months, 100,000 IU (30 mg) in infants aged 6-12 months, and 200,000 IU (60 mg) in children over 12 months, repeated every 4 months [54]. Cochrane Database Systematic Reviews have showed that vitamin A supplementation is effective in reducing morbidity related to measles in randomized controlled trials in children aged between 6 months and 5 years, but do not significantly affect the rate of hospitalization due to pneumonia [55]. It has been reported that measles virus infection impairs the immune system response, reduces plasma vitamin A levels and causes epithelial damage [56,57]. The possible interaction model between vitamin A and measles virus infection is shown in Fig. 4.

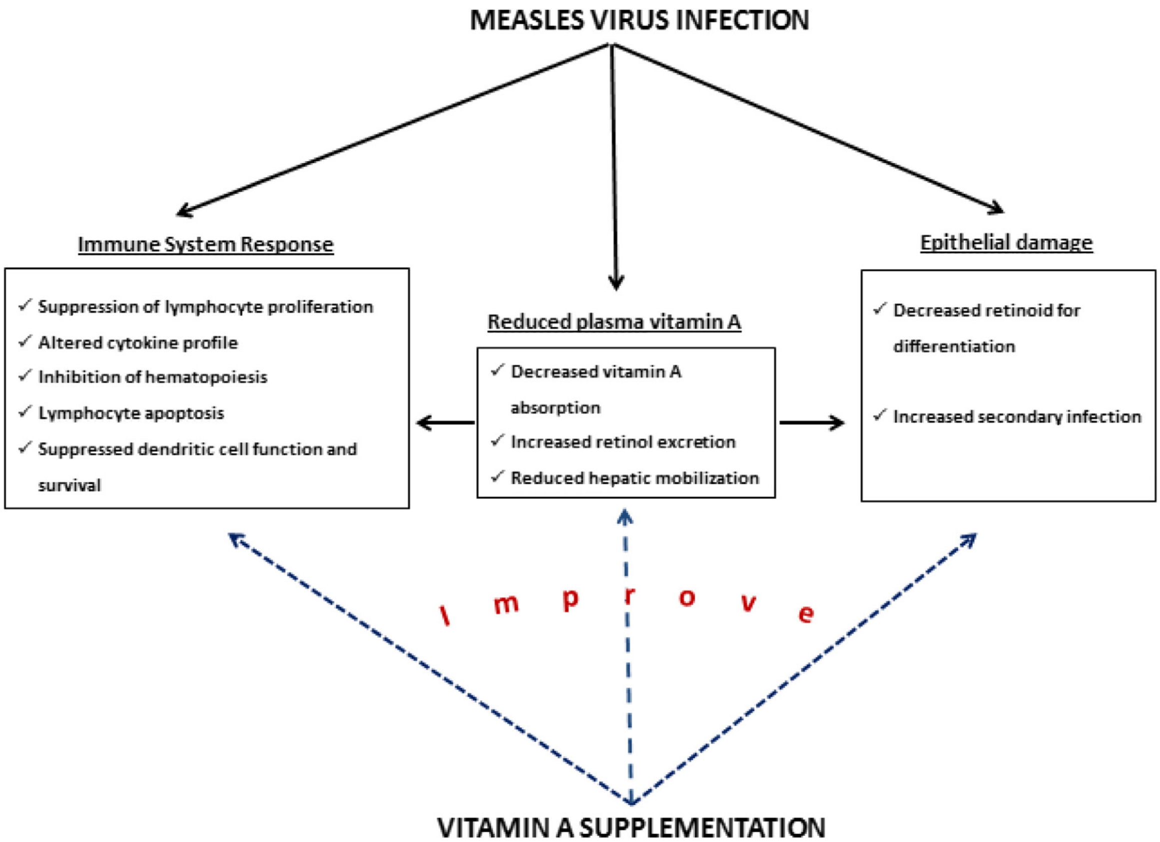

Fig. 4. The model of possible interaction between vitamin A and measles virus infection: Measles virus infection impairs the immune system response, causes epithelial damage and reduces plasma vitamin A level. However, decreased plasma vitamin A level also impairs the immune response and increases epithelial damage. Vitamin A supplementation reduces the severity of measles by improving decreased plasma levels, impaired immune response, and damaged epithelial tissue.

In a hospital-based cross-sectional descriptive study, significant vitamin A deficiency was found in hospitalized children with diarrhea [58]. Similarly, a longitudinal cohort study by Aibana et al. (2017) established links between vitamin A deficiency and tuberculosis [59]. In a randomized double-blind placebo-controlled study, a single dose of 200,000 IU of vitamin A-enriched zinc supplementation is reported to have reduced clinical malaria cases in children aged 6-72 months [60]. Although the prevalence of vitamin A deficiency was high in children with sepsis, the number of days in the intensive care unit was slightly, but not significiantly, reduced with 100,000 IU vitamin A supplementation in patients with sepsis [61,62]. However, data are not clear that vitamin A supplementation reduces mortality and morbidity and improves diarrhea in infected children [63]. Recently, it has recently been reported that pandemic SARS-CoV-2 virus, which recently appeared in Wuhan, China, inhibits the effects of IFN-I in the host cell [64,65]. Strikingly, the IFN-I potentiating effects of retinoids has already been documented in human clinical trials [66,67]. Therefore, retinoids that can increase IFN-I mediated antiviral response should be tested with antiviral drug combination in preclinical studies during the pandemic period.

In studies on inflammatory diseases, vitamin A has been reported to exert an anti-inflammatory effect by regulating the immune response of myeloid and lymphoid cells and suppression of the arachidonic acid pathway [40,45,68]. Therefore, vitamin A is also defined as an anti-inflammatory vitamin [6]. Korea National Health and Nutrition Examination Survey (KNHANES) has noted a negative correlation between serum retinol level and serum hs-CRP [69]. Also, the high prevalence of vitamin A-deficiency in Crohn's disease supports KNHANES findings [70]. Mohammadzadeh Honarvar et al. (2016) have reported that T-bet and IFNγ expression significantly decreased and Th1/Th2 balance improved after 25,000 IU retinyl palmitate supplementation for 6 months in patients with multiple sclerosis [71]. In a randomized controlled clinical trial, it has been reported that mucosal damage and rectal bleeding in patients with ulcerative colitis are reduced with 25,000 IU/day vitamin A treatment [72]. Djereba et al. (2013) have reported that ATRA treatment has an immunomodulatory effect by inhibiting NO production and NF-κB translocation in Behcet's patients [48]. Moreover, the positive effect of vitamin A on acne vulgaris has been proven by clinical studies in the last decades [73–75]. On the other hand, an important cause of metabolic syndrome, T2DM and cardiovascular atherosclerosis is thought to be adipose tissue inflammation. It is now appreciated that an array of inflammatory cytokines are increased in obese tissues, including IL-6, IL-1ß, CCL2, and others [76]. Farhangi et al. (2016) have reported that the level of IL-6 is significantly higher in obese women compared to a control group, and a significant decrease in IL-6 levels has been found following 4 months 25,000 IU retinyl palmitate supplementation [77].

Environmental and nutritional factors are known to be effective in the pathogenesis of allergic diseases. Research has shown that there is a negative relationship between antioxidant intake and asthma symptoms such as bronchial inflammation and decreased pulmonary function [78–80]. It is reported that levels of vitamin A are lower in asthmatic patients and that vitamin A deficiency causes squamous metaplasia by decreasing the proliferation of respiratory mucus and basal cells. In a systematic review and meta-analysis study by Morabia et al. (1990), it is reported that vitamin A consumption and serum vitamin A levels are lower in asthmatic patients than in non-asthmatic patients [81]. Similarly, the study showed lower serum vitamin A levels in asthmatic children than in the control group [51]. Although observational studies have shown a negative relationship between serum vitamin A level and asthma symptoms, there is insufficient clinical evidence to suggest that vitamin A improves asthma symptoms. Conversely, there are clinical studies reporting that atopy increases with vitamin A supplementation in neonates [82,83]. There are findings regarding the effectiveness of the use of alitretinoin in combination with topical corticosteroids in patients with chronic hand eczema. It is reported that alitretinoin significantly reduced symptoms of severe chronic hand eczema in patients resistant to potent topical corticosteroids in phase 3 clinical trial [84].

There are studies showing that vitamin A is associated with cancers. Vitamin A and synthetic analogs have been reported to be potent agents for the prevention of carcinogenesis in normal and pre-neoplastic epithelial cells and the control of cell differentiation [85]. Bakker et al. (2016) has found that there is an inverse relationship between plasma ß-carotene and α-carotene levels and breast cancer risk [86]. Higher serum retinol levels have also been shown to be associated with increased risk of prostate cancer and lower risk of liver and lung cancer [87]. However, Hu et al. (2015) have reported that there is no significant relationship between plasma retinol level and breast cancer risk [88]. The role vitamin A plays in cancer treatment has been known for a long time and it is recently reported that Ipilimumab plus ATRA significantly decreased the frequency of circulating myeloid-derived suppressor cells (MDSCs) compared to Ipilimumab treatment alone in advanced-stage melanoma patients [52]. In a phase III clinical trial carried out by the ULM study group, it is noted that the use of ATRA in combination with chemotherapy in myeloid leukemia patients aged over 61 years is advantageous [89]. However, recent studies indicate that a ATRA and arsenic trioxide (ATO) combination is more effective in treatment than ATRA alone [90–92].

5. The role of vitamin A and its precursors in the immune system

Vitamin A is a multi-functional vitamin that plays a role in a wide variation of biological processes. This vitamin is important for both the development and functional outgrowth of almost all cells associated with innate and adaptive immune cell responses. This condition is of great importance on the intestine surface where absorbtion of vitamin A begins. Vitamin A performs most of its effect through the ligation of nuclear receptors with RA. In this sense, the formation of the RA-RAR complex is important in the generation of innate and adaptive immune response [93].

Immune organs or tissues are located where the immune cells multiply, differentiate, mature and form an immune response. Research notes that immune tissues are in need of a steady dietary consumption to retain vitamin A concentration [94,95]. In addition, RA has also been found to be effective in regulating apoptosis of thymocytes [96]. In cases of vitamin A deficiency, the cell apoptosis is inhibited and the number of myeloid cells increase in bone marrow, spleen and bloodstream [95]. Moreover, studies have shown that vitamin A is not only effective in innate immune regulation but also in adaptive immune regulation [97–99].

In addition, vitamin A is also important in mucus secretion, morphological formation and functional maturation of epithelial cells. In this sense, it is an indispensable molecule for the epithelial surface and mucus layer of both the intestine and the respiratory tract [100]. Intestinal epithelial cells form the first line of defense against pathogens. Therefore, vitamin A contributes to the development of immunity by maintaining mechanistic defense through the preservation of epithelial integrity and increase of mucus secretion [101].

5.1. *Immunobiology of intestinal epithelial cells and the role of vitamin A*

Intestinal epithelial cells may secrete certain cytokines or chemokines such as IL-6, IL-7, IL-1ß, IL-8, GM-CSF and TGF-ß [102]. Some of them have proinflammatory properties, while others show anti-inflammatory properties [103]. Cytokine and chemokine receptors are also expressed in intestinal epithelial cells [104,105]. In addition, expression of pattern recognition receptors (PRRs) occurs in intestinal epithelial cells. Two important families of these receptors are Toll-like receptors (TLRs) and Nod-like receptors (NLRs). TLR activation is known to be effective in T cell mediated immune response by stimulating cytokine production and T cell differentiation [106].

Epithelium is not a passive barrier. Antimicrobial peptides from paneth cells and mucus secretion from goblet cells can be secreted when encountered with an antigen [107]; and IL-22, which is responsible for defense and tissue repair, can be produced from epithelial cells [108]. Thanks to the polimeric immunoglobulin receptor (pIgR), it can also facilitate immunoglobulin transition to lumen [109]. Moreover, it can prevent mucosal leakage through the tight junction between the cells [110]. In addition, it carries out the destruction of intestinal bacteria and abnormal intracellular proteins thanks to their autophagosomes [111].

In a study by Xiao et al. (2018) using both the necrotizing enterocolitis rat model and human Caco-2 cells, patients with necrotizing enterocolitis displayed lower levels of serum retinol than the control group. Both in vivo and in vitro studies have showed that retinoic acid and vitamin A treatment significantly decreased the level of inflammatory factors and increased expression of intestinal epithelial barrier proteins (claudin-1, occludin, ZO-1) [112]. This study also found that numbers of goblet and panet cells are higher in RARα-deficient mice and more antimicrobial peptide (Reg3γ) was secreted from human Caco-2 cells. This situation caused dysbiosis by affecting the diversity and number of intestinal microorganisms in mice [113].

Another study by Yang et al. (2011), specific pathogen-free Sprague Dawley rats with and without vitamin A supplementation were divided into two groups and intestinal infection induced in the rats via salmonella inoculation. Three days after infection, the rats were sacrificed and the amount of mucosal dendritic cells and TLR2/TLR4 expression examined. TLR expression and the amount of dendritic cells increased in the non-supplemented group, thus showing an impaired immune response [114]. Also, 1 μM Cis-9 RA and ATRA was found to increase the expression of pIgR together with TNF-α and improve mucosal immunity in human colonic adenocarcinoma cells [115].

5.2. *Myeloid cell immunobiology and the role of vitamin A*

Myeloid cells function as essential mediators of innate immune response and play an important role in host defense against infections and tissue damage [116]. Granulocytes migrate from the bloodstream to tissues as a response to chemoattractants, such as IL-8 (neutrophil) or eotaxin (eosinophil, basophil), and are fully activated by stimulation of cytokines (or molecules) released from damaged cells or pathogens after extravasation [117]. Monocytes are mononuclear phagocytic cells, which exist in the bloodstream before migrating to tissues. Monocytes can evolve into macrophages, dendritic cells or osteoclasts depending on the type of inflammatory stimulus. However, specific subunits of macrophages and dendritic cells may originate directly from bone marrow progenitors independent of monocytes [118]. Macrophages and dendritic cells contain a large number of surface receptors. They phagocytize specific antigens by their enzymes and present them to T cells [119] (Fig. 5). However, macrophages

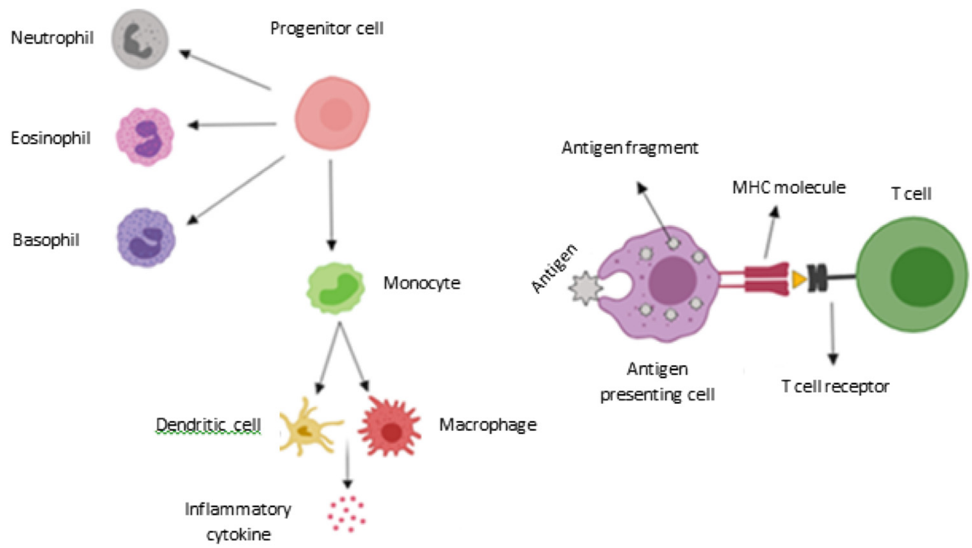

Fig. 5. Differentiation of myeloid cells and antigen presenting cell illustration: granulocytes and monocytes differ from myeloid progenitor cells. Monocytes can evolve into macrophages and dendritic cells depending on the type of inflammatory stimulus. However, specific subunits of macrophages and dendritic cells may originate directly from bone marrow progenitors independent of monocytes. Monocytes and dendritic cells phagocytize specific antigens by their enzymes and present them to T cells. Retinoic acid, the most active form of vitamin A, regulates the transcription of some hematopoietic genes. Dendritic cells can produce retinoic acid required for effective antigen presentation and T cell activation. However, RA regulates the pro-inflammatory and anti-inflammatory macrophage response.

display morphologically a heterogeneous subunit structure with different physiological characteristic. The presence of heterogenous macrophage subunits is important in maintaining balance of immune response.

RARα and RARγ receptors are abundantly expressed in the hematopoietic system. While RARα is expressed in various bone marrow cells, RARγ is expressed in primitive hematopoietic progenitor cells. A reduction in these receptors results in a decrease in the quantity of HSCs [120]. In a study using human embryonic stem cells, it is stated that certain hematopoietic genes are highly expressed and myeloid cells proliferate in RA treated cells [121]. Dendritic and stromal cells in gut associated lymphoid tissue (GALT) can synthesize retinaldehyde dehydrogenase enzymes (RALDH) to produce the active metabolit RA required for T cell activation. In mice with decreased RALDH2 mRNA expression in dendritic and stromal cells in the mesenteric lymph node, it is shown that RA-mediated signal and RALDH enzyme activity increase after vitamin A supplementation. [122].

In a study on human monocyte cells by Klassert et al. (2014), the efficiency of ATRA in the innate response against *Candida albicans* was measured. It is stated that the expression and secretion of *C. albicans*-induced TNFα, IL6 and IL12 were significantly reduced by ATRA [40]. However, studying the effect of ATRA deficiency and supplementation on monocyte response investigated in individuals with alcoholic liver disease, a negative correlation was found between serum ATRA level and disease severity score. At the same time, it is reported that LPS-induced TNFα production in peripheral blood mononuclear cells (in vivo) decreased with ATRA pretreatment [123].

5.3. Lymphoid cell immunobiology and the role of vitamin A

Lymphoid cells differentiating from pluripotent stem cells and common lymphoid progenitor cells are responsible for the adaptive immune response. Adaptive immune response functions either as B cell-mediated (humoral) or T cell-mediated (cellular). Both types of adaptive immune response are initiated by antigens. The essential function of B cells is to generate antibodies against pathogens [124]. B cells also serve as antigen-presenting cells, such as macrophages and dendritic cells [125]. However, T cells play a central role in adaptive immune response. B cells are able to recognize the antigen directly, but T cells respond when bound to the major histocompatibility complex (MHC) proteins on the surface of the antigen presenting cells [126].

T cells are of three main types. These are helper T cells (Th), cytotoxic T cells and regulator T cells (Treg). Cytotoxic T cells are called CD8+ cells, while helper T cells and regulatory T cells are called CD4+ cells [127]. Cytotoxic T cells are critical to the annihilation of malignant or infected cells and are considered an important therapeutic target [128]. However, regulator T cells are defined as an immune-suppressive subset of CD4+ T cells [129]. The number of regulatory T cells is low under normal conditions, but it has been reported that the number is increased in cancer patients [130]. This increase reduces survival in patients [131]. Helper T cells stimulate proliferation of cytotoxic and regulatory T cells via secreted lymphokines (Fig. 6). These lymphokines also stimulate B cell growth, plasma cell formation and then antibody generation.

Lymphocytes have a different universe called natural killer (NK) cells. There is limited information about the progenitors and maturation processes of these cells produced in the bone marrow [123]. Additionally, new lymphocytes have recently been identified; innate lymphocyte cells. These cells have three main subunits: ILC1, ILC2, ILC3. It has also been reported that ILC2 and ILC3 increase the production of amphiregulin (AREG) and IL-22, thereby increasing tissue repair and antimicrobial peptide release, respectively [132]. NKs and ILCs are not specific to a particular antigen. These cells express pattern recognition receptors (PRRs), which enable them to respond rapidly to stimuli [41].

In a study by Pantazi et al. (2015), it is reported that silencing the RA signal reduced the number of IgA-secreting cells in mice (in-vivo and in-vitro). This suggests that RA have an effect directly on B cells through the RARα affecting IgA synthesis and secretion [133]. However, both 5 mg/kg and 10 mg/kg daily single dose ß-cryptoxanthin has been found to significantly increase serum IgA, IgM and IgG levels in New Zealand white rabbits. [134]. Also, Seo et al. (2017) have reported that IgE levels increase in rats with vitamin A deficiency and retinoic acid has a suppressive effect on IgE-secreting cells [135]. These results indicate that vitamin A has the potential to increase antibody mediated immune response and to suppress allergic inflammation.

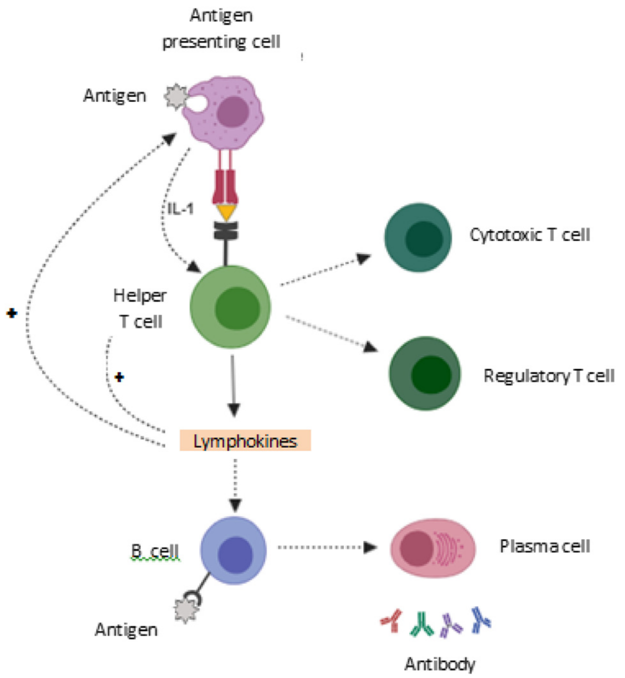

Fig. 6. The central role of T cells in the immune system: T cells are of three main types. These are helper T cells (Th), cytotoxic T cells and regulator T cells (Treg). Helper T cells constitute the largest group of T cells and they stimulate proliferation of cytotoxic T cells, regulatory T cells and plasma cells via secreted lymphokines. Cytotoxic T lymphocytes are critical to the annihilation of malignant or infected cells and are considered an important therapeutic target. Regulator T cells are defined as an immune-suppressive subset of CD4+ T cells and they represent a low number of T cell populations under normal conditions. Retinoic acid has an inductive effect directly on IgA-secreting B cells and has a suppressive effect on IgE-secreting cells. It also induces the Th2 cell response-enhancing transcription factors such as GATA3 and STAT6, while blocking T-bet expression, the Th1 cell master regulator. However, retinoic acid has a critical role in stabilizing regulatory T cell.

Research shows that integrin α4ß7 and CCR9 (T cell chemokine receptor) are essential for T cell migration into the intestines under inflammatory conditions. Iwata et al. (2004) have showed that RA increases the expression of integrin α4ß7 and CCR9 in T cells isolated from mice splenocytes [136]. Some studies have noted that vitamin A deficiency inhibits Th2 cell response [137] and vitamin A supplementation reduces the cytokines production from Th1 cell [68]. RA stimulates Th2 cell differentiation by inducing IL-4 gene expression [138]. In addition, RA induces the Th2 cell response-enhancing transcription factors such as GATA3 and STAT6, while blocking T-bet expression, the Th1 cell master regulator [139]. In this way, RA provides T cell regulation and balances the pro-inflammatory and anti-inflammatory response.

ATRA is the main regulator of TGFß-mediated immunity. TGF-ß stimulates proliferation of Treg cells [140]. Studies have shown that ATRA promotes proliferation of Treg cells by increasing FOXP3-expression in the presence of TGF-ß and inhibits IL-17 expression [141,142]. In vitro experiments have shown that Treg cells are unstable under proinflammatory conditions and they can be differentiated into various inflammatory cells such as Th17 because of IL-6 and similar cytokines. Conversely, ATRA treatment inhibits the conversion of Treg cells to Th17 or other helper T cells even in the presence of IL-6 [143,144]. Kwok et al. (2012) have created a model of arthritis in mice, treated with 0.5 mg/kg intraperitoneal ATRA three times a week. They have shown that clinical and histological signs of arthritis reduce in ATRA-treated mice [145].

In previous years, it was believed that only defective Th2 cell function was responsible for increased prevalence of mucosal infections in malnutrition and vitamin A deficiency. With the discovery of innate lymphoid cells (ILC), cytokines produced by ILCs are also believed to be responsible. Vitamin A is thought to affect the functional integrity of ILC cells as well as its effect on T cells [43,146]. ILCs can interact easily with immune system cells and stromal cells in the mucosa due to their proximity to adaptive immune cells and epithelium [147]. Vitamin A regulates the balance between ILC2 and ILC3 to maintain the immune response balance in autoimmune, inflammatory and allergic diseases. ILC2 accumulation increases in vitamin A deficiency and accelerates inflammatory cytokine production. However, ILC3 accumulation decreases with vitamin A deficiency [43]. It is also known that RA significantly increases the production of IL-22 inducing epithelial cells to produce RegIII (Regenerating islet derived III), the antimicrobial peptide in the colon [148].

Studies explaining the effect of vitamin A on NK cells are quite limited. In a study by Chang and Hou, it has stated that RA reduces NK cell-based interferon-γ((IFNγ) production [149]. In another study, mice were given 20 mg/kg/day ATRA for 7 days and then the mice were inoculated with polynosinic acid (poly 1:c). In this way, cathepsin C levels, an enzyme that increases inflammation and cytotoxicity in bone marrow-derived phagocytic cells, have been increased. At the end of the study, it was reported that cathepsin C expression was reduced in ATRA-treated mice and thus NK cell cytotoxicity decreased [150].

6. Carotenoids and immune system

Carotenoids, which are predominantly vitamin A precursors, usually show an immunomodulatory effect through retinoic acid [44]. However, all carotenoids, together with carotenoids that are not vitamin A precursors, have been shown to have a modulating effect on the immune system from different pathways [151]. The mechanism of action of carotenoids on the immune system is generally thought to occur through T cell proliferation, activation of NK cells and suppression of the arachidonic acid pathway [44].

In a study by Park et al. (2011), 12-week treatment program is established using 1, 5 and 10 mg/kg astaxanthin daily, and peripheral blood mononuclear cell proliferation response was investigated after astaxanthin treatment. The study concluded that helper T cell proliferation increases significantly in all treatment groups [152]. Also, ß-carotene treatment at 30 mg twice daily for 4 weeks caused to an increase in CD4+ cells and increased immune response in HIV infections [153]. Cui et al. (2012) have reported that respectively 20, 40 and 60 mg/kg ß-carotene treatments for 30 days in hepatocellular carcinoma-induced Wistar rats increase the number of NK cells in a dose-dependent manner [154]. Similarly, 50 μL x 10^6 MCF-7 cells were inoculated in mice with thymus resection and it is found that palm oil ß-carotene treatment for 20 weeks increases the NK cell number [155].

Some carotenoids are thought to suppress the production of Prostaglandin E2 (PGE2), an immunosuppressor agent, by inhibition of cyclooxygenase enzyme [44]. In a study using rodent macrophage cells, it is found that cyclooxygenase-2 (COX2) and PGE2 production increase in LPS-induced macrophage cells, and COX2 and PGE2 protein levels decrease with ß-carotene treatment in a dose dependent manner [45].

7. Conclusion

The role of vitamin A in the immune system has been investigated since 1928, with comprehensive studies being undertaken in the 1980s and 1990s and continuing to date. As a result of recent multidisciplinary studies, the relationship between vitamin A and the immune system has become more understood. Dietary retinol usually exerts its effect on the immune system via the retinoic acid form. Carotenoids, the precursor of vitamin A, are also involved in the homeastasis of the immune system through retinoic acid signaling pathway but these carotenoids can also function independently of retinoic acid. Vitamin A has an active role in both innate and adaptive immune response by acting on myeloid and lymphoid immune cells. Vitamin A also contributes to the development of the immune response by improving epithelial cell function. As such, it remains a leading component in inflammatory, allergic and infectious diseases and cancers. More studies and advanced clinical trials are still needed for better understanding the role of vitamin A on the immune system, however it is conceivable that vitamin A will play a critical role in modern treatment.

Disclosure of interest

The authors declare that they have no competing interest.

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