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Review

How Micronutrients Fuel Immune System at the Molecular Level: An Approach to the Immune Response Against Respiratory Viruses

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Micronutrients • Immune response • Respiratory viral infections

Abstract
Viral respiratory infections could range from a common cold to severe pneumonia, and their resolution mainly relies on appropriate immune system function. The widespread popular knowledge that nutritional habits influence immune system function has been demonstrated over the past decades in which increasing scientific evidence unveils certain nutrients as critical drivers of immunity. Micronutrients encompass minerals and vitamins necessary for a broad range of biological processes; since their deficiency could cause several clinical manifestations, such as weakness, growth retardation, and susceptibility to infections; hence, micronutrients represent one of the multiple factors that modulate immune function. Among micronutrients are those that act mainly as antioxidants, regulating gene expression and as a structural part of proteins for their proper function. Here, we review how some of the most recognized micronutrients are participating at the molecular level in each step of the innate and adaptive immune response against viruses focusing on viral respiratory tract infections, such as those caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

Introduction

Respiratory tract infections (RTI) can range from a self-limiting cold to severe pneumonia with sepsis development [1]. Although several etiologies exist, viruses have gained significant attention due to the current global sanitary situation caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Among causal viruses of RTI, besides SARS-CoV-2 and other coronaviruses, are the enterovirus, respiratory syncytial virus (RSV), metapneumovirus, rhinovirus, parainfluenza virus, influenza virus, and adenovirus [2].

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Despite the causal virus and the pathogenic evasion mechanisms of each one, all of them evoke the activation of the innate and adaptive immune response, which in general involves the following steps:

- 1.) The epithelial barrier is the first defense restricting infections; the airway epithelial barrier performs mechanical actions such as cilia movement and warming air; this also contains in the airway liquid surface (ALS) mucins (MUC) and antimicrobial peptides (AMP), molecules which help to reduce the possible infection.
- 2.) Once viruses bypass epithelial barrier actions and molecules, they infect target cells and cause cellular stress. In response, host cells will use their pattern recognition receptors (PRRs) to recognize viral pathogen-associated molecular patterns (PAMPs), triggering an antiviral alarm state in which interferons (IFN) type I and III are synthesized, natural killer (NK) cells are activated, and inflammation is generated. At this time-point viral infection might resolve, but if that is not, the antigen-presenting cells (APC) are ready to trigger the next steps.
- 3.) APC such as macrophages and dendritic cells (DC) process endogenous and exogenous antigens to further present them on their major histocompatibility complex (MHC) molecules class I or II, respectively. Antigens loaded on MHC-I molecules are presented to the T cell receptor (TCR) of T cytotoxic (Tc) CD8+ lymphocytes, whereas antigens loaded on MHC-II are presented to the TCR of T helper (Th) CD4+ lymphocytes, giving rise to the adaptive immune response.
- 4.) Tc CD8+ lymphocytes are the major players in the adaptive cellular response that aims to kill infected cells. On the other hand, Th CD4+ lymphocytes could also participate in cellular response; however, they mainly cooperate with B lymphocytes to elicit the adaptive humoral response characterized by antibody production [3].

The expected result of the antiviral immune response is the control and elimination of the pathogen (Fig. 1 and 2); however, some factors could affect the infection resolution, such as evasion mechanisms of the viruses, stress, environmental pollution, hormonal status, comorbidities, and nutrition [4-10].

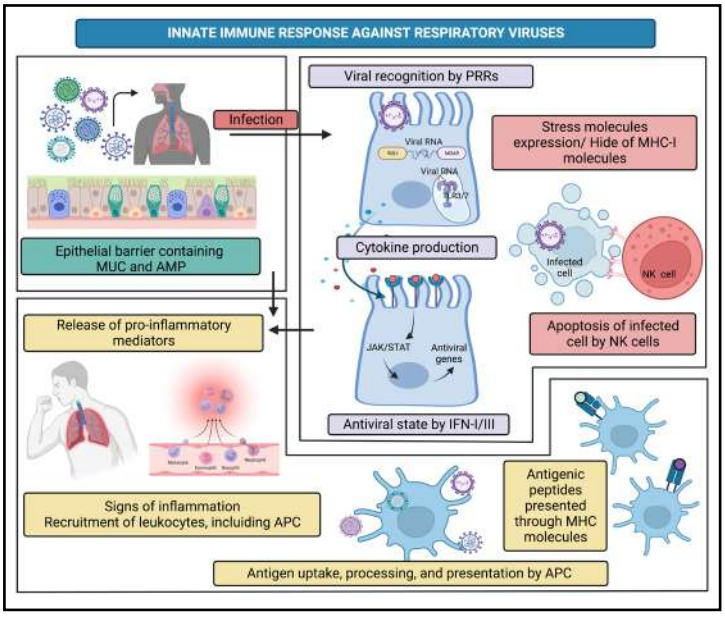

Fig. 1. Innate immune response against respiratory viruses. a) The mucins (MUC) and antimicrobial peptides (AMP) that are present on the airway epithelial barrier; the type I and III interferons (IFN) produced by the recognition of viral components by the pattern recognition receptors (PRRs); the activation of the Janus kinase (JAK)/ signal transducer, and activator of transcription proteins (STAT)/interferon regulatory factors (IRF) pathway in the neighboring cells; the activation of natural killer (NK) cells; the induction of inflammatory response; and the activation of antigen-presenting cells (APC) are part of the innate immune response against respiratory viruses. Figure created with BioRender.com.

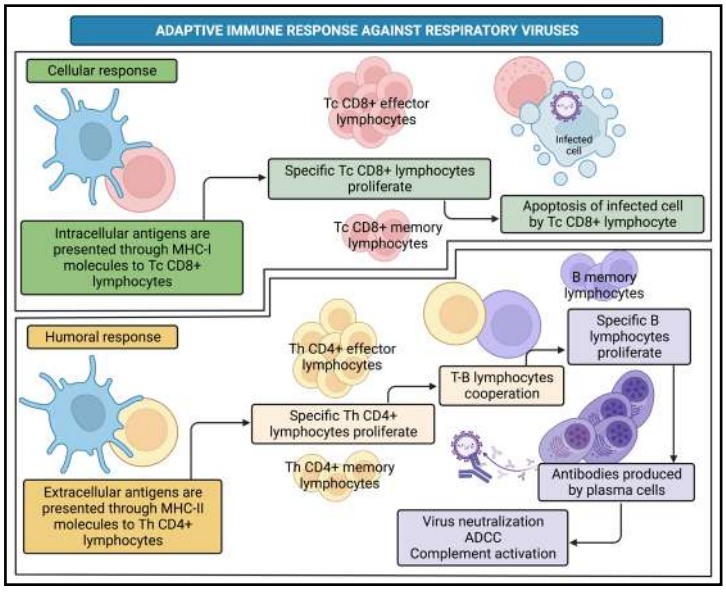

Fig. 2. Adaptive immune response against respiratory viruses. The adaptive cellular response involves the presentation of endogenous antigens onto the major histocompatibility complex (MHC)-I molecules to T cytotoxic (Tc) CD8+ lymphocytes, which aim to kill the infected cell. In contrast, the adaptive humoral response involves the presentation of exogenous antigens onto the MHC-II molecules to the T helper (Th) CD4+ lymphocytes and their cooperation with B lymphocytes that subsequently produce antibodies to neutralize viruses, induce the classical pathway of complement, or trigger the antibody-dependent cellular cytotoxicity (ADCC). Figure created with BioRender.com.

In this regard, SARS-CoV-2 infection causes a severe inflammatory response in patients with comorbidities such as diabetes, hypertension, and obesity [11], pathologies tightly related to metabolic and nutritional alterations.

Indeed, micronutrient imbalance is associated with the risk of complicated respiratory tract infections, as has been reported for vitamins A, D, E, and C and the trace elements zinc and magnesium [12-20]; therefore, their supplementation improves the effector function of the immune system, as has been excellently reviewed elsewhere [21, 22]. Here we will focus on how those micronutrients mentioned above, in which deficiency or supplementation impacts immune function, participate at the molecular level in each step of the immune response against respiratory viruses. Considering their three main action mechanisms as antioxidants, gene-expression regulators, and structural components of proteins, we will revise their functions as immuno-stimulators, immuno-regulators, or even both.

General overview of micronutrients

Micronutrients encompass vitamins and minerals typically considered cofactors involved in many enzymatic reactions; however, they perform several other functions. For example, vitamins C and E act as antioxidants, vitamins A and D regulate the expression of several genes, and the trace elements zinc and magnesium are structural parts of transcriptional factors (Fig. 3).

- 1.) Antioxidant vitamins: Oxidative stress is a typical process occurring during respiratory viral infections that requires to be tightly regulated to avoid its contribution to the pathology progression [23]. The two vitamins, well known for their antioxidant properties, vitamins C and E, are also involved in each step of the immune response through their antioxidant and other mechanisms.

Vitamin C, also known as ascorbate or its oxidized form dehydroascorbate (DHA), is taken up by cells via sodium-dependent vitamin C transporters (SVCT) and glucose transporters (GLUT) [24]; in immune cells, SVCT2 and GLUT3 seem to be especially relevant for vitamin C uptake, and the contribution of each one depends on the lineage and differentiation status [25-27].

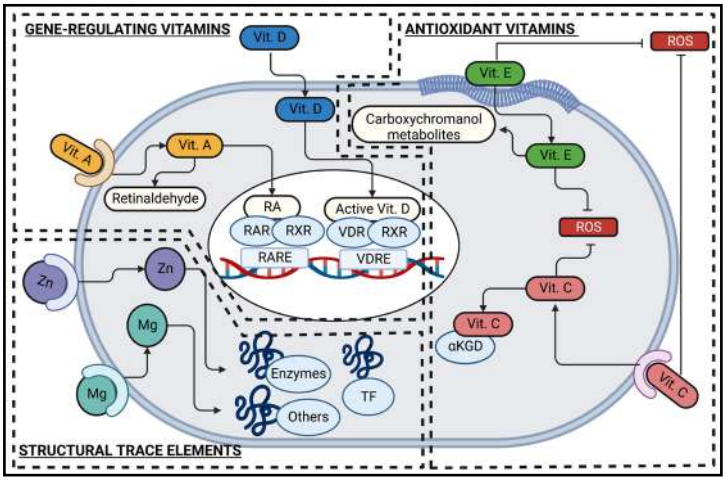

Fig. 3. Action mechanisms of micronutrients, in addition to being cofactors. Vitamin A (Vit. A) is metabolized to retinaldehyde and retinoic acid (RA); which is recognized through the RA receptor (RAR) that, in turn, interacts with the retinoid X receptor (RXR); RAR/RXR dimer functions as a transcriptional factor that binds genes containing RA response elements (RARE). The active form of vitamin D (Vit. D) binds to the vitamin D receptor (VDR), which also interacts with RXR, functioning also as a transcriptional factor that binds to genes containing vitamin D response elements (VDRE). Vitamin E (Vit. E) can be part of the plasma membrane to regulate its curvature, acts as an antioxidant, and can be metabolized to carboxychromanols which exert other functions. Vitamin C (Vit. C) is an antioxidant and a cofactor of several alpha-ketoglutarate-dependent dioxygenases (αKGD), enzymes that regulate epigenetics and metabolism. Zinc (Zn) and magnesium (Mg) interact with and support the function of many biomolecules, mainly proteins such as enzymes and transcriptional factors. Figure created with BioRender.com.

The antioxidant function of vitamin C relies on its electron donor capacity but also functions as a metabolic and epigenetic modulator through the alpha-ketoglutarate-dependent dioxygenases (αKGD), enzymes that use this vitamin as a cofactor [28-30].

On the other hand, vitamin E embraces eight lipophilic molecules sharing a chromanol ring structure, four tocopherols isomers (α, β, γ, δ) and four tocotrienols isomers (α, β, γ, δ); these can be distinguished among them by the number of bonds of the side chain and by the methyl groups in the chromanol ring structure. Due to its chemical nature, vitamin E could easily conjugate with lipophilic compounds such as bile acids, cholesterol, and other lipids and is taken up by cells mainly through the scavenger receptor B type I (SR-BI) but also by the cluster of differentiation (CD)36 [31-33]. Interestingly, CD36 is a molecule highly expressed on phagocytic cells such as neutrophils, monocytes, and macrophages; and its expression is affected by respiratory viruses, as has been reported for influenza virus and RSV infections *in vitro* [34, 35]. Once inside cells, vitamin E is transformed into carboxychromanol (COOH) metabolites through different steps of oxidation and shortening the side chain length [31, 32].

Besides its chromanol ring structure-dependent antioxidant function, other functions of this vitamin are to regulate plasma membrane curvature under stress conditions, modulate the inflammatory process, and even suggest controlling gene expression through the pregnane X receptor (PXR) [36-40].

- 2.) Gene-regulating vitamins: The liposoluble vitamins A and D can bind to their receptors to activate their transcriptional factor function and promote the expression of several genes, including some involved in the innate and adaptive immune responses.

Vitamin A, also referred to as retinol, requires to be transported by the retinol-binding protein (RBP) to enter cells by passive diffusion or through the receptors SR-BI, adenosine triphosphate (ATP)-binding cassette transporter (ABCA4), and stimulated by retinoic acid gene 6 (STRA6) [41, 42]. Inside cells, retinol is metabolized to retinaldehyde and retinoic acid (RA) through retinol dehydrogenase and retinaldehyde dehydrogenase, respectively. While retinaldehyde is involved in the visual cycle, RA regulates the expression of several genes through its recognition by the RA receptor (RAR). RAR, together with the retinoid X receptor (RXR), functions as a transcriptional factor when bound to hundreds of genes that contain

RA response elements (RARE) [41]; among these are immune response genes, such as the RA inducible gene-I (RIG-I), a PRR that recognizes viral RNA; and the 2'-5'-oligoadenylate synthase 1 (OAS1), a protein involved in the viral RNA degradation [43, 44].

Vitamin D can be acquired from dietary sources as vitamin D2 (ergocalciferol) from plants or as vitamin D3 (cholecalciferol) from animals; however, its primary source is the 7-dehydrocholesterol in the skin, which is converted to vitamin D3 by the action of ultraviolet light. Vitamin D is transported by the vitamin D binding protein (DBP) to the liver, where hepatocytes convert it to 25-dihydroxy vitamin D3 (25(OH)D3 to then reach the kidneys, where tubular cells transform it into the active form of vitamin D, the 1,25-dihydroxy vitamin D3 (1,25(OH)2D3). Interestingly, some immune cells, such as macrophages, dendritic cells, and T cells, can also produce the active form of vitamin D [45-47].

The active form of vitamin D acquired or synthesized by cells is recognized by the vitamin D receptor (VDR), which also interacts with RXR to function as a transcriptional factor that binds several genes containing vitamin D response elements (VDRE) to regulate their expression [48]. The most know function of vitamin D is the induction of the expression of the transient potential vanilloid type 6 (TRPV6) required for the promotion of calcium absorption; however, it also promotes the expression of several genes associated with immunoregulatory functions [49].

- 3.) Structural trace elements: Zinc and magnesium are two metals that stabilize the structure of hundreds of biomolecules, mainly proteins, and therefore allow them to function.

Zinc is one of the most relevant metals in the organism; estimating that it interacts with near of 10% of the human proteome, mainly enzymes and transcriptional factors [50, 51]. Zinc is taken up by cells through the Zrt/Irt-like proteins (ZIP), intracellularly this mineral is found inside organelles and vesicles or bound to proteins named metallothioneins (MT); and its concentration is regulated by the ZIP-dependent uptake, as well by its release through the zinc transporters (ZnT) [52]. A relevant finding from nearly two decades ago is that zinc deficiency affects immune system development, causing thymic atrophy in rodents [53, 54] since the zinc-dependent hormone thymulin produced by thymic epithelial cells is necessary for proper T lymphocyte development [55, 56].

On the other hand, magnesium is well known for its participation in stabilizing DNA, its requirement for DNA polymerase reactions, and for being bound to ATP, facilitating the phosphate group transference; however, as occurs with zinc, it participates in several cellular processes due to its interaction with hundreds of proteins. Different transporters take up this metal in immune cells, such as the transient receptor potential cation channel subfamily M (TRPM)6 and 7, the solute carrier family 41 members 1 and 2 (SLC41A1/A2), and the magnesium transporter 1 (MAGT1) [57, 58]. Among its different functions, the involvement of magnesium in immune response was initially discovered because a defect in its transport due to a mutation of the MAGT1 gene in humans causes a combined immunodeficiency mainly affecting T lymphocytes response [59].

Functions in airway epithelial barrier

The respiratory tract is a tightly impermeable barrier covered by ALS, which plays a fundamental role in clearing pathogens and other foreign molecules. ALS is composed of several substances, including MUC and AMP.

In vitro, MUC homogenates have been reported to restrict infection of several viruses in epithelial cell cultures [60], particularly MUC1 interacts with the influenza virus and restricts the infection in lung epithelial cells *in vitro* and *in vivo* [61], also decreases the production of the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) in RSV-infected lung epithelial *in vitro* [62]. Although there is no evidence yet of the effect of MUC1on SARS-CoV-2 replication, severe COVID-19 patients show increased levels of this in bronchial mucus [63].

On the other hand, the β-defensins (BD) are AMP widely expressed in epithelia that, in addition to their antibacterial functions, can also interact with viruses to prevent their entry into the host cells. Mouse BD (MBD) 3, MBD4, and a fusion peptide that contains MBD1 and MBD3 have been reported that interact with the influenza virus and impair the experimental infection *in vitro* and *in vivo* [64-66]. Similarly, human BD (HBD) 2 has been reported to disrupt the envelope of RSV, reducing its infection *in vitro* [67]. A short peptide derived from MBD4 named P39 also has been shown to decrease *in vitro* infection with the influenza virus, middle east respiratory syndrome (MERS)-CoV, and SARS-CoV, although interaction with the viruses is still unexplored [68]. Another interesting function of BD is enhancing antibody production, as has been demonstrated for HBD2 and MBD2 in mice immunized with MERS-CoV spike (S) protein and influenza virus [69, 70].

BD has not been reported to have a direct effect on SARS-CoV-2; however, the human neutrophil peptides (HNPs) 1, 2, and 3, and the human defensin (HD) 5, all of them α-defensins (AD), have shown to limit the infection *in vitro* [71]. AD are found mainly in neutrophil granules [72]; therefore, their release involves neutrophil activation and degranulation, although this has been associated with poor outcomes in COVID-19 patients [73].

Cathelicidins are another type of AMP found in neutrophil granules involved in protection against respiratory viruses since they have been shown to limit RSV and influenza virus infection *in vitro* and *in vivo* by disrupting viral membranes [74-77]. Human, porcine, and ovine cathelicidins also have been reported to diminish rhinovirus infection *in vitro* [78]; however, an evasion mechanism of rhinovirus to avoid cathelicidins function is to modify their cationic to a neutral charge [79]. In the case of SARS-CoV-2, it has been reported that human cathelicidins interact with the viral S protein restricting the *in vitro* and *in vivo* infection [80].

Among the micronutrients that support the airway epithelial barrier integrity and the production of MUC and AMP with antiviral activity are vitamins A, D, E, C, and zinc (Fig. 4).

Vitamin A is relevant in embryogenesis, particularly in the respiratory tract; its deficiency causes malformations in the trachea, lung, and smooth muscle [41, 81]. In mature airways, this vitamin has been shown to participate in tissue remodeling upon injury, promoting the activation of the mitogen-activated protein kinase (MAPK) and modulating the extracellular matrix composition [82-84]; while, through RAR/RXR activation can promote the expression of MUC2, MUC5A, MUC5B, and cathelicidins in airway epithelial cells [85-87].

Vitamin D also has been demonstrated to induce the expression of cathelicidins, and some BD in airway epithelial cells and other cell types [87-92], particularly the LL-37 cathelicidin and the HBD2 genes are known to contain a VDRE that promotes their expression [91].

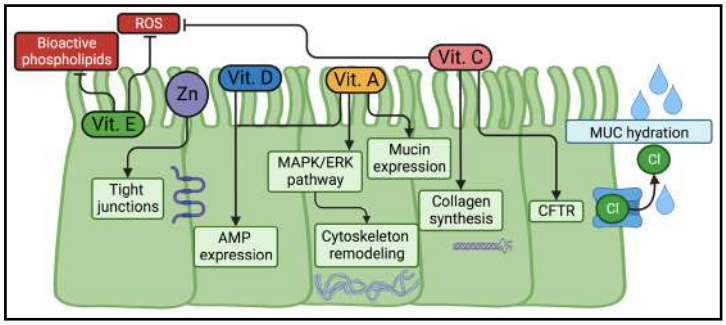

Fig. 4. Micronutrients functions in the airway epithelial barrier. Vitamin A (Vit. A) induces the expression of mucins (MUC) and antimicrobial peptides (AMP); it also promotes the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway upon injury to promote tissue remodeling. Vitamin D (Vit. D) influences the expression of AMP. Vitamin E (Vit. E) can be part of the plasma membrane regulating its fluidity, blocking bioactive phospholipids, and mitigating reactive oxygen species (ROS). Vitamin C (Vit. C) also functions as an antioxidant, participates during collagen synthesis for tissue remodeling, and promotes cystic fibrosis transmembrane conductance regulator (CFTR) activity, a channel that induces chloride secretion and hydrate airway liquid surface (ALS) and MUC. Zinc (Zn) is necessary to preserve tight junctions in the epithelial barrier. Figure created with BioRender.com.

The antioxidant function of vitamin E indirectly modulates the inflammatory response in airway epithelium [93] and, as a component of the plasma membrane, has been shown to contribute to its fluidity and that interact and neutralize dangerous lipids such as lysophosphatidylcholine and platelet-activating factor (PAF) [94], molecules released during respiratory viral infections that have been reported to promote inflammation and epithelial barrier leakage [95-97].

On the other hand, vitamin C, as vitamin A, has been demonstrated to be relevant for proper healing since, during airway injury, the prolyl hydroxylase (PHD)-dependent type VI collagen synthesis requires this vitamin as a cofactor [98, 99]. In the ALS, vitamin C has been discovered that promotes the activation of the cystic fibrosis transmembrane conductance regulator (CFTR), a channel that elicits chloride secretion for fluid hydration in nasal and tracheal epithelial cells [100]; therefore, since MUC are released as dehydrated polymers, vitamin C indirectly impacts on MUC fluidity [101].

Under stress conditions, it has been described that airway epithelial cells increase zinc uptake through the ZIP8 transporter, hypothesizing that it functions as a second messenger to maintain the barrier impermeability; since zinc depletion causes paracellular permeability due to reduced levels of the thigh junctions proteins zonula occludens-1 (ZO-1) and claudin-1 [102, 103].

Roles in the antiviral response mediated by interferons (IFN)-I

Viruses infect using different host cell receptors, as has been reported for CoV through ACE2 [104]; RSV through C-X3-C Motif Chemokine Receptor 1 (CX3CR1) [105]; influenza virus, parainfluenza virus, and enterovirus through sialic acid [106-108]; metapneumovirus through integrins [109]; rhinovirus through low-density lipoprotein receptor (LDLR) and very-LDLR (VLDLR) [110]; and adenovirus through desmoglein [111].

Once inside, viral nucleic acids can be recognized by different PRRs. For example, single-strand (ss) RNA could be identified by toll-like receptor (TLR) 7, TLR8, and nucleotide-binding oligomerization domain-containing protein 2 (NOD2); double-strand (ds)RNA could be recognized by retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated protein 5 (MDA5) and TLR3; moreover, other receptors such as the NOD-like receptor family pyrin domain-containing (NLRP) 1 and NLRP9b also have been reported to recognize dsRNA [112, 113]. On the other hand, viral DNA is identified through TLR9, cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING), DExH-Box Helicase (DHX) 9, and DHX36 [114, 115].

PRRs activation triggers several signal pathways that activate transcriptional factors such as the interferon regulatory factors (IRF) and the nuclear factor kappa B (NF-κB); these transcriptional factors induce the expression of IFN-I, IFN-III, and pro-inflammatory cytokines to induce an antiviral state in the neighboring cell and promoting the inflammatory response [116, 117].

IFN-I act in paracrine through IFN α/β receptors (IFNAR), whereas IFN-III act through the IFN-λ receptor (IFNLR). IFNAR and IFNLR ligation activate the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway to induce an antiviral state characterized by the expression of interferon-stimulated genes (ISG) [116]. Besides the antiviral state induction, IFN-I also participates in the development and modulation of NK cells [118-120], as well as in the promotion of dendritic cell maturation for a proper antigen presentation [121, 122].

IFN-I response could vary among viral challenges; for example, IFN-I pretreatment reduces straightly viral replication of SARS-CoV-2 compared to influenza and SARS-CoV *in vitro* [123]. However, some respiratory viruses can subvert IFN-I production through their non-structural protein 1, which has been reported for the influenza virus, RSV, and SARS CoV-2 [124-127]. Indeed, the impaired production of IFN-I has been associated with disease worsening in COVID-19 patients [128-130], probably by a delayed production, as demonstrated in a SARS-CoV mice model [131].

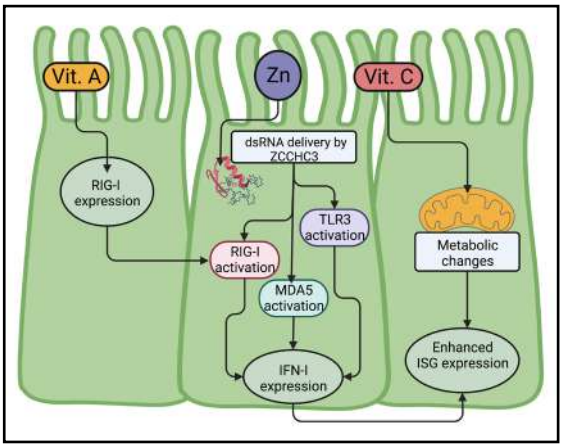

Fig. 5. Roles of micronutrients in the antiviral response mediated by interferons (IFN)-I. Vitamin A (Vit. A) promotes the expression of the retinoic acid-inducible gene I (RIG-I), a receptor that detects viral double-strand (ds)RNA. Vitamin C (Vit. C) enhances interferon-stimulated genes (ISG) expression by stimulating mitochondrial metabolic changes. Zinc (Zn) is necessary for the function of the zinc finger CCHC domain-containing protein 3 (ZCCHC3), a protein that interacts with viral dsRNA to facilitate its delivery to different receptors such as RIG-I, melanoma differentiation-associated protein 5 (MDA5), and toll-like receptor 3 (TLR3). Figure created with BioRender.com.

The micronutrients implicated in stimulating the IFN-I response include vitamins A, C, and zinc (Fig. 5).

Vitamin A has been reported to enhance RIG-I expression [44, 132], a kind of PRR that recognizes influenza virus, SARS-CoV2, metapneumovirus, parainfluenza virus, and RSV [126, 133-136].

On the other hand, vitamin C has been demonstrated to enhance the expression of several ISG, including MDA-5 and RIG-I, which are involved in the viral dsRNA recognition; and Mx1, a protein that interferes with the viral polymerase activity of the influenza virus [137-139]. However, the antiviral response influenced by this vitamin could be an indirect effect since it has been reported that it preserves mitochondrial functions [140, 141] and prevent the decrease of the mitochondrial antiviral signal-protein (MAVS) induced by influenza virus infection in mice [142]. MAVS is an outer mitochondrial membrane protein necessary to anchor MDA-5 and RIG-I during their activation for IFN-I production [143].

Zinc has been reported to enhance the antiviral action of IFN-I *in vitro* [144]. One reported mechanism is by the action of the zinc finger CCHC domain-containing protein 3 (ZCCHC3), a protein that facilitates viral dsRNA and dsDNA delivery to different PRRs such as RIG-I, MDA5, and cGAS [145, 146]; moreover, ZCCHC3 also has been shown to promote oligomerization of RIG-I, MDA5, and TLR3 for their activation [146, 147].

Vitamin D's role seems to be immunomodulatory since it downregulates ISG expression and IFN-I production in an NF-κB-dependent manner during RSV infection in tracheal epithelial cells without affecting viral replication [148].

Functions in NK cell differentiation and activation

Under a steady state, NK cells remain inactive due to inhibitory signals from their killer Ig-like receptors (KIR), such as NKG2A and Ly49, which recognize MHC-I molecules from self-cells in an antigen-independent manner. Although some respiratory viral infections have been reported to decrease MHC-I molecules to avoid the adaptive cellular response [149, 150], NK cells are ready to respond. These will be activated due to the loss of KIR inhibitory signals, by the recognition of molecules on infected cells by the killer activation receptors (KAR) such as NKG2D and NKp46, and through the ligation of CD16 to finally execute their cytotoxic effect on infected cells by releasing perforins and granzyme B and producing cytokines such as IFN-γ [151-153].

However, some respiratory viruses subvert NK cell response, such as has been described for metapneumovirus, which reduces KAR ligands on infected cells *in vitro* [154]; or SARS-CoV-2, which increases surface levels of the inhibitory receptor NKG2A on NK cells, resulting in less degranulation and IFN-γ production [155].

Although NK cells with an activation phenotype are necessary to eliminate infected cells, a subset of NK cells with a regulatory phenotype is also required to avoid harmful effects [156]. Indeed, enhanced NK cell numbers with activated phenotype in the lungs have been associated with severe lung injury during experimental models of influenza virus and RSV infections, probably by the exacerbated release of perforins, granzymes, and cytokines that potentiate the inflammatory response [157-159].

Several micronutrients are involved in modulating the development and function of NK cells. It has been described that vitamin D and zinc promote their differentiation; these same micronutrients, together with magnesium, favor their activation, while vitamins C, A, and zinc favor their regulation. (Fig. 6).

Vitamin A, through RAR, has been reported to decrease NK cell's cytotoxicity and IFN-γ production by diminishing granzyme B and the KAR NKp46 levels in an NF-κB-dependent manner [160]. However, long-term vitamin A deficiency in rats also has been reported to result in lower levels and function of NK cells [161, 162], thus could suggest that this vitamin is required for both NK cell regulation and activation.

Similarly, vitamin D deficiency has been associated with reduced numbers of NK cells during pneumonia-derive SARS-CoV2 infection in humans [163], probably compromising NK cell generation, since it has been demonstrated that vitamin D induces the expression of the vitamin D upregulated protein 1 (VDUP1), a protein that promotes the differentiation of NK cells [164]. On the other hand, mature NK cells treated with vitamin D have been shown to increase their KAR levels and enhance their cytotoxic activity [165]. Moreover, *in vivo,* vitamin D supplementation has been reported to enhance the numbers and cytotoxic function of NK cells in healthy mice but not obese mice [166]; this could suggest that in obesity, which is considered a chronic inflammatory disease, vitamin D, instead being used by NK cells, it could be used by adipose tissue to regulate its metabolism and to limit the inflammatory response [167], as will be discussed below.

Vitamin C has been reported to stimulate the proliferation of NK cells and to promote a regulatory phenotype [168] by increasing the expression of KIR through the activity enhancement of an αKGD named ten-eleven translocation (TET) demethylase, which acts on KIR promoters to elicit their transcription [169].

On the other hand, zinc has been reported to be necessary for two zinc finger transcriptional factors involved in NK differentiation, GATA binding protein 3 (GATA-3) and zinc finger E-Box binding homeobox 2 (Zeb2) [170-172].

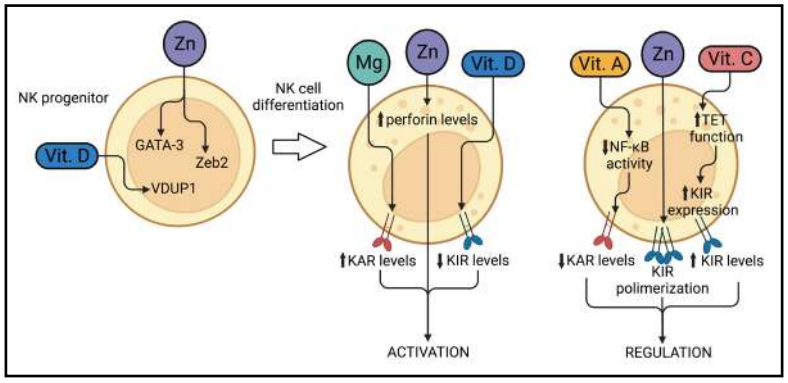

Fig. 6. Micronutrients functions during natural killer (NK) cell differentiation and activation. Vitamin D (Vit. D) promotes NK cell differentiation inducing vitamin D upregulated protein 1 (VDUP1) expression, while in mature NK cells promotes their activation by decreasing the expression of the killer Ig-like receptors (KIR). Zinc is required for the transcriptional factors GATA binding protein 3 (GATA-3) and zinc finger E-Box binding homeobox 2 (Zeb2), both involved in the NK cell differentiation; in mature NK cells, zinc has dual roles, promoting their activation by increasing perforin levels, or promoting their regulation by inducing KIR polymerization. Magnesium (Mg) promote NK cell activation by increasing killing activation receptor (KAR) levels. Vitamin C (Vit. C) and vitamin A (Vit. A) promote the regulation of NK cells by decreasing KAR levels and increasing KIR levels, respectively. Figure created with BioRender.com.

In differentiated NK cells, zinc supplementation has been demonstrated to increase perforin levels and enhance their cytotoxic effect triggered by IL-2 [151]; interestingly, zinc also has been reported to be necessary for the inhibitory signals of NK cells since it binds to the extracellular domain of KIR for their proper polymerization and inhibitory effect [173]; these findings could suggest that the effects of this metal could be different if it is found intracellularly, probably acting as a second messenger or bound to transcriptional factors; or if it is found in the extracellular environment bound to surface receptors.

Magnesium also seems to support the cytotoxic function of NK cells since it has been reported that in cells derived from magnesium-deficient patients, there is an impairment in their functionality, which can be reversed by *in vitro* supplementation with this trace element by increasing KAR levels and restoring the cytotoxic function [174].

Functions in the inflammatory response

Inflammation involves a series of vascular and cellular events in response to external or internal dangerous stimuli, which aims to eliminate or control them until the tissue homeostasis is recovered; hence, during a normal process, the onset phase is followed by the resolution phase. A wide variety of mediators participate during this process, including those already pre-formed and released immediately, those quickly generated by enzymatic reactions, and those transcriptionally induced by an upstream signal such as PRRs ligation; together, all of these mediators act on endothelial, tissue, and immune cells to drive their function [175, 176].

During the onset phase, vasodilation is one of the first events in which mast cells and platelets release histamine; this already pre-formed mediator increases blood flow and vascular permeability, as well as stimulates the release of molecules from endothelial cell Weibel-Palade bodies (WPB), contributing to the activation of neighboring cells [177-179].

Prostaglandins (PG), thromboxanes (TX), and leukotrienes (LT) are other types of mediators that, in addition to being involved in vasodilation and coagulation as histamine and WPB molecules, also participate in the generation of fever and leukocyte chemotaxis; these mediators are generated from arachidonic acid (AA) by the action of cyclooxygenase-2 (COX-2), in case of PG and TX; or 5-lipoxygenase (5-LOX), in case of LT [180].

Like the AA-derived mediators, the reactive oxygen species (ROS) are generated by enzymatic reactions of several enzymes, such as the NADPH oxidases (NOX). Although the most known function of ROS in the immune response is their involvement in the respiratory burst of the phagocytic process, ROS also perform other functions. Among these are the induction of vascular permeability by stimulating the enzymes phospholipase D (PLD) and phosphatase type 2A (PP2A) [181-183]; and the activation of several signal pathways; indeed, ROS signaling can activate the transcriptional factors NF-κB and hypoxia-inducible factor 1 (HIF-1) to drive the synthesis cytokines and cellular metabolic adaptations, respectively [184-190].

The most noticeable transcriptionally induced mediators in inflammation are cytokines and chemokines, such as interleukin (IL)-1β and IL-8. These are induced by different stimuli such as the mentioned ROS and PAMPs; these mediators can act in an autocrine, paracrine, and endocrine manner in different cells; for example, in APC could promote their migration, antigen processing capacity, expression of co-stimulatory molecules, and even the production of other cytokines [191-193].

On the other hand, once the dangerous stimuli are eliminated, the mediators of the onset phase are no longer produced or are counteracted by others, giving rise to the resolution phase. During this, the vascular tone is recovered, necrotic and apoptotic cells are eliminated, and the tissue is repaired [194].

Nitric oxide (NO) is an enzymatically produced mediator with anti-inflammatory properties; especially, NO produced by the endothelial nitric oxide synthase (eNOS) regulates the vascular tone and inhibits leukocyte migration [195]. Lipoxins, resolvins, protectins,

and maresins are lipid-derived mediators that also limit leukocyte migration; moreover, these also limit ROS production and pro-inflammatory cytokines production and promote phagocytosis of apoptotic cells and the production of anti-inflammatory cytokines [196, 197].

Modulating cytokines of the onset phase involve their negative feedback and the production of anti-inflammatory ones [198]. A20 is a ubiquitin-editing enzyme induced as a negative regulator of pro-inflammatory cytokines signal, this functions as an upstream negative regulator of NF-κB, thus limiting pro-inflammatory cytokines production [199]. On the other hand, anti-inflammatory cytokines, such as IL-10 and transforming growth factor-beta (TGF-β) also are produced to shape the response of epithelial cells, fibroblasts, macrophages, and other cells during tissue repair [194, 200, 201].

Some respiratory viruses subvert the inflammatory process leading to pathological consequences. For example, it has been demonstrated that SARS CoV-2 takes advantage of histamine recognition by its H2 receptors on endothelial cells to increase its entry to them [202]. Also, in patients with severe COVID-19, it has been reported that in blood leukocytes, there is ROS overproduction, as well as the expression of its related transcriptional factor HIF-1α [203, 204]; it has even shown *in vitro* that HIF-1α facilitates SARS CoV-2 infection and other respiratory viruses [204, 205].

As SARS-CoV-2, severe influenza infections also have been reported to develop a hyper-inflammatory state in which oxidative stress and the expression of TNF-α, IL-1β, and IFN-I and their related genes coexist simultaneously [206-211].

Several micronutrients participate in the modulation of the inflammatory response in different types of cells, mainly to avoid harmful effects due to its overactivation (Fig. 7).

Vitamin C has been recognized to modulate the inflammatory response directly by scavenging ROS or indirectly by inhibiting ROS-triggered signaling pathways. Its administration has been reported to diminish tissue damage and lower several pro-inflammatory mediators in lung injury induced by lipopolysaccharide (LPS) and influenza virus infection [212, 213]. *In vitro*, endothelial cells treated with 500μM of vitamin C have been shown to reverse LPS- and IFNγ-induced vascular dysfunction [183], probably due to its function as a stabilizer of the tetrahydrobiopterin (BH4), a cofactor of the eNOS required for its proper function [214, 215]. However, it is essential to note that higher doses of

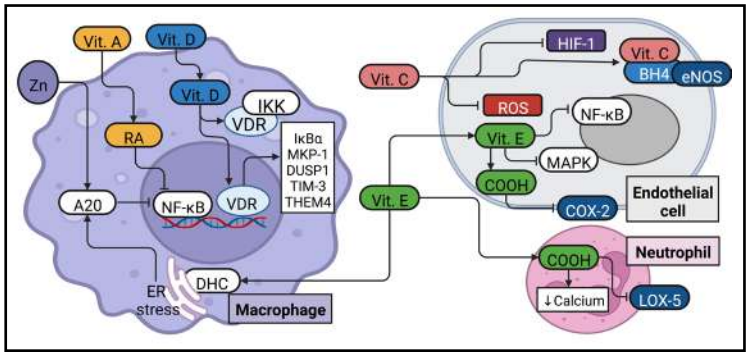

Fig. 7. Micronutrients modulate the inflammatory response. Vitamin A (Vit. A) inhibits the nuclear factor kappa B (NF-κB) in macrophages. Vitamin D (Vit. D) induces the expression of several negative regulators of NF-κB and mitogen-activated protein kinases (MAPK), such as the inhibitory kappa B alpha (IκBα), MAPK phosphatase-1 (MKP-1), dual-specificity phosphatase 1 (DUSP1), thioesterase superfamily member 4 (THEM4), and T-cell Immunoglobulin 3 (TIM-3); as well promotes the function of the inhibitor of the nuclear factor-kB kinase (IKK) in macrophages. Zinc (Zn) is necessary to function the anti-inflammatory protein A20 in macrophages. Vitamin E (Vit. E) increases A20 levels through the dihydroceramide (DHC)/endoplasmic reticulum (ER) stress axis in macrophages, inhibits 5-lipoxygenase (5-LOX) activity in neutrophils, and decreases cyclooxygenase-2 (COX-2), NF-κB and mitogen-activated protein kinase (MAPK) activation in endothelial cells. Vitamin C (Vit. C) scavenges reactive oxygen species (ROS), stabilizes tetrahydrobiopterin (BH4), a cofactor of the endothelial nitric oxide synthase (eNOS); and promotes proteasomal degradation of hypoxia-inducible factor 1 (HIF-1) in endothelial cells. Figure created with BioRender.com.

vitamin C (3-10 mM) have been reported to have the opposite effect on endothelial cells [216], taking into account that 28-100μM are the serum physiological levels [217]. In addition, vitamin C has been reported to negatively regulate the transcriptional factors NF-κB and hypoxia-inducible factor 1 (HIF-1) [218]. However, this could be the effect of its antioxidant functions, for HIF-1 regulation could also be involved in its proteolytic degradation by the HIF-prolyl hydroxylase (HPHD), a type of αKGD which requires this vitamin as a cofactor [219].

Vitamin A seems to be a dual modulator of inflammation. *In vitro* anti-inflammatory functions have been reported in LPS-stimulated macrophages, in which RA doses from 10 to 100 mM diminish NF-κB activity. Conversely, in macrophages stimulated with different pro-inflammatory stimuli, the addition of lower concentrations ranging from 10 nM to 1 mM has shown the opposite effect, enhancing NF-κB activity, increasing IL-1β production, and inducing a metabolic shift [220, 221]. On the other hand, the anti-inflammatory effects of this vitamin have been observed in a sepsis model in mice, decreasing NF-κB target genes expression [222-224]; also, during parainfluenza virus infection in guinea pigs, RA treatment has been reported to diminish leukocyte infiltration and promote the expression of muscarinic receptors in the lungs improving their function [225]. Although these findings could seem contradictory, a possible explanation is that RA could exert different functions depending on concentration and the presence of another stimulus in the cellular environment.

Vitamin D negatively regulates the inflammatory response through different mechanisms, mainly in monocytes and macrophages. This vitamin could exert its functions through genetic expression induced by the VDR or physical interaction with other proteins. VDR has been reported to upregulate the expression of the inhibitory kappa B alpha (IκBα), MAPK phosphatase-1 (MKP-1), dual-specificity phosphatase 1 (DUSP1), and thioesterase superfamily member 4 (THEM4) which are negative regulators of NF-κB and MAPK, thus limiting the pro-inflammatory response [92, 226-229]. VDR also has been shown to promote the expression of the T-cell Immunoglobulin 3 (TIM-3) in macrophages, a molecule involved in the acquisition of the M2 phenotype, which is required in the resolution of inflammation phase [230]; moreover, it has been described that VDR has other target genes with immunomodulatory functions in monocytes [49]. VDR also has been demonstrated to interact with the inhibitor of the nuclear factor-kB kinase (IKK), thus avoiding the NF-κB pro-inflammatory activity [231, 232]. Such is the relevance of immunomodulatory functions of this vitamin that it has been proposed as a treatment for airway inflammation in asthma [233], COPD [234], convalescent COVID-19 patients [235], and even as a preventive therapy for acute respiratory infections [236, 237].

Vitamin E also modulates the inflammatory response since it has been reported that during an LPS-induced acute airway inflammation model in mice, the α-tocopherol administration diminishes neutrophil infiltration to the lungs and reduces tissue damage [238]. Similarly, *in vitro*, it has been shown that lung epithelial cells under inflammatory conditions treated with α-tocopherol reduce IL-8 and adhesion molecule levels due to decreased NF-κB and MAPK activity [93]. Although these effects could be by the directly scavenging of ROS induced during inflammation, vitamin E could also act at different levels, as has been reported for γ-tocopherol, δ-tocopherol, and some carboxychromanol metabolites that inhibit the COX-2-dependent prostaglandin E2 (PGE2) production in lung epithelial cells; or the carboxychromanol metabolites and γ-tocopherol that inhibit LOX-5-dependent leukotriene B4 (LTB4) production in neutrophils and eosinophils [37, 38]. Tocotrienols γ and δ have also been reported to regulate inflammatory response promoting the expression of A20 in macrophages through dihydroceramide (DHC) induction in the endoplasmic reticulum [239-241].

As mentioned, A20 is a negative regulator of NF-κB that requires zinc for its function [242]; indeed, in activated macrophages, zinc supplementation has been demonstrated to induce the expression of A20 while decreasing the activity of NF-κB resulting in lower expression of TNF-α and IL-1β [243]. Another mechanism that has been reported in which zinc regulates the inflammatory response is through the inhibition of phosphodiesterase

function (PDE), leading to increased intracellular levels of cyclic guanosine monophosphate (cGMP) and the consequent protein kinase A (PKA) activation [244, 245], a kinase involved in negative regulation of NF-κB [246]. Additionally, zinc has been demonstrated to be required for superoxide dismutase (SOD) function [50], a zinc-dependent antioxidant enzyme relevant to lung damage limitation [247].

The role of magnesium during the inflammatory response was described more than twenty years ago in an LPS-induced sepsis model in rats with a deficient magnesium diet, showing a hyperinflammatory state and increased mortality [248]. *In vitro*, it has been reported that magnesium decreases the expression of IL-6 and TNF-α in LPS-stimulated monocytes; moreover, in acute lung injury in mice, magnesium treatment increases antioxidant response and reduces inflammatory cytokines through NF-kB inhibition [249]. Although the exact mechanism is not fully understood yet, one possible mechanism may be the antagonism between magnesium and calcium, as calcium depletion has been shown to replicate the anti-inflammatory effects of magnesium *in vitro* and *in vivo* [250, 251].

Roles in the adaptive cellular response

Specific cellular response against viruses involves processing endogenous antigens and the consequent loading of their derived peptides onto MHC-I molecules. Although all nucleated cells can carry out this process, for the initiation of the adaptive cellular response, this must be carried out by APC that present the antigenic peptides to a TCR of a specific Tc CD8+ lymphocyte. Upon TCR activation, co-stimulatory signals and cytokines are required to complete the activation of the Tc CD8+ lymphocytes to induce their clonal proliferation. Almost all Tc CD8+ lymphocytes have effector functions; however, a pool of memory cells is generated for future encounters with the antigen [252].

Effector Tc CD8+ lymphocytes, through their TCR, detect MHC-I molecules with the antigenic peptide of the infected cells. Once recognized, Tc CD8+ lymphocytes kill infected cells by expressing death ligands or releasing perforins and granzyme B. Tc CD8+ lymphocytes also could produce cytokines such as IFN-γ and TNF-α, which are relevant for the autocrine stimulation and reinforcement of immunological memory [252-255]. To avoid an excessive response that could drive pathologic consequences, a late phase of contraction is necessary for which the majority of Tc CD8+ effector lymphocytes die, but a small portion becomes memory cells; this process requires the restriction of IL-2 production and the production of immunomodulatory cytokines derived from T regulatory (Treg) lymphocytes [255-258].

Some viruses such as metapneumovirus, influenza, and SARS-CoV-2 have been reported to alter Tc CD8+ lymphocytes response, resembling an exhaustion phenotype that impairs effector and memory functions, predisposing to delayed viral clearance and reinfections [155, 259-261].

In addition, influenza virus and SARS-CoV-2 have been reported to downregulate MHC-I expression in infected epithelial cells [149, 150]; therefore, even if Tc CD8+ lymphocytes were generated, they could not effectively recognize infected cells.

Many micronutrients support the adaptive cellular immune response since antigen presentation to Tc CD8+ lymphocyte effector functions (Fig. 8).

Vitamin A, as mentioned above, acts through the RAR, which is highly expressed in mature Tc CD8+ lymphocytes and plays a critical role in their function. It has been reported that the genetic ablation of the RARγ isoform in hematopoietic cells results in low IFNγ production, impaired cytotoxic function, and decreased proliferation of Tc CD8+ lymphocytes without compromising their development; however, RARγ deletion also affects cytokine production of macrophages [262]. Moreover, the specific deletion of RARα isoform, but not RARγ, in Tc CD8+ lymphocytes also has been shown to decrease the percentage of IL-2-producer and lower levels of the integrin α4β7 and chemokine receptor CCR9 [263], molecules required for T cells mucosal migration. This evidence suggests that RARα acts directly on Tc CD8+ lymphocyte function, whereas RARγ could act indirectly via other cells, such as APC. In addition, since it has been reported that there is a RARE in the second intron of the MHC-I

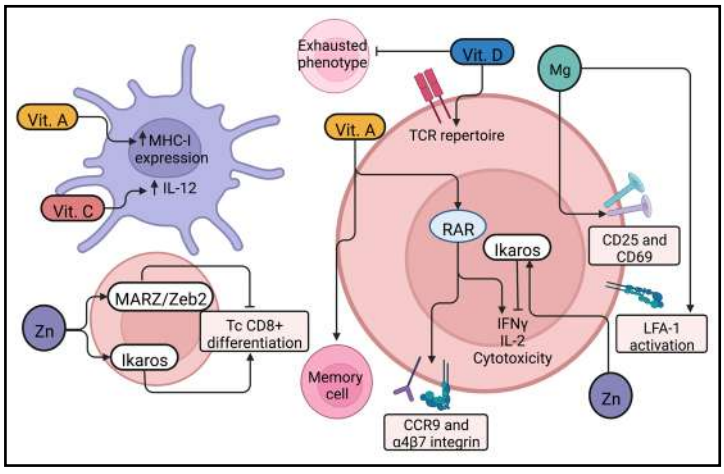

Fig. 8. Micronutrients functions in adaptive cellular response. Vitamin A (Vit. A) acts on dendritic cells (DC), increasing major histocompatibility complex (MHC)-I molecules; on T cytotoxic (Tc) CD8+ lymphocytes induce the expression of migration-associated molecules such as the C-C motif chemokine receptor 9 (CCR9) and the integrin α4β7: also promotes cytotoxicity, IL-2, and interferon-gamma (IFN) γ production; in addition, stimulates memory cell. Vitamin C (Vit. C) stimulates IL-12 production on DC. Vitamin D (Vit. D) participates in the T cell receptor (TCR) repertoire generation and could revert the exhausted phenotype on Tc CD8+ lymphocytes. Magnesium (Mg) stimulates the expression of the activator molecules CD25 and CD69; it is also necessary to activate leukocyte function-associated antigen 1 (LFA-1). Zinc (Zn) regulates the transcriptional factors for Tc CD8+ lymphocyte differentiation since it is required for the negative regulators Myc-associated zinc finger-related factor (MARZ) and zinc finger E-Box binding homeobox 2 (Zeb2), and the positive regulator Ikaros. In mature Tc CD8+ lymphocytes, Ikaros also inhibits cell activation. Figure created with BioRender.com.

gene in different species [264], vitamin A could increase MHC-I expression. Vitamin A also has been demonstrated to serve as an excellent adjuvant for vaccines, enhancing memory Tc CD8+ lymphocyte population with a more significant proliferative potential, as has been reported in a viral vector vaccination to lymphocytic choriomeningitis virus (LCV) glycoprotein in mice [265].

Vitamin D signaling also is necessary for proper T CD8+ lymphocytes function since it has been observed that genetic ablation of VDR in mice reduces their TCR repertoire, decreases granzyme B levels, and retains them in lymph nodes, affecting both their effector and memory functions [266]. *In vitro*, the treatment with vitamin D has been reported to revert the exhausted phenotype of blood-derived Tc CD8+ lymphocytes from lung cancer patients, and even its oral administration shows similar results [267]; suggesting that the beneficial effects of this vitamin in respiratory viral infections that promote an exhausted phenotype could be due in part to this same mechanism.

Since IL-12 expression, a cytokine required for T lymphocytes proliferation, involves the action of the Jumonji-C domain-containing histone demethylases (JHDM), a type of αKGD [268, 269], vitamin C could support the cellular response through the activity of this enzyme; indeed, this vitamin has been reported to enhance IL-12 production in APC [270, 271], that in turn results in an increased number of IFNγ-producers Tc CD8+ lymphocytes [271]. Directly to Tc CD8+ lymphocytes, vitamin C has been shown to improve their cytotoxic function [272] and increase a memory phenotype, probably due to metabolic antioxidant adaptation [273].

Magnesium also has been demonstrated to participate in Tc CD8+ lymphocyte function since, in a mice model of influenza virus infection, a magnesium-deficient diet results in increased viral replication associated with decreased numbers of Tc CD8+ and Th CD4+ lymphocytes [274]; moreover, activated Tc CD8+ lymphocytes cultured in depleted magnesium medium have decreased proliferation capacity and reduced levels of the activation markers CD25 and CD69 both molecules required for T lymphocytes activation and proliferation [275]. In addition, extracellular magnesium has been reported to support the activation of the co-stimulatory molecule leukocyte function-associated antigen 1 (LFA-1) in memory T CD8+ lymphocytes, a molecule necessary for the switch to a cytotoxic effector phenotype [276].

Finally, zinc participates in adaptive cellular response through the function of different zinc-finger transcriptional factors required for Tc CD8+ lymphocytes development and activation. It has been demonstrated that Myc-associated zinc finger-related factor (MARZ) and Zeb2 repress their differentiation, whereas Ikaros promotes it [277-279]; also, in mature Tc CD8+ lymphocytes, Ikaros has been reported to restrain Tc CD8+ lymphocytes activation [280].

Functions in the adaptive humoral response

This part of the response involves the processing and presentation of exogenous antigens, such as inactive viral particles or viral components contained in apoptotic bodies, onto MHC-II molecules to Th CD4+ lymphocytes. Also, co-stimulatory signals and cytokines are required for the complete activation of these cells. Once activated, Th CD4+ lymphocytes proliferate to become memory and effector cells that cooperate with B lymphocytes. Effector Th CD4+ lymphocytes could acquire different profiles driven by particular transcriptional factors; for example, T-bet drives to Th1, GATA-3 drives to Th2, the retinoid orphan receptor gamma t (RORγt) drives to Th17, and forkhead box P3 (FoxP3) drives to Treg; each profile is characterized besides their associated transcriptional factor, by the production of specific cytokines. Memory cells could remain in the SLO or become tissue memory cells. Lastly, for the B lymphocytes activation, BCR antigen recognition facilitated by the SLO's follicular DC (FDC) and cooperation with the T CD4+ follicular helper (Tfh) lymphocytes occur to promote their activation and differentiation to antibodies-producer plasma cells (PC) as well as the generation of memory cells [281, 282].

During viral infections, the Th1 profile, characterized by IL-2, IFNγ, and TNF-α production [283], has protective effects, as has been reported during SARS-CoV-2 and influenza infections [284, 285], in part due to its role in supporting the Tc CD8+ lymphocyte response [286]. Treg lymphocytes are also fundamental to controlling the overactivation of the Th1 and Tc CD8+ lymphocytes and aiding tissue repair once the infection is resolved [287, 288]. On the other hand, PC's most relevant effector function to avoid viral infections at mucosal and systemic levels is the production of IgA and IgG antibody isotypes, as reported during SARS-CoV-2 and influenza infections [289-291]. These antibodies can neutralize viral particles or trigger the elimination of infected cells by their opsonization or antibody-dependent cell-mediated cytotoxicity (ADCC) [292].

A broad range of respiratory viruses alters lymphocytes response in different ways, such as causing lymphopenia that has been reported in SARS CoV-2, influenza virus, parainfluenza virus, and RSV infections [261, 293-296] or inducing a T lymphocyte exhaustion phenotype caused by SARS CoV-2 and influenza virus infections [261, 297]. Moreover, respiratory viruses also could subvert Th1/Th2 balance in different manners, leading to pathological consequences; for example, PBMC derived from RSV patients stimulated *in vitro* have been shown to impair IFNγ and IL-2 production, both cytokines of Th1 profile; but able to produce IL-4, a cytokine of the Th2 profile [298, 299]. In contrast, rhinovirus infection, which is highly associated with the development of chronic obstructive pulmonary disease (COPD), has been shown to induce the production of Th1 cytokines but no Th2 cytokines *in vitro* [300]; and during metapneumovirus experimental infection, it has been demonstrated the convergence of Th1, Th2, and Th17 profiles [301]. In the case of severe SARS-CoV-2 infection in humans, there has been reported a marked increase in both Th1 and Th2 cytokines, contrary to pandemic H1N1 influenza infection, with a more discrete cytokine profile [302].

Regarding PC response, IgG antibody isotype is the most reported after immunizations and is related to protection and memory responses at the systemic level; however, in the case of respiratory viruses, mucosal IgA has been demonstrated to be more effective than IgG in serum, probably due to it resembles a natural infection [303-305]. Some viruses, such as RSV and SARS CoV-2, have been reported to impair IgA production [303, 306] or even to stimulate the IgE isotype switch, which is related to asthmatic complications, as has been demonstrated for RSV [307].

Several micronutrients regulate adaptive humoral response with a broad range of actions (Fig. 9).

Vitamin A functions on adaptive humoral response depending on the differentiation state of the cells. For example, the treatment of immature DC with vitamin A has been shown to induce apoptosis; conversely, in a mature phenotype under pro-inflammatory conditions stimulates the antigen-presentation capacity through the increased expression of MHC-II and co-stimulatory molecules although, under immunomodulatory conditions, enhances a tolerogenic phenotype [308-311]. In Th CD4+ lymphocytes, it has been shown that RARα is required for Th1 induction [312]; similarly to DC, vitamin A potentiates the Treg profile in immunomodulatory conditions by increasing FoxP3 expression, restricting, in both cases, the Th17 profile [313]. However, vitamin A has also been shown to support the Th2 profile [314, 315]. For the proper development of FDC, it has been reported that epithelial-derived RA is needed [316]; moreover, in mature FDC, RAR activation is necessary for the germinal center formation (GC) and in B lymphocytes to promote class switching to IgA isotype in the mucosa [317, 318]. However, the effects of vitamin A-derived RA on B lymphocytes seem to depend on their maturation stage since in common lymphoid progenitor cells (CLP) from mice embryos, RA has been shown to inhibit B cell differentiation, whereas in CLP from adult mice promote B cell differentiation [319]. *In vivo*, a RA-rich diet in mice has been demonstrated to promote B cell differentiation [320]; restricting the proliferation rate in stimulated mature B lymphocytes while increasing the activation-induced cytidine deaminase (AID) expression, a key enzyme for isotype class switch [321]. RA acid has also been reported to stimulate memory B cells proliferation and their differentiation to antibody-secreting PC [322].

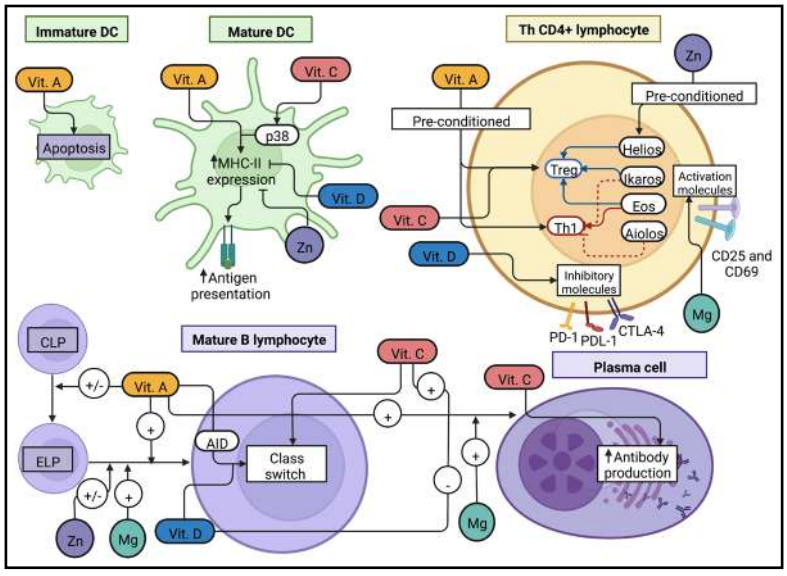

Fig. 9. Micronutrients functions in the adaptive humoral response. Vitamin A (Vit. A) induces apoptosis in immature dendritic cells (DC); whereas in mature DC increases major histocompatibility complex (MHC) II expression and, therefore, increases antigen presentation capacity; on T helper (Th) CD4+ lymphocytes, depending on the environment, could drive to Th1, or T regulatory (Treg) profile; on common lymphoid progenitor (CLP) and early lymphoid progenitor (ELP) stimulates B lymphocyte and plasma cell differentiation, and also promotes antibody class switching. Vitamin D (Vit. D) inhibits MHC-II expression on DC; increases the expression of the inhibitory molecules programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) on Th CD4+ lymphocytes; stimulates antibody class switching on B lymphocytes, although it inhibits plasma cell differentiation. Vitamin C (Vit. C) stimulates MHC-II expression on DC; promotes Treg profile depending on environmental conditions; stimulates antibody class switching on B lymphocytes and their differentiation to plasma cells. Zinc (Zn) inhibits MHC-II expression on DC; promotes the Treg profile through the zinc-dependent transcriptional factors Ikaros, helios, and eos (solid lines); whereas it promotes Th1 by eos, and restricts it by Ikaros and aiolos (dotted lines); zinc could also modulate positively and negatively B lymphocyte differentiation. Magnesium (Mg) is necessary for the surface expression of the activating molecules CD25 and CD69 on Th CD4+ lymphocytes; it also stimulates B lymphocyte and plasma cell differentiation. Figure created with BioRender.com.

T-independent B lymphocyte response also could be protective against respiratory infections, such as those caused by influenza [323]; in this context, RAR also participates in T-independent B response promoting the localization of B lymphocytes in the marginal zone of secondary lymphoid organs (SLO), and the consequent production of IgM [324].

Vitamin D has an immunomodulatory effect on humoral response as described above for inflammatory response. In mature DC from mice, it has been reported that vitamin D treatment generates a tolerogenic profile characterized by reduced production of IL-12 and chemokines, decreased MHC-II and co-stimulatory molecules, and increased IL-10 production, which drives a reduced Th CD4+ lymphocyte proliferation [325, 326]. Directly on Th CD4+ lymphocytes, vitamin D also has been demonstrated to exert regulatory effects inducing the expression of the inhibitory surface markers programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) [327]; molecules that drive contraction phase and Treg induction [327-329]. However, vitamin D has been shown to have the opposite effect under immunosuppressor conditions, increasing Th CD4+ lymphocyte numbers and IL-2 production [330]. Immunomodulatory effects of vitamin D also have been reported on B lymphocytes, reducing their proliferation and PC differentiation [331], regulating their APC function, and inducing the expression of IL-10 [332], suggesting that vitamin D modulates B activation, which could result in decreased antibody production. However, as occur with vitamin A, this effect seems to depend on the environmental conditions since vitamin D, in conjunction with vitamin A through VDR/RARα axis, sustains TGFβ expression to induce isotype change to IgA [333].

Vitamin C has been reported to activate p38 MAPK on DC, leading to increased co-stimulatory and MHC-II surface levels [270, 334]; moreover, LPS-stimulated DC increases IL-12 production, driving a Th1 profile. However, as with other micronutrients, the effect of vitamin C depends on the environment since this vitamin has been reported to drive Th17 or Treg profiles by activating JHDM and TET demethylases, respectively [335-337]. On activated B lymphocytes, vitamin C has been shown to promote the differentiation to antibody-producing PC *in vitro* and *in vivo* through TET demethylases [338, 339]. In addition, vitamin C seems to promote isotype switching to IgG2 *in vitro*, although contradictory results have been found *in vivo* [340]; whatever the case, vitamin C appears to reinforce antibody production, as has been reported in patients infected with the SARS-CoV-2, in which oral supplementation for 42 days with vitamin C and zinc increase the levels of neutralizing antibodies [341].

Due to the broad range of proteins that require zinc for their function, this micronutrient act positively and negatively at different levels of the humoral response. In DC, it has been reported that zinc reduces MHC-II molecules' surface levels and induces a tolerogenic phenotype, probably through the action of the anti-inflammatory zinc-dependent A20 protein [342, 343]. Interestingly, it has been reported that intracellular zinc is highly enriched in Treg lymphocytes compared to Th1 lymphocytes, and its depletion reverts the Treg profile leading to increased IFNγ production [344]. Other zinc-dependent proteins, mainly transcriptional factors, dictate each Th profile in addition to their respective master transcription factors. For example, the Th1 profile is promoted by Eos and inhibited by Ikaros and Aiolos, whereas the Treg profile is promoted by Ikaros, Helios, and Eos [345]. In B lymphocytes, zinc is required during development, activation, and PC differentiation since it has been reported that during B cell development in mice, zinc uptake by the transporter ZIP10 is necessary during the transition of pro-B to pre-B lymphocyte stage, whereas ZIP7 is necessary during the transition of pre-B to immature-B lymphocyte stage [346, 347]. Also, the early B cell factor (EBF), the ATM Chk2-interacting zinc finger protein (ASCIZ), the zinc finger X-chromosomal protein (Zfx), and the Myc interacting zinc finger protein 1 (Miz-1) are zinc-dependent transcriptional factors that have been reported to promote the process [348-351]. In contrast, the zinc-finger protein 521 (ZNF521) has been reported to regulate B cell development negatively [352]. During B lymphocyte activation, it has been reported that zinc uptake by ZnT7, ZIP7, ZIP9, and ZIP10 transporters is required [346, 353-355], leading to

increased intracellular zinc levels that activate the B cell lymphoma 6 (Bcl-6) and leukemia/lymphoma-related factor (LRF), molecules required for B lymphocytes proliferation [356-358]. Finally, during PC differentiation, the zinc finger and BTB domain (ZBTB)20 and the B-lymphocyte-induced maturation protein 1 (Blimp-1) have been reported to activate them, whereas the ZTBT18 negatively regulated their differentiation [359-361].

Magnesium, similar that zinc, interacts with a broad range of proteins; however, there is little information about its participation in the humoral response. Magnesium has been reported to be necessary for proper T lymphocyte activation since its depletion reduces Tc CD8+ and Th CD4+ lymphocytes numbers in response to antigenic stimulation *in vivo;* also, *in vitro* affects the TCR-induced signal pathway, reducing CD69 and CD25 activation molecules and decreasing intracellular calcium flux in stimulated T lymphocytes, signals highly relevant for lymphocytes proliferation [275, 362]. In B lymphocytes, the uptake of this micronutrient through TRPM7 has been demonstrated to be required for their proper development since its deletion causes cell arrest in the pre-B lymphocyte stage [363]. In contrast, the deficiency of MAGT1 has been shown to cause an increase in mature B lymphocytes and reduced PC numbers [364], suggesting that magnesium uptake by MAGT regulates the transition of activated B lymphocytes to PC differentiation.

Concluding remarks

The statement that micronutrients help improve the immune system has been proven by a significant number of scientific evidence; however, the mechanisms of action do not consistently boost effector functions of the immune system; instead, micronutrients function by modulating each step of the immune response at the molecular level. For example, vitamin A seems to boost immune response and even has been proposed as a vaccine adjuvant [365]; conversely, vitamin D, in general, appears to have immunomodulatory effects in almost all phases of the immune response, being an excellent candidate for treating hyperinflammatory conditions, such as severe SARS-CoV-2 [366]. In addition, knowing the patient clinical condition plays a central role in considering if the supplementation with some micronutrients alone or in combination is helpful in its therapeutical management, taking into account that some of these micronutrients could possess antagonism or synergistic effects.

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Author Contributions

A.P.J.U., conceptualization, literature searching, manuscript preparation; A.O.H., literature searching; Y.A.H, literature searching; J.P.C., conceptualization, manuscript revision, funding.

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Disclosure Statement

The authors declare that no conflict of interests exists.

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