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Micronutrients and many important factors that affect the physiological functions of toll-like receptors

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Abstract

Background: Toll-like receptors (TLRs) are type I integral transmembrane receptors involved in recognition and conveying of pathogens to the immune system. These receptors are located either on cell surfaces or within endosomes. They are activated by specific ligand leading to the release of cytokines via signal transduction pathway. The excess production of these cytokines leads to disrupt the immune homeostasis. There are several factors regulating TLR expression and consequently affecting their functions. Among these are inflammation, cytokines, some cellular process, air pollution, depression, stress, some drugs, genetic polymorphism, nutrition, and micronutrients. Some micronutrients (vitamins and trace elements) may be considered as important TLR regulators, as they have immunomodulatory functions. Vitamins D, B12, and A; zinc; copper; and iron have important role on innate immune responses.

Aim of work: This review gives a brief idea on TLR family and attempts to cover the factors affecting the physiological functions of them.

Conclusion: Of many factors affecting TLRs functions are micronutrients. There is a shortage of researches concerning the effect of micronutrients deficiency on the function of TLRs, all of which focused on vitamin D but other vitamins have not got the same importance that they deserve. This orients our efforts to work at this point in the future.

Keywords: Toll-like receptors, Pollution, Stress, Nutrition, Micronutrients

Background

Toll-like receptors (TLRs) is a family of pattern recognition receptors (PRRs) and the main components of innate immunity (Kawai and Akira 2010). They can protect the host against a vast array of microbial infections (Zhang and Liang 2016). TLR activation stimulates signaling cascades by the host as a defense mechanism against invaders and to repair the damaged tissue (Wang et al. 2015). The binding of ligand to TLR resulted in the recruitment of several adaptor proteins and led to activation of many transcriptional factors which drive the expression of cytokine genes (Kawasaki and Kawai 2014). The released cytokines promote inflammatory responses, affect the physiological processes of the host body, and represent as the master contributors of many diseases (Bresnahan and Tanumihardjo 2014). There are many factors regulating TLR function; some of these factors include inflammation (Schroeder 2009), cytokine (Miettinen et al. 2001), cellular processes such as cell migration and apoptosis (Herrera et al. 2011), air pollution (Zhang and Gallo 2016), neuropsychiatric disorders (García Bueno et al. 2016), drugs (Bode et al. 2014a), genetic polymorphism (Tsujimoto et al. 2008), physical exercise (Cavalcante et al. 2018), aging (Shaw et al. 2011a), and nutritional status (Vidya et al. 2017). Good nutrition is required for the immune system to function properly (Mora et al. 2010). Micronutrients are needed in small amounts, but are essential for good health (Fuhrman 2014). Their deficiencies could impair innate immunity and increase susceptibility to infections (Chandra 2002). Vitamin D, B12, and A were evaluated for their importance as they are modulators of the

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immune system (Todorova et al. 2017) as well as some minerals such as zinc, copper, and iron that are essential for efficient immune function (Djoko et al. 2015). This review gives an overview of the TLR family and discusses the different factors affecting the physiological functions of TLRs.

Overview of Toll-like receptors

TLRs belong to type I transmembrane glycoproteins with 20-27 leucine-rich repeat motifs for ligand recognition at N-terminus, a single transmembrane helix and a conserved cytoplasmic Toll/Interleukin-1 (IL-1) receptor (TIR) domain at C-terminus for intracellular signaling transduction (Bryant et al. 2015). They can functionally recognize external pathogen-associated molecular patterns (PAMPs) and internal damage-associated molecular patterns (DAMPs) (Yu and Feng 2018). While external ligands include lipopeptides, lipopolysccharides (LPS), and bacterial flagellin (Ayres and Schneider 2012), internal ligands include hyaluronan, fibrinogen, heat shock proteins, and elements of damaged/fragmented DNA and RNA (Fig. 1) (Murad 2014). Currently, a total of 13 TLRs have been identified; TLRs 1–10 are expressed in humans despite the function of TLR10 being still unclear, in addition to TLR11 and 12 that are expressed in mouse (Moresco et al. 2011). TLRs are expressed in a variety of immune cells including dendritic cells, monocytes, macrophages, and B lymphocytes and non-immune cells such as epithelial cells, endothelial cells, and fibroblasts (Delneste et al. 2007). TLR1, 2, 4, 5, 6, and 10 are expressed largely on the cell surface while TLR3, 7, 8, and 9 are primarily expressed in the endosomes (Fig. 2) (Gay et al. 2014). The main characteristics that distinguish different TLRs are ligand specificity, signal transduction pathways, and subcellular localization (Singh et al. 2014). The molecular pathways of TLR signal transduction require two main adaptor proteins: myeloid differentiation factor 88 (MyD88) that is utilized by all TLRs except TLR3 and TIR-domain-containing adaptor-inducing interferon-β (TRIF) that is utilized by TLR3 and 4 (Kawasaki and Kawai 2014), resulting in the generation of pro-inflammatory and type 1 interferon through the activation of nuclear factor kappa-B (NF-κB) and interferon regulatory factors (IRFs) (Zhang and Liang 2016).

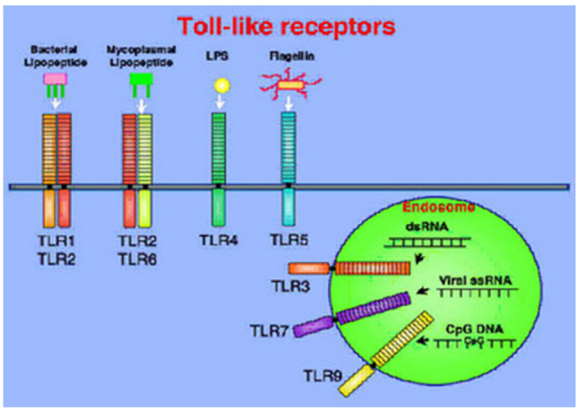

Fig. 1 Exogenous and endogenous ligand of TLRs

Factors affecting the physiological functions of TLRs

Expression of TLRs by the host immune system is a crucial step in detection of infection (Hug et al. 2018). However, various factors control the extent of their expression according to the prevalence and regulation of these factors (Vidya et al. 2017; Singh et al. 2014), of these factors are inflammation, cytokines, some cellular processes, air pollution, depression, stress, glucocorticoids and other drugs, genetic polymorphism, physical exercise, aging, and nutritional status.

Inflammation

Inflammation is the biological response to harmful stimuli that can be a double-edged sword, although it plays a protective role in eliminating pathogenic factors, but uncontrolled inflammation is associated with several chronic diseases (Dong et al. 2016). It is an integral part of immune response (Schroeder 2009). Whatever the stimulus is, TLRs play a main role in the initiation and propagation of inflammation through the production of the pro-inflammatory cytokines (Zhang and Gallo 2016).

Cytokines

Cytokines have been shown to modulate the expression and activation of TLRs (Noppert et al. 2007). While TNF-α induces pro-inflammatory activity in TLR signaling, mainly in TLR2, and is involved in many illness (Gambhir et al. 2012; Schnetzke et al. 2015), IFN-α and IFN-β have immunomodulatory anti-inflammatory activities that are involved in some disease treatment (Rathinam et al. 2012). Viral infection of human macrophages induces TLR1, 2, 3, and 7 mRNA expression in type 1 interferon-dependent process (Miettinen et al. 2001).

Cellular processes

Some cellular processes have been found drastically to alter the gene expression of the cell thus affecting TLRs expression (Vidya et al. 2017). These processes include epithelial-mesenchymal transition (EMT) process, where the epithelial cells loss their cell polarity and cell-cell adhesion and the damaged cells alter their physical and chemical properties during tissue repair and wound healing (Polyak and Weinberg 2009); migration process, where the cells that do not undergo EMT migrate to the injury site (Lauffenburger et al. 1996); apoptosis that is

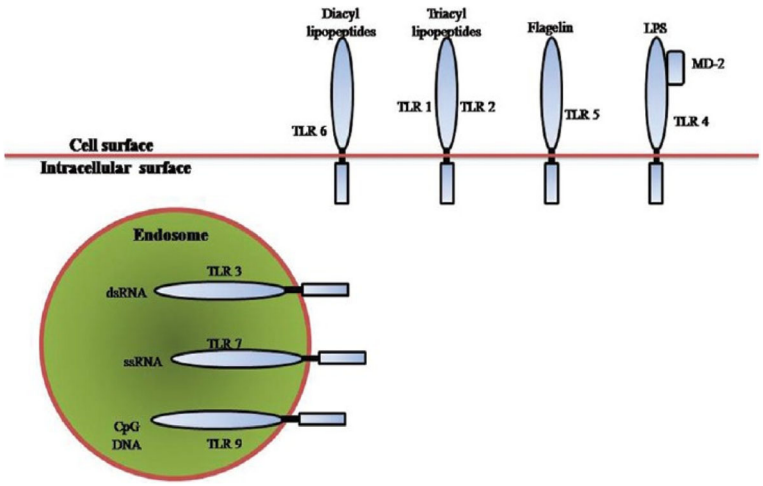

Fig. 2 Members and location of TLRs

induced by cellular or environmental stimuli where every apoptotic pathway involves the transcription of various genes (Brachat et al. 2000); and cell cycle where it regulates the gene associated with the shutdown of cell division (Herrera et al. 2011).

Air pollution

Exposure to air pollutants is found to modify innate TLR signalling (Bauer and Diaz-SD 2012). Air pollutants include particulate matter (PM)-associated biological components (bacteria, fungal spores, viruses, pollen and endotoxin), cigarette smoke (CS), and ozone (Fig. 3), which can work to stimulate a pro-inflammatory response in the respiratory air way mediated by TLR activation through either direct interaction with the receptor (Plummer et al. 2012) or via production of DAMPs (Lafferty et al. 2010). In respiratory tract infection, TLR2 and TLR4 signaling is upregulated in neutrophils of the air way (Bauer and Diaz-SD 2012) and alveolar macrophage (Cottey et al. 2010) with altered cytokine profile (TNF-α, IL-6) and type 1 interferon (IFN-α,β).

Depression

Several studies revealed the effect of neuropsychiatric diseases in the expression/activity of TLRs (García Bueno et al. 2016). TLR3 and 4 expression was significantly increased in the brain of depressed subjects, and

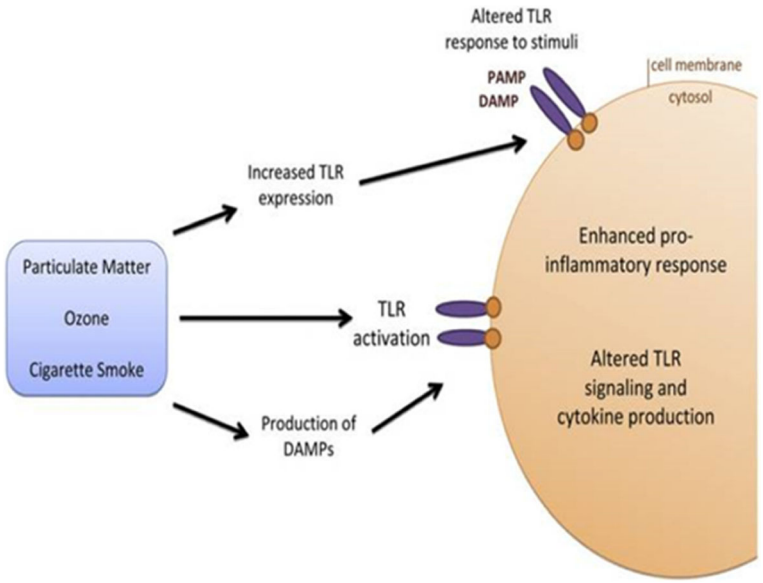

Fig. 3 Effect of air pollutants on TLRs signalling

their overexpression caused the abnormalities in cytokine levels in the brain and peripheral samples of suicidal victims (Pandey et al. 2014). Furthermore, TLR4 was highly expressed in PBMC of patients with major depressive disorder (MDD), and this heightened expression was reduced following treatment and paralleled amelioration in depressive symptoms (Kéri et al. 2014). The responsiveness toward depressive status indicates that TLR4 activity could directly be involved in the pathophysiology of MDD (Liu et al. 2014). It was also revealed that the expression of TLR3, 4, 5, and 7 was high in animal model with MDD (Hung et al. 2014). TLR2 and 4 activation was associated with IL-1, IL-6, and TNF-α production in irritable bowel syndrome patients with depression (Jizhong et al. 2016). Enhanced peripheral TLR4 expression/activity has been described in subjects with neuropsychiatric diseases and in autistic children (García Bueno et al. 2016).

Glucocorticoids (GC) and other drugs

Natural and synthetic GC have immunosuppressive and anti-inflammatory activity for the majority of autoimmune and inflammatory diseases, despite dangerous side effects associated with GC therapy (Flammer and Rogatsky 2011). TLR expression is influenced by GC (Imasato et al. 2002). The activation of NF-κB is also inhibited by GC (Lancaster et al. 2005). TLR signaling is modulated by GC in liver cell line resulting in downregulation of TLR1 and 9 expression, suppression of pro-inflammatory cytokines, and upregulation of anti-inflammatory cytokines (Broering et al. 2011). Other drugs include antibiotics found to regulate the immune response in different degrees by modulating TLR1, 2, 4, and 6, and cytokine expression (IL-1β and IL-6) such as in sepsis inflammatory condition (Bode et al. 2014b). Antidepressants normalize the increased TLR3, 5, 7, 8, and 9 profile in MDD patients (Hung et al. 2016). Semapimod, an anti-inflammatory drug, is found to inhibit TLR4 and 9 signaling in an experimental model (Wang et al. 2016). Estradiol and progesterone is found to modulate TLR1, 2, 3, 4, 5, and 6 gene expression in human fallopian tube cell line (Zandieh et al. 2016).

Stress

TLR4 mRNA in the rat brain has been shown to upregulate in response to different protocols of stress exposure such as repeated social defeat, restraint stress, and chronic mild stress. NF-kB activation and cellular oxidative/nitrosative damage are reduced when TLR4 pathway was disturbed (Gárate et al. 2013; Gárate et al. 2014). TLR4 is involved in immune changes as a result of endogenous stress signals (Liu et al. 2014). Activation of peripheral and brain TLR4 triggers sickness behavior, and its expression is a risk factor of depression (Hines et al. 2013). Stress exposure elicits a NF-kB pro-inflammatory response in brain driven by a prior activation of TLR4 (Trotta et al. 2014).

Genetic polymorphisms

Genetic polymorphisms in TLR4 gene affect sensitivity to allergens (Zhang et al. 2011). The reduced asthma risk may be correlated with TLR4 gene as indicated by the association between TLR4 polymorphisms and the development of asthma (Tizaoui et al. 2015). The polymorphisms of both TLR4 and TNF-α may increase the risk of developing tuberculosis after exposure to mycobacterium (Jafari et al. 2018). In addition to TLR4, variants of TLR2 gene affect lung function in children with asthma (Klaassen et al. 2013). Polymorphisms of TLR2 and 4 affect the risk of infectious complications in patients with acute myeloid leukemia subjected to chemotherapy (Schnetzke et al. 2015).

Physical exercise

The effects of physical exercise on TLR expression and on inflammatory cytokines production have been demonstrated in few studies, till now it is still an area of controversy. Furthermore, the effect of acute exercise on TLR expression has received even less attention (Cavalcante et al. 2018). Early studies state that prolonged strenuous exercise causes suppression of both TLR expression and function. Individuals who participated in intensive exercise training have an increased susceptibility to upper respiratory tract infections (Peters et al. 1993). It is possible that the exercise-induced suppression in TLR expression and function was involved in TLR signaling (Lancaster et al. 2005). Both acute aerobic and chronic resistance exercise have been reported to decrease monocyte cell surface expression of TLR4 (Stewart et al. 2005), while (McFarlin et al. 2004) found no effect of an acute resistance exercise on monocyte cell surface TLR4 expression. The difference in these findings might be related to the age of the subject and severity/duration of the exercise stimulus (Gleeson et al. 2006). Exercise may act as an anti-inflammatory modulator through different processes including cytokines and TLR signaling (Mikkelsen et al. 2017). While animal studies globally showed a marked downregulation of TLR2 and 4 after endurance exercise accompanied with a reduction in the activation of NF-κB signaling and cytokine production, evidences in human were not strong enough to conclude the same effect (Rada et al. 2018).

Aging and immunosenescence

Aging is a complex phenomenon that leads to many changes in the physiological systems of the body. Immunosenescence is one of the most important changes that occur in all elements of the immune system (Montgomery 2016). It is associated with a low-grade inflammation,

inflammaging (Fulop et al. 2017). Aging is also associated with the emergence of many diseases via inflammaging, for example, innate immune response in elderly people is impaired and the susceptibility to infection increased as in pulmonary infection (Boe et al. n.d.). The function of human TLRs is impaired with aging. Age-associated alteration in innate cells appeared to have reduced TLR signaling through NF-κB resulting in decreased production of inflammatory cytokine and altered chemotaxis responses as well as decreased phagocytosis and antigen presentation capacity (Shaw et al. 2011b).

Nutrition

Nutrition, (Fig. 4) (https://foodandhealth.com/make-a-nutrition-poster/) is one of the various factors that govern TLR expression (Vidya et al. 2017). Some diets were found to be important sources of increased TLRs inflammatory stimulants (So and Ouchi 2010).

Processed food containing microbial stimulants

Food containing inflammatory stimuli was the main interest of scientist *Clett Erridge*. He assessed the presence of TLR2 and 4 microbial stimulants bacterial lipopeptides and LPS, respectively, in a variety of common foodstuffs. He detected the highest levels of TLR-stimulants in processed foods, minimally processed vegetables (MPV), and dairy products while fresh fruits and vegetables contained minimal or undetectable amounts (Erridge 2010). The amount of TLR2 and 4 stimulants in food extracts is found to promote insulin resistance and atherosclerosis in an animal model and correlated with their capacity to induce TNF-α (Erridge 2011). In a more recent study, he demonstrated that the pro-inflammatory stimulants of TLR2 and 4 in some processed foods were associated with the risk of cardiometabolic diseases (Erridge et al. 2016). In addition, bacterial polysaccharides identified in eatable plants such as apple or ginseng were found to interact also with TLR4 (Zhang et al. 2016).

High-fat diet

TLR2 and TLR4 have been involved in inflammatory responses to high-fat diet (HFD)-induced obesity in rats (Wan et al. 2014; Lee et al. 2015). HFD resulted in decreased TLR2 and 4 expression on CD14 monocytes and impaired their function which was detected by the increased secretion of IL-1β, IL-6, and TNF-α from PBMCs in human (Wan et al. 2014). HFD induced TLR4-dependent macrophage cell activation with significant increase in NF-κB and IL-6 (Lee et al. 2015). The expression of TLR2 and 4 were upregulated, and the translocation of NFκB into the nucleus was activated in high cholesterol/HFD fed mice lung. In vitro, oxidized low-density lipoprotein (oxLDL) could directly upregulate the expression of TLR2 and 4 in lung epithelial cell lines (Fang et al. 2017).

Non-microbial stimulants

Plant polyphenols from cranberries, tea, and grapes are non-microbial activators that inhibit LPS-induced NF-kB activation in TLR4 signaling (Delehanty et al. 2007). W-3 polyunsaturated fatty acids (PUFA) were found to suppress the excessive inflammatory response by decreasing the expression of TLR2 and 4 and some related inflammatory factors in PBMCs of patients with severe multiple trauma (Yi et al. 2011). Saturated fatty acids (SFAs) are also non-microbial activators of the TLR-signalling pathways (Lee et al. 2015; Erridge and Samani 2009). Lauric acid of coconut oil activates the TLR4 and regulates the expression of several pro-inflammatory genes (Wong et al. 2009; Calder 2013; Rocha et al. 2016). A similar effect was also described for the palmitic and stearic acids of palm oil and Shea butter, respectively, whose regulation of pro-inflammatory genes occurs primarily via the TLR4/NF-κB signalling pathway (Choi et al. 2012; Eguchi et al. 2013). Non-bacterial polysaccharides have also been discovered in fungi and algae, including glucans isolated from oat, barley, and wheat which were found to stimulate TLR4 to prevent diseases (Ina et al. 2013; Zhang et al. 2014). As glucans, B-fructans were also found to activate TLR2/NF-κB in human immune cells (Ende 2013; Vogt et al. 2013). In a cell culture, β-fructans protected the integrity of intestinal epithelial monolayers (Vogt et al. 2014). Pectins, such as lemon pectin, activate TLR2 and TLR4 and increase intestinal epithelial function in cellular cultures via activation of MyD88/NF-κB pathway (Vogt et al. 2016).

Fig. 4 Nutrition; an important factor affecting TLRs

Selected micronutrients

Some micronutrients (vitamins and trace elements) can influence several components of innate immunity in addition to their various physiological roles (Chandra 2002), "they may be considered as important TLRs regulators," as they have immunomodulatory functions (Erickson et al. 2000). Of micronutrients; vitamins D, B12, and A; zinc; copper;and iron (Mora et al. 2010; Vázquez et al. 2014; Kogan et al. 2017) have important role on innate immune responses (Fig. 5) (https://www.thaqafnafsak.com/2015/10/htmI/).

Vitamins

Vitamin D Vitamin D is found to influence both innate and adaptive immunity (Wei and Christakos 2015). The discovery of vitamin D receptors (VDR) (Kamen and Tangpricha 2010) and its activating enzyme 1-α-hydroxylase (Prietl et al. 2013) attracted researchers' attention to focus on its importance. VDR are expressed in many cells of immune system including macrophage, dendritic cells, T cells, and B cell (Korf et al. 2014). Vitamin D received its importance as it is well involved in promoting innate immune response, stimulating cell proliferation and differentiation (Myszka and Klinger 2014) and downregulating dendritic cell responses (Chen et al. 2007; Jeffery et al. 2009). The immunomodulation of vitamin D includes attenuation and stimulation of Th1 and Th2 cell proliferation (Battault et al. 2013). Vitamin D was reported to suppress the Th1 cells by inhibition of pro-inflammatory (IL-1, TNF-α, IFN-γ) secretion (Pettengill et al. 2014). Regarding Th2, vitamin D enhances the synthesis, secretion, and release of anti-inflammatory cytokines (IL-4 and IL-10) (Bivona et al. 2017). Deficiency in vitamin D causes pro-inflammatory stress (Barker et al. 2013), which increased risk of infections, chronic inflammation, and autoimmune diseases (Slusher et al. 2015; Vanherwegen et al. 2017).

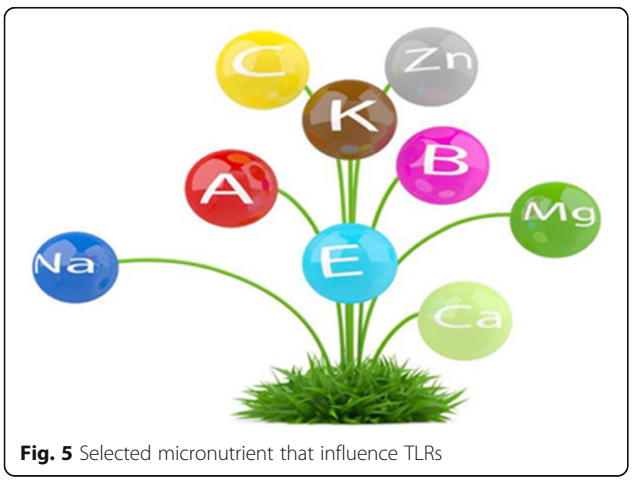

Fig. 5 Selected micronutrient that influence TLRs

- The source of vitamin D

The source of vitamin D can be either synthesized in the human skin after exposure to ultraviolet sunlight (Bendik et al. 2014) or obtained from very few foods such as fatty fish, cod liver oils, beef liver, and eggs (Smith et al. 2017).

- Regulatory role of vitamin D on TLRs

The link between TLRs and vitamin D-mediated innate immunity has been reported (Fig. 6) (Arababadi et al. 2018). In an early study, the accurate signal system by which TLR activation induces expression of VDR and 1-α-hydroxylase remains obscure (Liu et al. 2006). Recently, it was revealed that vitamin D effects on innate immunity were predominantly linked to Toll-like receptors (Sadeghi et al. 2016). The innate immune response includes an obvious inflammatory component, and vitamin D opposed these events by promoting over response to PAMPs through downregulation of TLRs on monocytes. CD14, a co-receptor of TLR4 that recognizes LPS, is vigorously stimulated by vitamin D (Wang 2004). The upregulation of VDR by LPS may further enhance vitamin D (Tang et al. 2012). It was proved that vitamin D influence on TLR4 in response to ligand leads to antigen presenting cell activation (Gambhir et al. 2012), and it was observed that vitamin D enhances innate antiviral immune response by upregulating IFN-β expression in human hepatocytes with hepatitis C virus (HCV) (Gal-Tanamy et al. 2011). The activation of vitamin D decreased the inflammatory status in innate immune response (Calton et al. 2015). Vitamin D has been found to regulate IL-10 secretion from Tregs where TLR9 was highly expressed. In vitro study has shown that vitamin D was found to downregulate INF-γ gene expression through the adjustment of gene activity (Urry et al. 2009), leading to the decrease of pro-inflammatory INF-γ release (Ragab et al. 2016). Regarding bacteria fighting, activation of TLRs triggers antimicrobial activity against intercellular bacteria, by upregulating VDR expression and the 1-α-hydroxylase genes, leading to the induction of antimicrobial peptide cathelicidin that is responsible for killing bacteria, while deficiency of vitamin D negatively impacts that mechanism (Liu et al. 2006), besides it induces autophagy and phagocytosis in human monocytes/macrophages (Yuk et al. 2011). Vitamin D can inhibit the NF-κB signaling pathway after TLR2 and TLR4 stimulation in patients with tuberculosis and HIV co-infection (Coussens et al. 2014). In autoimmune diseases, monocyte exposure to vitamin D causes downregulation of TLR2, 4, and 9 expression and reduces IL-6 secretion (Sadeghi et al. 2016). The expressions of TLR2 and 4 on monocytes of active Behcet's disease and type 1 diabetes

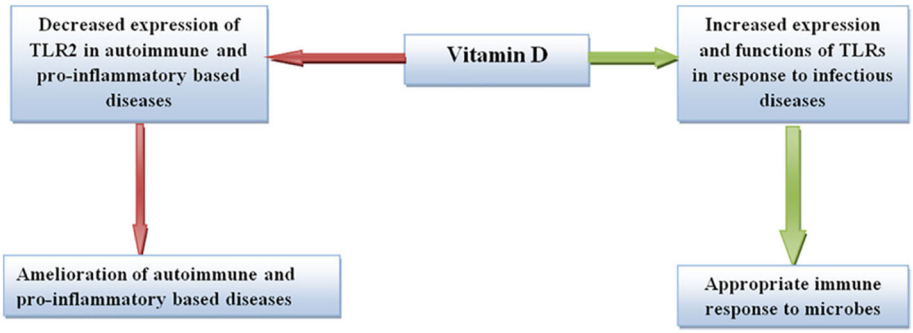

Fig. 6 The relation between vitamin D and TLRs

patients were negatively associated with their vitamin D levels, and TNF-α synthesis was also decreased upon TLR stimulation in vitamin D-treated monocytes (Do et al. 2008; Devaraj et al. 2011).

A marked increase in IL-6, TNF-α, and IFN-α cytokine profile was shown in vitamin D-deficient participants after TLR2 stimulation, and this response was reversed after supplementation with vitamin D (Ojaimi et al. 2013). Adding of vitamin D to the cell culture of PBMNs isolated from healthy adults after stimulation with the bacterial ligands showed a significant reduction in inflammatory cytokines TNF-α, IFN-γ, and IL-1β as well as the chemokine IL-8 production while the anti-inflammatory response was promoted through the upregulation of IL-10 (Hoe et al. 2016). Vitamin D was found to downregulate mRNA overexpression of TLR2 and 4 and pro-inflammatory cytokines; TNF-α in cultured human keratinocytes lead to the activation of these cells for further innate immune responses to pathogens (Schauber et al. 2007). It was revealed that vitamin D deficiency and TLR activation were the contributing factors in the pathogenesis of cardiovascular diseases (Adamczak 2007).

Vitamin B12 Vitamin B12 is an essential micronutrient that improves overall function of the immune system (Vázquez et al. 2014). It has been known as anti-inflammatory immunomodulator (Todorova et al. 2017; Hosseinzadeh et al. 2012). It prevents excessive expression and synthesis of inflammatory cytokines in human (Badawi et al. 2013). Deficiency in B12 resulted in reduced white blood cells (Ghatpande et al. 2016) and increased susceptibility to infection and diseases (Maggini et al. 2007). B12 deficiency increased the level of TNF-α in anemic adults (Killen and Brenninger 2013) and in children (Ghatpande et al. 2016).

- Dietary sources of vitamin B12

Vitamin B12 cannot be obtained from plants or sunlight (Boran et al. 2016), but it should be ingested from animal proteins such as meat, poultry, fish, eggs, milk, and most other dairy products (Kwak et al. 2010); therefore, vegans are at risk for B12 deficiency (Pawlak et al. 2013).

Vitamin A Since early time, vitamin A has been known as anti-infective vitamin as it is crucial for immune system to function properly (Langan et al. 2014). It helps to maintain the structural and functional integrity of the skin (Green and Mellanby 1928) and mucosal cells of eye and respiratory, gastrointestinal, and genitourinary tracts (Mora et al. 2008). It is also important to the normal function of several types of innate immune system, including NK cells, macrophages, and neutrophils (Sun et al. 2007). In severe inflammation, the body cells increased their abilities to convert retinol form into retinoic acid (RA), the active form (Combs 2008). The inability to make this conversion is considered as a risk factor for increased susceptibility to infection (Spinas et al. 2015). During immune responses, enzymes metabolizing vitamin A are induced in dendritic cells (DCs) and in cells of intestinal mucosa to induce RA production. As a result, the induced RA regulates gene expression, differentiation, and function of immune cells including neutrophils, macrophages, and DCs (Harrison 2005; Hammerschmidt et al. 2011). Vitamin A deficiency (VAD) impaired the components and the inflammatory responses of innate immunity (Kim 2011; Czarnewski et al. 2018). It reduced mucosal epithelial regeneration and killing activity and number of NK cells, as well as the function of neutrophils and macrophages (McDowell et al. 1984). In addition, VAD results in altered cytokine signaling which would affect inflammatory responses of innate immunity (Blomhoff et al. 1992). The risks of VAD can be reversed by supplementation (Semba et al. 2004).

- Dietary sources of vitamin A

Retinoid forms of vitamin A are provided by animal source of foods, including milk, cheese, yogurt, eggs, livers, shrimp, salmon, sardines, tuna, and chicken, while carotenoid forms are provided by most colored fruits as apricot, papaya, and mango (Semba 2012) and vegetables as sweet potato, tomatoes, spinach, pumpkin, carrots, broccoli, peppers, Kale, and pea (Imdad et al. 2017; Fennema 2008). Fish oil, cod liver oil, and butter contain also high concentration of vitamin A (Tang et al. 2055). Red palm oil (RPO) has been investigated for preventing VAD where low level of PRO intake (≤ 8 g RPO) could increase serum retinol concentrations (Solomons 2006). Sweet potato is a rich source of β-carotene, which the body converts into vitamin A and can treat VAD (Roos et al. 2010).

- Regulatory role of vitamin A on TLRs

Many clinical trials revealed that vitamin A supplementation downregulate the secretion of pro-inflammatory cytokines (TNF-α, IL-6) by macrophages in response to particular pathogen infections (Blomhoff et al. 1992; Dong et al. 2017). Although VAD resulted in altered cytokine signaling which would affect TLRs response, the exact mechanism by which vitamin A can regulate TLRs is still unknown, and this may be attributed to the fact that vitamin A was tightly to be linked in maintaining the structural and functional integrity of mucosal cells, and for the normal functioning of immune cells including macrophages, NK cells, and neutrophils (McDowell et al. 1984; Low et al. 2017).

Trace elements

Zinc, copper, and iron are essential trace elements for optimal innate immune function, and their nutritional deficiency leads to increased susceptibility to bacterial infection (Djoko et al. 2015).

Zinc Zinc is an essential micronutrient that is important for maintaining normal physiological functions (Kogan et al. 2017). Zinc has received the most attention for its ability to support immune function (Long et al. 2004). It is needed for basic cell activities such as cell growth, differentiation, and survival (Bhaskaram 2011). Appropriate levels of zinc are required for the proper functioning of the immune system while excessive zinc intake has shown negative effects on it (Wessels et al. 2017). In innate immunity, zinc keeps the epithelial membrane of natural barrier structure and function (Hojyo and Fukada 2016). Acute zinc deficiency causes a decrease in innate immunity (Gruber and Rink 2013; Rink and Gabriel 2000), while chronic deficiency increases inflammation (Maares and Haase 2016; Barnett et al. 2016).

Zinc deficiency received the most important impact on children's resistance to infectious diseases including the risk, the recurrence, and the severity of infection leading to diarrhea (Bonaventura et al. 2015). Deficiency in zinc impaired the complement system; reduced cytotoxicity of natural killer cells, phagocytic activity of neutrophils, chemotactic responses of both macrophages and monocytes (Gammoh and Rink 2017); and reduced the ability of immune cell to generate oxidants that kill invading pathogens (Krebs 2013; Ibs and Rink 2003). These effects were readily reversible by zinc supplementation (Krebs 2013; Prasad et al. 2011). The main sources of zinc are red meat, poultry, and sea food (Prasad 2013). Nuts, legumes, and wholegrain cereals (Buracco et al. 2018) and dairy products are rich in zinc (Solomons 2001).

- Regulatory role of zinc on TLRs

There is growing evidence that zinc acts as a signaling molecule, involved in a variety of signaling cascades such as TLR signaling of innate immunity (Bhaskaram 2011). Zinc can modulate inflammation through TLR signaling at different levels and pathways (Maret and Sandstead 2006). The stimulation of TLR4 by LPS changed the expression of zinc transporters in DCs and thereby decreasing intracellular free zinc (Mocchegiani et al. 2013). Zinc is known to inhibit NF-κB activation which in turn decreased the production of pro-inflammatory cytokines, TNF-α, IL-1β, and IL-6 (Brieger et al. 2013; Kitamura et al. 2006). It may contribute to the numbers and function of monocyte, macrophage, and NK-mediated host defense through promoting and regulating TLR responses (Haase and Rink 2009; Liu et al. 2013). In monocytes, it has been observed that TLR4 activation initiates zinc-mediated signaling in a MyD88- and TRIF-independent manner (Liu et al. 2013).

Copper Copper is required for different metabolic processes (Stafford et al. 2013), but can be toxic when present in excess (Djoko et al. 2015). It is central to maintain immune system (Haase and Rink 2014). Like zinc, copper is a co-factor for Cu-Zn-superoxide dismutase (SOD) enzyme that is required to maintain immune function (Petris et al. 2003), by catalyzing the production of H_2O_2 from superoxide in neutrophils and monocytes (Badawi et al. 2013). In addition, copper has been found to modulate macrophage response (Veldhuis et al. 2009). The regulatory effect of copper on macrophages antimicrobial pathways was demonstrated by in vitro studies (Steiger et al. 2010). The elemental analysis of macrophage phagosomes showed that the macrophage-activating cytokines such as TNF-α and IFN-γ promoted the accumulation of

copper within the phagosomes of *Mycobacterium avium*-infected macrophages (Halfdanarson et al. 2008).

Copper deficiency is associated with impaired development of immune cells such as phagocytic cells (Babu and Failla 1990). Early studies recorded that mild copper deficiency in humans and animals resulted in (Wagner et al. 2005; White et al. 2009; Xin et al. 1991). Copper deficiency also resulted in a reduction in the ability of leukocytes to kill ingested microbes that may increase the susceptibility to infection (Percival 1995). The numbers of myeloid precursors in the bone marrow were decreased in copper-deficient patients, as well as vacuolization of these cells (Veldhuis et al. 2009). The best dietary sources of copper include seafood, livers, legumes, whole grain, nuts (including peanuts, hazelnut, and pecans), grains such as wheat and rye, sesame seeds, and fruits including lemon, oranges and raisins (Percival 1998). Cereals, potatoes, peas, red meat, mushrooms, vegetables (like kale, parsley, and turnip), and fruits such as coconuts, papaya and apples were found to contain high quantities of copper (Lazarchick 2012).

- Regulatory role of copper on TLRs

The direct contribution of copper in macrophage antimicrobial responses was found through regulating innate TLR responses (Haase and Rink 2009). Recently, it was found that Cu/Zn-Mt supplementation decreased the mRNA levels of TLR4 and its downstream signals in MyD88 signaling pathways upon *Escherichia coli* LPS-induced intestinal injury in weaned piglets, and these finding lead the author to suggest that dietary Cu/Zn-Mt attenuated this injury by alleviating intestinal inflammation, influencing TLR4-MyD88 signaling pathway (Mason 2016).

Iron Iron is crucial for main cellular functions. It is essential for proper functioning of the immune system (Jiao et al. 2017). It is required to build effective immune responses against invading pathogens such as the differentiation and proliferation of T lymphocytes and production of reactive oxygen species (ROS) to kill pathogens (Beard et al. 2007). Deficiency in iron increases infection susceptibility and causes the reduction in number and action of neutrophils (Doherty 2007), but excessive iron is highly toxic as it increases the severity of some pathogens (Katona and Katona-Apte 2008). Iron is essential for both host and pathogen, and complex systems of acquisition and utilization have evolved in a competition or a battle in between, indicating that iron is a key regulator of host-pathogen interactions, the concept of "nutritional immunity" (de Pontual 2017). Iron sequestration is a vintage host defense against invading pathogens in animal (Johnson and Wessling-Resnick 2012; Weinberg and Weinberg 1995) and in human innate immunity to limit their pathogenicity, where serum iron decrease while iron-storage ferritin increase, keeping iron away from pathogens however available it is to the host (Ong et al. 2006; Cassat and Skaar 2013). Well-adapted microbes have in turn developed techniques to abstract iron from host storage proteins or to interfere with host iron sequestration (Zackular et al. 2017; Ganz and Nemeth 2015). Food rich in iron include spinach, fresh parsley, lettuce, broccoli, cabbage, and spices such as thyme, cumin, turmeric, or cinnamon. Beef, lamb, chicken, turkey, and seafood as oysters and octopus are rich in iron. Soybeans, lentils, and beans are considered also to be food high in iron (Verbon et al. n.d.)

- Regulatory role of iron on TLRs

Iron was recognized as an extracellular signalling molecule that affects innate immune response via TLR-mediated mechanism (http://wiki-fitness.com/iron-rich-foods/). Macrophages are essential for cellular iron recycling via TLR2 and 4/MyD88-dependent pathway (Figueiredo et al. 2007). TLR signaling mediates hypoferremia-induced activation of innate response by marked iron reduction coupled with iron sequestration within macrophages (Balounová et al. 2014). A strong correlation between enhanced bacterial colonization of the upper respiratory tract of MyD88-deficient mice and the inability to lower serum iron was early described (Layoun et al. 2012). Increased TNF-α and IFN-β is associated with the impaired TLR4 signaling in mice-deficient iron upon LPS stimulation (Albiger et al. 2005). TLR4 plays a role in patients with hereditary hemochromatosis (Wang et al. 2009). TLR2 and 4 up-regulated the hepcidin (a key regulator for iron absorbed from diet and iron recycling by macrophages) expression in macrophages via MyD88 and TRIF signaling pathway (Balounová et al. 2014). The regulation of iron accumulation in macrophages by hepcidin may affect the levels of pro-inflammatory cytokine production (Krayenbuehl et al. 2010). Mice lacking MyD88 accumulate iron in their livers in response to dietary iron loading as they are unable to control hepcidin levels (Layoun and Santos 2012; Layoun et al. 2018). Iron potentiated the inflammatory response to LPS by damaging mitochondrial homeostasis and increasing the mitochondrial ROS levels upon incubation with macrophage or injection to mice (Hoeft et al. 2017).

Conclusion

There are several factors affecting the physiological functions of TLRs. Among these are inflammation, cytokines, air pollution, stress, depression, some drugs, genetic polymorphism, nutrition, and micronutrients. Vitamins

and trace elements may be considered as important TLR regulators; however, the area concerning the effect of their deficiencies on the function of TLRs is still with less progress. Unlike vitamin D, other vitamins have not yet received the attention that they deserve regarding their effect on the physiological function of TLRs despite their modulatory role to maintain the immune system, and this area remains a point of research in the future.

Recommendation

- Our main concern should be focused on maintaining TLRs functioning and keeping the integrity of innate immune system, and this could be achieved by avoiding all negative factors including stress, depression, and pollution.
- Eating healthy food, doing regular exercise, and supplementation with essential micronutrients are recommended to support innate proper immune response.
- Submitting projects on a wide scale for all governorates to study the effect of micronutrient deficiency on innate immunity, especially in childhood.
- Producing an awareness program to orient people's attention to the importance of vitamins and minerals and their impacts on immune system and if it is possible to get the media involved.
- Nutrition education is a concept that has been taught in many countries as in UK. In schools, there have nutrition classes to teach the importance of healthy food, food pyramid, vitamins, minerals, and physical activity and why processed food, high calories, and malnutrition should be avoided (Lean 2015). The hopeful success is to apply a program such that in Egypt.

Abbreviations

CD14: Cluster of differentiation 14; CS: Cigarette smoke; DAMPs: Damage-associated molecular patterns; DCs: Dendritic cells; EMT: Epithelial-mesenchymal transition; GC: Glucocorticoids; HCV: Hepatitis C virus; HFD: High-fat diet; HIV: Human immunodeficiency virus; IFN-α: Interferon alpha or other symbols; IL-1: Interleukin 1 or other numbers; IRFs: Interferon regulatory factors; LPS: Lipopolysccharides; MDD: Major depressive disorder; MyD88: Myeloid differentiation factor 88; NF-κB: Nuclear factor kappa-B; NK: Natural killer cells; oxLDL: Oxidized low-density lipoprotein; PAMPs: Pathogen-associated molecular patterns; PBMCs: Peripheral blood mononuclear cells; PM: Particulate matter; PRRs: Pattern recognition receptors; PUFA: Polyunsaturated fatty acids; RA: Retinoic acid; ROS: Reactive oxygen species; RPO: Red palm oil; SFAs: Saturated fatty acids; SOD: Cu-Zn-superoxide dismutase; TIR: Toll/interleukin-1 (IL-1) receptor domain; TLR1: Toll-like receptor 1 or other numbers; TLRs: Toll-like receptors; TNF-α: Tumor necrosis factor alpha or other symbols; TRIF: TIR-domain-containing adaptor-inducing interferon-β; VAD: Vitamin A deficiency; VDR: Vitamin D receptors

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Authors' contributions

SRE-Z collected the scientific material and wrote the whole manuscript. HS participated in the scientific material collection and reviewed the whole manuscript. FAM reviewed the whole manuscript. All authors read and approved the final manuscript.

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