

Our Immune System IS What We Eat. A Nutritional Immunology Approach

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Abstract

Nutritional Immunology combines two fields of knowledge that did not interact to each other a few years ago. Recently, there are a great interest into assess the impact of different kind of foods or part of these, beyond of their nutritional roles. It is well known that this particular interest is related with the impact of food on the immune system either health or illness point of view. According to this, different nutrients such as proteins, carbohydrates, lipids, vitamins and minerals, among others and interact with both innate and adaptive immunity and determine the outcome of a specific challenge. In addition, microbiota is fundamental for the development and maintenance of the immune system determining its dynamics and composition, and a diet-microbiota-immune system triad is fundamental for people's development and health. The most important effects of each group of nutrients and its impact on health and disease are reviewed with special emphasizes on human and animal studies.

Keywords: Nutritional Immunology; Docosahexaenoic Acid; Eicosapentaenoic Acid; Docosahexaenoic Acid; Microbiota; Food

Abbreviations: IgG: Immunoglobulin G; Glu: L-glutamine; iNOS: inducible Nitric Oxide Synthase; GABA: Gamma Aminobutyric Acid; HSP: Heat Shock Proteins; Ala: Alanine; Linoleic Acid: n-6 polyunsaturated fatty acids; EFA: Essential Fatty Acids; EPA: Eicosapentaenoic Acid; DHA: Docosahexaenoic Acid; NF-Kb: kB Nuclear Transcription Factor; PUFA: Polyunsaturated fatty acid; LTB4: Leukotriene B4; LTB5: Leukotriene B5; PGE2: Prostaglandin E2; PGE3: Prostaglandin E3; TNF: Tumor Necrosis Factor; IkB: Inhibitory Subunit; PPAR γ : Peroxisome Proliferator-Activated Receptor Gamma; LPS: Lipopolysaccharides; Cu: Copper; HLA II: Human Leucocyte Antigen-class II; SOD: superoxide dismutase; Zn: Zinc; Fe: Iron; Se: Selenium; GSH-Ph: Glutathione Peroxidase; IgA: Immunoglobulin A; BLs: B-lymphocyte; TLs: T-lymphocyte; TGF- β : Transforming Growth Factor Beta; GALT: Gut-associated lymphoid tissue; IgD: Immunoglobulin D; PAMPs: Pathogen-associated molecular patterns; IL-12: Interleukin 12; IFN- β : Interferon gamma.

History and importance

Understanding the impact food has on health comes from ancient days from the Egyptians and the Hindu. Hippocrates, the father of western medicine, recommended his students to assess certain diets to understand some diseases. Nevertheless, the earliest evidence regarding the role of nutrition on the immune system comes from 1810 when Dr. Menkel described a thymic atrophy of malnourished people in England. Said observations and others gave rise to Nutritional immunology, which continued evolving as a scientific discipline studying nutritional deficiencies caused by malnutrition and described as nutritionally acquired immunodeficiencies [1]. From the early the 1800s and with new information generated about vitamins in the 1900s, the emphasis on nutritional immunology was to study how nutritional deficiencies affected the immune system [2]. Nevertheless, today, it is a matter of going beyond the study of a population in a world with malnutrition problems. Today's challenge is to study other types of characteristics from the point of view of nutritional immunology including senior citizens, higher natural stress, and abuses and insults from a nutritional point of view.

Malnutrition and infection are the greatest obstacles for animal and human survival, health, growth and reproduction [3]. This global concern has led the development of nutritional immunology as a new scientific discipline which integrates nutrition and immunology

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research methods to define the role nutrients play on metabolism and the function of immune system cells at molecular, cellular, tissue and systemic levels [4].

The benefits of having an immune system in optimal conditions go beyond a simple protection from infections. Immunological health or a lack of health has severe metabolic consequences, and recent studies have shown that it greatly affects body systems including the brain and knowledge [5].

Immune system activation to neutralize and eliminate an infection involves physiological changes including fever, inflammation, cell responses to T lymphocytes and antibodies which may eliminate said agent directly [6]. Even though said response is essential for survival, it has a nutritional price which is paid with precious resources. Increasing body temperature 1°C (fever associated to an active infection) involves an energy consumption of almost an additional 3-10 Kcal/kg a day depending if the fever is mild, medium or [7]. Other metabolic effects as the loss of lean body mass, glucose intolerance and effects on the immune system have also been described. Clearly, this type of response to combat infection may cause great metabolic changes as energy consumption [8], giving priority to the immune system over other process as reproduction, lactation and growth. Furthermore, continuous stimulation of the immune system has other secondary consequences including an increase in oxidative stress which is specifically hazardous for senior citizens. Recently, it has been demonstrated that age-related dementia and HIV-virus-related dementia were associated with “poor” immune systems from the point of view of cell population and cytokines.

Proteins

Receptors, cytokines, immunoglobulins, bactericidal complements and molecules are protein-like. Recent studies have demonstrated that high-protein diets were concomitants with high levels of total serum proteins, transferrin (an acute-phase protein), complement molecules and IgG. Nevertheless, it is important to mention that its mechanisms of action greatly depend on the amino acid composition of said proteins.

Amino acids

Actually, our immune system does not need all nutrients just some very specific ones which when provided in suitable amounts optimize its function. L-glutamine (Glu) is perhaps the most well-known immunonutrient because of its functions as participation in lymphocyte metabolism and function [9]. In the synthesis of nucleotides of lymphocytes [10]. It is the main source of principal energy for enterocytes [11], a regulator of inducible nitric oxide synthase (iNOS) in certain tissues like the brain [12]. It is a substrate for the synthesis of gamma aminobutyric acid (GABA) which is present in both lymphocytes and macrophages. It is an immediate precursor of glutathione because it plays a key role in the removal of oxidative molecules, and modulates in the expression of heat shock proteins (HSP) [13]. All these functions act as a set to improve cell life time, maintenance and the proliferation of the immune system.

For instance, during extreme exercise, muscle cells demand large amounts of glutamine (Glu) to be used as a source of energy caused by a decrease of circulating glutamine. The favorite source of energy for immune system cells is also Glu, and since it is found in low levels in circulation after extreme exercise, immune system cells do not function optimally if they are challenged making the host vulnerable (Figure 1).

Alanine (Ala) is the main substrate for a hepatic glucose synthesis, a key energy substrate for lymphocytes [14]. *In-vitro* studies have demonstrated that Ala supplementation comes from apoptosis potentiating the growth of B lymphocytes and antibody production [15]. In patients having total parenteral nutrition schemas, the inclusion of Ala is highly beneficial to support gluconeogenesis and leukocyte metabolism [16]. Arginine and citrulline have been greatly decreased in individuals with malnutrition, prolonged fasting, trauma, burns and inflammation, sepsis and liver transplants [17]. Arginine is an important substrate for the inducible form of nitric oxide synthase (iNOS) which turns this amino acid into nitric oxide, a potent microbicide molecule. There is evidence in animal studies that demonstrate the function of arginine as a fundamental amino acid in lymphocyte development. Furthermore, it has been demonstrated that its supplementation potentiates the immune system in various models of immunological challenges [18]. In particular, inadequate arginine ingestion (0.3% in a diet) has shown an NO synthesis compromised by constitutive synthase of NO (NOS) and inducible nitric oxide synthase

(iNOS) in rats and a decrease in the weight of primary and secondary lymphoid organs in broiler chickens or chickens for fattening [19]. Arginine supplementation (about 0.8-1% of the diet) in animals with inflammations caused by burns, bacterial peritonitis or intestinal damage reduced translocation of bacteria, increased phagocytic bactericidal activity and prolonged host survival [20]. Likewise, mortality and morbidity were reduced in sows and newborn piglets in response to infectious agents [21]. Cancer studies have demonstrated that the incidence of tumors decreases. Latency periods are reduced, and reduce intervals required for tumor regression [22].

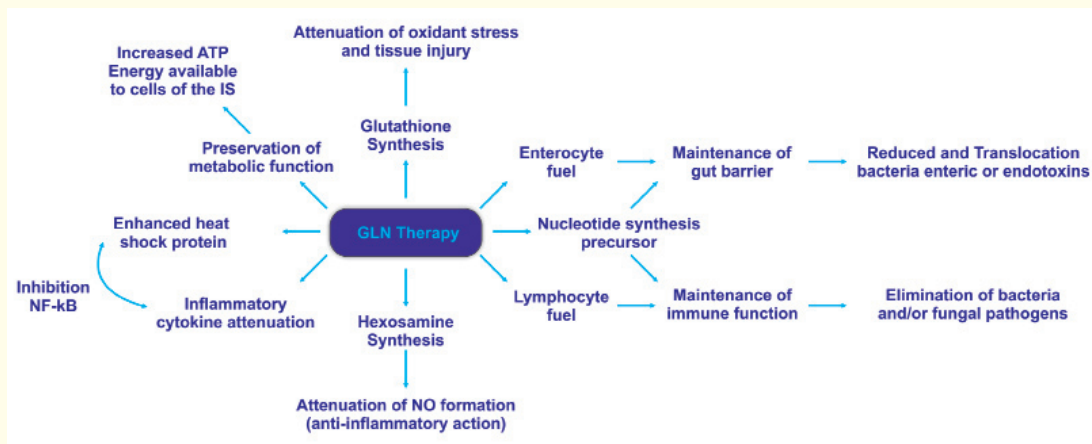


Figure 1: Glutamine action mechanisms.

Lipids

The metabolism of lipids is not just a source of energy for bodies for they may influence metabolic and immunological parameters. Body fat is the body’s greatest reserve source of energy for extreme situations of nutrient deprivation. Nevertheless, under stressful circumstances, oxidation of fats may generate effects as cardiopulmonary dysfunctions, platelet dysfunction and may compromise the immune system. Research on the influence of fatty acids on the immune system dates back to 1970. In that research the effects of short-chain fatty acids and n-6 polyunsaturated fatty acids (linoleic acid) were compared [23]. New studies have shown that said results greatly depend on doses and on a relation of Essential fatty acids (EFA) of the omega-3 and omega-6 family. Also, it has been demonstrated that long-chain polyunsaturated fatty acid supplementation is incorporated at the expense of omega-6, especially, arachidonic acid [24]. Faber et al (2011) [25] reported a significant incorporation of EPA and DHA after 1 d of supplementation which has allowed the establishing of quick incorporation of n-3 fatty acids in mononuclear cells around a 7 d post-supplementation.

Among the main action mechanisms of n-3 long-chain fatty acids, we can mention the following: eicosanoids opposite action (arachidonic acid vs EPA), new anti-inflammatory protein families produced from EPA and DHA as resolvins, inhibition of the activation of the kB nuclear transcription factor (NF-kB) and the modulation of the formation of a signaling platform (Lipid rafts) on the T lymphocyte membrane and other immune system cells .

Eicosanoids are lipid mediators produced from PUFA, mainly from n-6 arachidonic acid. Once the scenario of an n-3 fatty acid supplementation increases, fatty acids directly occupy a place on the cell membrane, and this is directly associated with a decrease in the production of series 2 prostaglandins and series 4 leukotrienes [26]. EPA is also a substrate for enzyme action as COX, lipoxygenase and cytochrome p450 enzymes. It produces different mediators when the substrate is arachidonic acid (i.e. PGE3 instead of PGE2 and LTB5 instead of LTB4) [27]. The biological and functional meaning of the above results is that the eicosanoids produced from EPA are less active biologically and have less affinity towards their respective receptors than those produced from arachidonic acid [28].

Inflammation has a process called resolution which mainly consists of turning off an inflammation activated by a previous stimulus. Flaws in this system have being associated to diverse inflammatory pathologies which cannot control this system [29]. EPA and DHA

lipid mediators play an important role in the resolution of inflammation through some molecules named resolvins. Those produced from EPA are called E-series resolvins while those produced from DHA are called D-series resolvins. Also, there are other related components called protectins which are produced from DHA. Recent studies showed high E-1 and D-1resolvin levels in the plasma of healthy volunteers after a 3-week fish oil supplementation [30]. It has been demonstrated that among the functions of resolvins and protectins one can include the inhibition of the transendothelial migration of neutrophils preventing their infiltration into the site of inflammation and inhibiting inflammatory cytokines as IL-1b and TNF [31]. NFkB is a key transcription factor in generating pro-inflammatory cytokine, adhesion molecules and COX-2 genes [32]. Inactively, NFkB is a trimer located in cytosol, which is activated by a signaling cascade activated by extracellular inflammatory stimuli (as LPS and UV radiation) which start the phosphorylation of the inhibitory subunit (Ikb) which dissociates allowing the translocation of the remaining dimer to the nucleus of cells specifically in zones that are the promoters of the genes which encode for pro-inflammatory cytokines [32]. DHA has the capability of stimulating an anti-inflammatory transcription factor, PPAR γ which has the capability of inhibiting the activation of NFkB avoiding Ikb phosphorylation. On the other hand, other saturated fatty acids as lauric acid promote Ikb phosphorylation, and this activates NFkB. As a result, it causes the activation of macrophages and dendritic cells resulting in an inflammatory process [33].

Lipid rafts are cell membrane regions that have a characteristic structural composition which is rich in sphingolipids and cholesterol where the side chains of phospholipids are usually enriched in saturated fatty acids compared to regions which are not raft-like in the membrane [34]. As a result of the presence of cholesterol and saturated fatty acids, the rafts are structures which are more rigid than the ones which are not rafts in the membrane. The rafts act as cellular signaling platforms facilitating the interaction of molecules associated to those processes. Particularly, in the immune system, the activation of T lymphocytes mediated by this type of rafts has been demonstrated [35]. Nevertheless, EPA addition modifies the formation of rafts in T lymphocytes causing a flaw in signal transduction mechanisms just as other immune system cells like macrophages, B lymphocytes and dendritic cells which causes an opposite effect with lauric [36].

Effect	Mechanisms of action involved
Decrease in the production of eicosanoids from arachidonic acid	Decrease in arachidonic acid in membrane phospholipids
Increase in the production of eicosanoids from EPA	Signs of slight inflammation. Increase in arachidonic acid in membrane phospholipids
Increase in resolvin and protectin production	Decrease in the expression of pro-inflammatory cytokine genes (via NFkB deactivation), PPAR γ induction and activation, disruption of intracellular signs from Lipid rafts, activation of the GPR120 signaling pathway (avoids NFkB deactivation and keeps it inactive in cytosol combined with Ikb)
Decrease in leukocyte chemotaxis	Low production of chemokines and their receptors, and low MHC molecule expression
Decrease in la function of T lymphocytes effectors	Interrupted signs of Lipid rafts
Decrease in the presentation of the antigen	Low expression of MHC molecules resulting from the disruption of Lipid rafts

Table 1: EPA and DHA mechanisms of action and their effect on the immune system.

Adapted by: Calder, 2013.

Carbohydrates

Polysaccharides have immunomodulatory properties as it was demonstrated by the incorporation of lipopolysaccharides (LPS) as stimulating agents in various experimental immunology models [37]. Nevertheless, LPS are not carbohydrates in food although they are soluble carbohydrates of some immunogens. Carbohydrates are important from a point of view of glycemic control particularly in stressed, diabetic or obese patients. Generally, euglycemic patients have fewer episodes of acute kidney failure, fewer transfusions and fewer frequencies of polyneuropathies, fewer infectious complications and a lower death rate [38]. Hyperglycemic states affect the

function of neutrophils decreasing their capacities for chemotaxis, phagocytosis, respiratory burst and antibacterial capacity. Furthermore, slight hyperglycemia promotes a proinflammatory state by increasing TNF and NF- κ B [39].

Minerals and Vitamins

Although they are required in small concentrations in people's diet, they may be considered metabolic "glue" which is behind all anabolic and catabolic reactions of the body. Electrolytes play an important role in cellular structure and in the flow of regulating molecules. Trace minerals and vitamins facilitate complex metabolic reactions, and they are essential components of antioxidant activities, which currently receive great attention in the modulation of the immune system in both health and disease. Copper (Cu) is important in the generation of IgG antibodies, cell-mediated immunity and for the generation of inflammatory responses. A deficient ingestion of Cu produces an antibacterial activity, phagocytosis and altered HLA II expression causing high susceptibility to infection [40]. These effects have been reversed with the addition of adequate amounts of Cu in people's diet. Ceruloplasmin, an acute phase reactant, and superoxide dismutase (SOD), a potent endogenous antioxidant which scavenges free radicals in immune system cells, depend on Cu [41]. The above means that Cu is a fundamental item in phagocyte function. The relation between Zn and the immune system is complex, for there are four types of influences associated with Zn. The first refers to the influence it has as diet consumption and Zn re-absorption and its relation with age and state of illness. The second is that Zn is a cofactor of more than 300 enzymes that influence various organs which have an indirect effect on the immune system. The third is that Zn has direct effects on the production, maturation and function of leukocytes and the fourth is that Zn influences the function of some immune stimulants in pilot studies, and its therapeutic use has been proposed in some pathologies [42].

Iron (Fe) is perhaps one of the most important trace minerals, for it plays a key role in transporting oxygen and in the oxide reduction pathways of many systems. Iron has been traditionally associated with malnutrition as a result of low intake or excess iron loss [43]. Lymphocytes require Fe for cell division, the transportation of electrons and oxide reduction reactions. Fe is transported via transferring in the immune system cells which present morphological abnormalities when this mineral is not present in optimal amounts. The above is explained because in iron-deficient states, there is a flaw in the response to mitogens, T_H lymphokine production, antibody production, phagocytic activity and an increased susceptibility to infection [44]. Selenium (Se) and vitamin E share a unique relation which involves the generation of anti-oxidant enzymes as glutathione peroxidase (GSH-Ph). In the particular case of Se which incorporates via selenoproteins, it plays a key role in the regulation of an inflammation and of the immune system. Suitable levels are essential to start an immune response. Nevertheless, Se is also involved in regulating an excessive response of the immune system and chronic inflammation [45]. Se deficiency has a negative impact on the immune system especially in critical stages as activation, differentiation and proliferation of their effector cells [45]. The above is related with oxidative stress which is generated in these responses in addition to other effects as the correct transportation of proteins rolled from the endoplasmic reticulum and the flow of calcium (which is at the same time fundamental to regulate respiratory burst to start an optimal immune response). They are compromised in this deficiency [46]. Nevertheless, selenium supplementation beyond suitable levels may interfere in the immune response in some particular types of inflammation [47]. Selenium in diets and selenoproteins are not just important to start or potentiate an immune response, for they participate actively in immune regulation processes, and this is crucial to prevent excessive uncontrolled responses which may lead to autoimmune diseases or chronic inflammation. For instance, at a cellular level, dietary Se influences adherence, migration, phagocytosis, cytokine secretion and potentiation of an immunological synapsis increasing the intensity of a signal with a TCR and influencing a Th1 or Th2 phenotype depending on levels of supplementation (Figure 2).

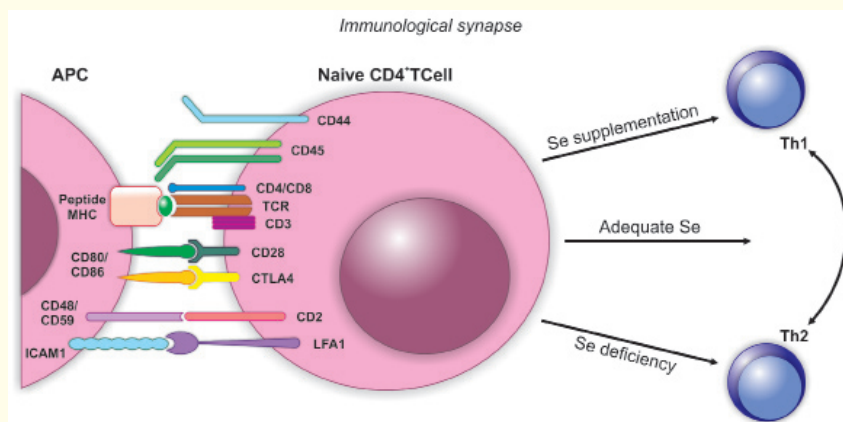


Figure 2: Effects of a lack or excess of selenium on a diet based on the differentiation of t helper cells or cd4 lymphocytes. Suitable levels of selenium do not bias a T lymphocyte differentiation. That means that a differentiation towards a Th1 or Th2 phenotype is mainly determined by signs coming from a cell presenting the antigen or by cytokines in the environment. Selenium supplementation causes a bias towards Th1 phenotype. On the other hand, a lack of Selenium biases the response towards a Th2 phenotype. Adapted from Huang., et al. 2012 [45].

Vitamin E has inhibiting effects on COX-2 showing important potential in the prevention and treatment of autoimmune diseases, cancer, type 1 diabetes and aging [48]. Vitamin E’s most known function is its lipophilic antioxidant capacity which can prevent the spread of polyunsaturated fatty acid peroxidation, and this way neutralize the damage they may cause on the lipid membrane or on proteins associated to cell-signaling [49]. It is worth noticing that naive CD4 lymphocytes are highly susceptible to oxidative damage [50]. Vitamin C affects countless components of the immune system as the function of neutrophils increasing their chemotaxis, phagocytosis, lysozyme action, protection against the toxic effects of superoxide anion, and myeloperoxidase-pre oxidase-halide system inhibitions on a pronounced bactericidal effect [51]. The role of vitamin C is more focused on a cellular type of response versus a humoral response which was demonstrated on patients that had Crohn’s disease. T lymphocyte hypo responsiveness was reversed administering vitamin C but not with a humoral response [52]. On the other hand, studies on animals have demonstrated that vitamin C supplementation causes better performance on humoral immunity, especially, increasing serum antibody levels and protein levels of the complement of the classic way as C1q in Guinea pigs which cannot synthesize vitamin C as humans do [53].

Vitamin A is fundamental for IgA secretion, mucous secretion (a component of innate immunity) and for epithelial conservation (to avoid its keratinization). Also, it modulates BLs activation, cytokine production, antibody production and cellular differentiation [54]. Beta-carotene, the main component in vitamin A potentiates the generation of T_H1 and B_Ls. Furthermore, it has been demonstrated that vitamin A along with short-chain volatile fatty acids produced by intestinal bacteria regulate the generation, traffic and Treg function specifically through TGF- β secretion and homing in GALT causing maintenance of the immunological tolerance in intestinal mucosa [55,56].

Vitamin B complex, especially B6 (pyridoxine) has been associated to failed humoral and cellular responses when there is a lack of B6, and low levels of circulating IgD and of TLsh. Table 2 presents a summary of the effects of vitamins and minerals on the immune system

Nutrient		Action on the immune system
Minerals	Iron	Necessary for the optimal function of neutrophils and lymphocytes; free Fe is necessary for the growth of microorganisms
	Copper	A lack of copper has been associated to an increase in infection rates, RES, microbicidal activity and an altered antibody response, decrease in thymic hormones. Copper is a fundamental component of SOD and a scraper of cells and detritus damaged by FOR
	Zinc	A lack of Zinc is associated with susceptibility to infection, abnormal cell-mediated immunity, low thymic hormones in circulation, phagocyte function and an altered complement. Zinc is a fundamental component of SOD and a scraper of cells and detritus damaged by FOR
	Selenium	A lack of Selenium reduces antibody response, and is part of antioxidant enzymes glutathione peroxidase GSH-Px which scrape cells and detritus damaged by FOR
	Iodine	In hypothyroid people, there is a decrease in the microbicidal activity of neutrophils which is reversed with treatment
	Magnesium	A lack of Magnesium causes thymic hyperplasia, failed immunological cellular and humoral responses and low levels of IgG1, IgG2 and IgA
	Manganese	Manganese is necessary for the synthesis and secretion of antibodies. Excess Manganese inhibits the formation of antibodies and chemotaxis, and it increases a susceptibility to pneumococcal infections.
Vitamins	Sodium	Cells on the edge of the brush are Sodium dependent to transport glutamine, and this is fundamental in the maintenance of a gut barrier
	A	A lack of vitamin A reduces a response of Ls to mitogens and to Ags; b-carotenes and retinol stimulate immune system responses
	B	A lack of vitamin B is associated with a poor antibody response and failed cell-mediated immunity
	C	An extreme lack of vitamin C affects phagocyte function and cellular immunity
	D	A lack of vitamin D causes anergy in tuberculin tests
	E	A lack of vitamin E causes a decrease in the effectivity of antibody responses against antigens dependent on TLs. Vitamin E supplementation has shown an improvement in some immune system functions

Table 2: Immunomodulatory properties of vitamins and minerals.

Abbreviations: GSH-Px: glutathione peroxidase; RES: reticuloendothelial system; FOR: free oxygen radicals; SOD: superoxide dismutase; TLs: T B lymphocytes Ls: B Lymphocytes.

Microbiota, food and the immune system

Despite receiving a huge nutrient input, the intestine is one of the most active organs of the immune system for it hosts more than 65% of the intestine cells and more than 90% of antibody-producing cells [6]. The intestine contains 3 times more antibody-producing cells (7×10^{10}) compared to bone marrow (2.5×10^{10}) [6]. It has been estimated that approximately 3g of IgA is secreted every day towards intestinal lumen [57]. Furthermore, the immune system hosts more than 100 trillion bacteria which form the microbiota with archaea, fungi and viruses. Microbiota colonizes the intestine increasing its density reaching a luminal content of 10^{11} /g in the colon, and it may have more genes than the human genome. With this huge group of genetic information, microbiota may influence human life beyond nutrition and the immune system [58]. Nevertheless, microbiota is fundamental for the development and maintenance of the immune system determining its dynamics and composition, and a diet-microbiota-immune system triad is fundamental for people’s development and health. Lately, it has been seen that changes in this triad have been responsible for an increase in the incidence of diseases as type 2 diabetes, intestinal inflammatory disease and some cancers [55]. In the particular case of probiotic bacteria (Enterococcus faecium, Lactobacilli sp, Bifid obacteria sp, among others), they have the capacity to stimulate both the innate immune system and

the acquired immune system either through whole bacteria or their molecules like PAMPs (for instance: yeast beta-glucans) (Figure 3 a and b).

Figure 3 A Examples on how microbiota interacts with the innate immune system. Microbiota regulates the intestinal immune system through PAMPs and its byproducts. The secretion of one of those PAMPs like LPS stimulates the intestinal epithelial cell (IEC), the secretion of antimicrobial peptides as RegIII γ in which resistance to intestine colonization mediates. RegIII γ is also induced directly by receptors which recognize flagellin by dendritic cells of the lamina propria and which at the same time activate innate immunity lymphoid cells to produce IL-22 (a strong inducer of antimicrobial peptides). Bacteria degrade complex plant polysaccharides (like fiber) generating metabolites as short-chain fatty acids (SCFA) which act on the epithelial gut barrier inhibiting the apoptosis of an IEC. b. Action of microbiota on the adaptive immune system. Said microorganisms activate the activation factor of B cells of the TNF family (BAFF), its ligand (APRIL) and TGF- β in IECs and in dendritic cells, which at the same time convert BLs into IgA producing plasmatic cells. Follicular dendritic cells (FDC) play the same role on BLs, for they are the main producers of TGF- β in Peyer's patches. Polysaccharide A directly bonds to TLR-2 causing TLs differentiation towards a regulatory phenotype. SCFA also stimulates Treg differentiation via G protein-coupled receptors.

Colostrum

Newborn mammals acquire passive immunity during the first 24 hours of their lives, for their gastrointestinal tract allows the free entrance of large numbers of their mothers' immunoglobulins in this short period of time. Nevertheless, this period may be reduced and optimal periods are defined as 3 to 6 hours after birth [59]. Colostrum contains immunomodulatory molecules (Igs, cytokines, growth regulators, lactoferrin, lactoglobulin, lactalbumin and lactoperoxidase), probiotic bacteria regulators as Bifidobacteria and lactobacillus [60] and appetite stimulants (glycomacropeptide) [59]. Various studies have shown that bovine colostrum stimulates IL-12 and IFN- γ production which at the same time are fundamental in the defense against pathogens [60,61].

Conclusion

Nutritional immunology is defined as responsible for most part of the state of health, and it may be critical when influencing chronic diseases. Even if pharmacogenomics broke the paradigm that stated that a medication worked for everything and for everyone, nutrition has recently entered a new age in which the idea is not to only meet some nutritional requirements specific for each stage in life, but also to migrate towards functional food and then to promoting requirements, will promote the immune system to have the capacity to defend a host against any aggressor and the capacity to "shut down" this system when a stimulus is eliminated successfully. Nevertheless, up to now said discipline is quite incipient. To continue seeing in depth this new discipline, it is important to profoundly understand how everything that comes into our bodies as food or supplement affects our immune system, and at the same time, effect of age, sex on the response to the diseases each person develops.

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