Immune and Immunonutrition

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Abstract: The immune system is a biological structures to protect the organism from disease. The immune system detects a wide variety of agents and distinguish them from the organism's own healthy things. The immune system can be classified into subsystems, such as the innate immune system and adaptive immune system, or the humoral immunity and cell-mediated immunity. Immunonutrition can be defined as modulation of either the activity of the immune system, or modulation of the consequences of activation of the immune system, by nutrients or specific food items fed in amounts above those normally encountered in the diet.
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The following introduces recent reports as references in the related studies.

In living bodies the immune system is a biological structures to protect the organism from disease. The immune system detects a wide variety of agents and distinguish them from the organism's own healthy things. The immune system can be classified into subsystems, such as the innate immune system and adaptive immune system, or the humoral immunity and cell-mediated immunity.

The immune system is a host defense system comprising many biological structures and processes within an organism that protects against disease. To function properly, an immune system must detect a wide variety of agents, known as pathogens, from viruses to parasitic worms, and distinguish them from the organism's own healthy tissue. In many species, the immune system can be classified into subsystems, such as the innate immune system versus the adaptive immune system, or humoral immunity versus cell-mediated immunity. In humans, the blood–brain barrier, blood–cerebrospinal fluid barrier, and similar fluid–brain barriers separate the peripheral immune system from the neuroimmune system, which protects the brain (Wikipedia, 2019).

Several barriers protect organisms from infection, including mechanical, chemical, and biological barriers. The waxy cuticle of plant leaves, the exoskeleton of insects, the shells and membranes of eggs and animal skin are typical examples of mechanical barriers as the first line to defend the organisms from infection. As the organisms cannot be completely sealed from their environments, it needs some other systems to protect body from the open parts such as the lungs, intestines and the genitourinary tract, etc. In the lungs, coughing and sneezing mechanically eject pathogens and other irritants from the respiratory tract. The flushing action of tears and urine also mechanically expels pathogens, while mucus secreted by the respiratory and gastrointestinal tract serves to trap and entangle microorganisms. Chemical barriers also protect against infection. The skin and respiratory tract secrete antimicrobial peptides and proteins. Enzymes such as lysozyme and phospholipase A2 in saliva, tears, and breast milk are antibacterials. Vaginal secretions serve as a chemical barrier following menarche and the semen contains defenses and zinc to kill pathogens. In the stomach gastric acid and proteases are chemical defenses against ingested pathogens. Within the genitourinary and gastrointestinal tracts the commensal flora are biological barriers by competing with pathogenic bacteria for food and, which reduces the probability that pathogens will reach sufficient numbers to cause illness.

Even simple unicellular organisms have the immune system, such as bacteria have the rudimentary immune system to protect the bacteria from bacteriophage infections. Some other basic immune mechanisms existed in ancient eukaryotes and remain in their modern descendants such as plants and insects. These mechanisms include phagocytosis, antimicrobial peptides and the complement system, etc. Vertebrates have more sophisticated defense mechanisms including the ability to adapt over time to recognize specific pathogens more efficiently. Adaptive immunity creates immunological memory after an initial response to a specific pathogen, leading to an enhanced response to subsequent encounters with that same pathogen. Pathogens can quickly adapt to the host to avoid be detected and neutralized by the host's immune system. The natural properties of the immunological memory is related to the genetics and not complete clear.

Disorders of the immune system can result in autoimmune diseases, inflammatory diseases and cancer, etc. Immunodeficiency occurs when the immune system is less active than normal, resulting in recurring and life-threatening infections. In humans, immunodeficiency can either be the result of a genetic disease such as severe combined immunodeficiency such as HIV/AIDS or the use of immunosuppressive medication. In contrast, autoimmunity results from a hyperactive immune system attacking normal tissues as if they were foreign organisms. Immunology covers the study of all aspects of the immune system. Lack of immune functions lets the organisms more sensitive to the disease, and over of immune functions creates organism disease also.

The immune system firstly protects organisms from infection with layered defenses of increasing specificity and physical barriers prevent pathogens such as bacteria and viruses from entering the organism. If a pathogen breaches these barriers, the innate immune system provides an immediate and non-specific response. Innate immune systems exist in all animals and plants. If pathogens successfully evade the innate immune system, vertebrates will start a second layer of protection called the adaptive immune system, which is activated by the innate response. The adaptive immune system responses to the pathogens during an infection. This adaptive response is retained even after the pathogen has gone, which is called in the immunological memory. The immunological memory makes the adaptive immune system to respond faster and stronger.

Both the innate and adaptive immunity have the ability to distinguish self and non-self substance. In immunology, self substances are those components of an organism's body that can be distinguished from foreign substances by the immune system and non-self substances are those recognized as foreign substances. One class of non-self substances are antigens and are defined as substances that bind to specific immune receptors and elicit an immune response.

Microorganisms or toxins entering an organism encounter the innate immune system. The innate response is usually triggered when microbes are identified by pattern recognition receptors, which recognize components that are conserved among broad groups of microorganisms or when damaged, injured or stressed cells send out alarm signals. Innate immune defenses are non-specific and it does not confer long-lasting immunity against a pathogen. The innate immune system is the dominant system of host defense in most organisms.

The inflammation is one of the first responses of the immune system to infection. The symptoms of inflammation could be redness, swelling, heat and pain caused by increased blood flow into tissue. Inflammation is produced by eicosanoids and cytokines released by injured or infected cells. Eicosanoids include prostaglandins that produce fever and the dilation of blood vessels associated with inflammation, and leukotrienes that attract certain white blood cells. Common cytokines include interleukins that are responsible for communication between white blood cells; chemokines that promote chemotaxis; and interferons that have anti-viral effects, such as shutting down protein synthesis in the host cell. The cytokines and other chemicals recruit immune cells to the site of infection and promote healing of any damaged tissue following the removal of pathogens.

Phagocytosis is an important feature of cellular innate immunity performed by cells called phagocytes that engulf, or eat, pathogens or particles. Phagocytes generally patrol the body searching for pathogens, but can be called to specific locations by cytokines. Once a pathogen has been engulfed by a phagocyte, it becomes trapped in an intracellular vesicle called a phagosome, which subsequently fuses with another vesicle called a lysosome to form a phagolysosome. The pathogen is killed by the activity of digestive enzymes or following a respiratory burst that releases free radicals into the phagolysosome. Phagocytosis evolved as a means of acquiring nutrients, but this role was extended in phagocytes to include engulfment of pathogens as a defense mechanism. Phagocytosis probably represents the oldest form of host defense, as phagocytes have been identified in both vertebrate and invertebrate animals. Mast cells reside in connective tissues and mucous membranes and regulate the inflammatory response, which are most often associated with allergy and anaphylaxis. Basophils and eosinophils are related to neutrophils. They secrete chemical mediators that are involved in defending against parasites and play a role in allergic reactions, e.g. asthma.

The adaptive immune system came out in early vertebrates and it is a stronger immune response with the immunological memory, where each pathogen is remembered as an antigen. The adaptive immune response is antigen-specific and requires the recognition of specific non-self antigens during a process called antigen presentation. Antigen specificity allows for the generation of responses that are tailored to specific pathogens or pathogen-infected cells. The ability to mount these tailored responses is maintained in the body by memory cells. The cells of the adaptive immune system are special types of leukocytes, called lymphocytes. B cells and T cells are the major types of lymphocytes and are derived from hematopoietic stem cells in the bone marrow. B cells are involved in the humoral immune response,

whereas T cells are involved in cell-mediated immune response.

Both B cells and T cells carry receptor molecules that recognize specific targets. T cells recognize a non-self target, such as a pathogen, only after antigens have been processed and presented in combination with a self receptor called a major histocompatibility complex molecule. In contrast, the B cell antigen-specific receptor is an antibody molecule on the B cell surface, and recognizes whole pathogens without any need for antigen processing. Each lineage of B cell expresses a different antibody, so the complete set of B cell antigen receptors represent all the antibodies that the body can manufacture. When B cells and T cells are activated and begin to replicate, some of their offspring become long-lived memory cells. Throughout the lifetime of an animal, these memory cells remember each specific pathogen encountered and can mount a strong response if the pathogen is detected again. This is "adaptive" because it occurs during the lifetime of an individual as an adaptation to infection with that pathogen and prepares the immune system for future challenges. Immunological memory can be in the form of either passive short-term memory or active long-term memory.

An antibody is a protein molecule made up of two heavy chains and two light chains. The unique variable region allows an antibody to recognize its matching antigen. B lymphocytes and antibodies A B cell identifies pathogens when antibodies on its surface bind to a specific foreign antigen. This antigen/antibody complex is taken up by the B cell and processed by proteolysis into peptides.

The beginning of an immune response starts by the initial pathogen encounter and leads to the formation and maintenance of active immunological memory. Long-term active memory is acquired following infection by activation of B and T cells. Active immunity can also be generated artificially, through vaccination. The principle behind vaccination is to introduce an antigen from a pathogen in order to stimulate the immune system and develop specific immunity against that particular pathogen without causing disease associated with that organism. This deliberate induction of an immune response is successful because it exploits the natural specificity of the immune system, as well as its inducibility. With infectious disease remaining one of the leading causes of death in the human population, vaccination represents the most effective manipulation of the immune system mankind has developed.

Most viral vaccines are based on live attenuated viruses and bacterial vaccines are based on acellular components of micro-organisms, including harmless toxin components. Since many antigens derived from acellular vaccines do not strongly induce the adaptive response, most bacterial vaccines are provided with additional adjuvants that activate the antigen-presenting cells of the innate immune system and maximize immunogenicity.

Immunodeficiencies occur when one or more of the components of the immune system are inactive. The ability of the immune system to respond to pathogens is diminished in both the young and the elderly, with immune responses beginning to decline at around 50 years of age due to immunosenescence. In developed countries, obesity, alcoholism, and drug use are common causes of poor immune function.

Overactive immune responses comprise the other end of immune dysfunction, particularly the autoimmune disorders. The immune system fails to properly distinguish between self and non-self, and attacks part of the body. Under normal circumstances, many T cells and antibodies react with self peptides. One of the functions of specialized cells is to present young lymphocytes with self antigens produced throughout the body and to eliminate those cells that recognize self-antigens, preventing autoimmunity.

Hypersensitivity is an immune response that damages the body's own tissues. They are divided into four classes based on the mechanisms involved and the time course of the hypersensitive reaction. Type I hypersensitivity is an immediate or anaphylactic reaction, often associated with allergy. Symptoms can range from mild discomfort to death.

It is likely that a multicomponent, adaptive immune system arose with the first vertebrates, as invertebrates do not generate lymphocytes or an antibody-based humoral response. Many species, however, utilize mechanisms that appear to be precursors of these aspects of vertebrate immunity. Immune systems appear even in the structurally most simple forms of life, with bacteria using a unique defense mechanism, called the restriction modification system to protect themselves from viral pathogens, called bacteriophages. Bacteria also use the CRISPR-Cas system as the immune system. Pattern recognition receptors are proteins used by nearly all organisms to identify molecules associated with pathogens. Antimicrobial peptides called defensins are an evolutionarily conserved component of the innate immune response found in all animals and plants, and represent the main form of invertebrate systemic immunity. The complement system and phagocytic cells are also used by most forms of invertebrate life. Ribonucleases and the RNA interference pathway are conserved across all eukaryotes, and are thought to play a role in the immune response to viruses.

Unlike animals, plants lack phagocytic cells, but many plant immune responses involve systemic chemical signals that are sent through a plant. Individual plant cells respond to molecules associated

with pathogens known as Pathogen-associated molecular patterns or PAMPs. When a part of a plant becomes infected, the plant produces a localized hypersensitive response, whereby cells at the site of infection undergo rapid apoptosis to prevent the spread of the disease to other parts of the plant. Systemic acquired resistance is a type of defensive response used by plants that renders the entire plant resistant to a particular infectious agent. RNA silencing mechanisms are particularly important in this systemic response as they can block virus replication.

Macrophages have identified a cancer cell. Upon fusing with the cancer cell, the macrophages inject toxins that kill the tumor cell. Immunotherapy for the treatment of cancer is an active area of medical research. Another important role of the immune system is to identify and eliminate tumors. The transformed cells of tumors express antigens that are not found on normal cells. To the immune system, these antigens appear foreign, and their presence causes immune cells to attack the transformed tumor cells. The antigens expressed by tumors have several sources. Paradoxically, macrophages can promote tumor growth when tumor cells send out cytokines that attract macrophages, which then generate cytokines and growth factors that nurture tumor development. In addition, a combination of hypoxia in the tumor and a cytokine produced by macrophages induces tumor cells to decrease production of a protein that blocks metastasis and thereby assists spread of cancer cells.

Hormones can act as immunomodulators, altering the sensitivity of the immune system. For example, female sex hormones are known immunostimulators of both adaptive and innate immune responses. Some autoimmune diseases such as lupus erythematosus strike women preferentially, and their onset often coincides with puberty. By contrast, male sex hormones such as testosterone seem to be immunosuppressive. Other hormones appear to regulate the immune system as well, most notably prolactin, growth hormone and vitamin D.

It is conjectured that a progressive decline in hormone levels with age is partially responsible for weakened immune responses in aging individuals. Conversely, some hormones are regulated by the immune system, notably thyroid hormone activity. The age-related decline in immune function is also related to decreasing vitamin D levels in the elderly. As people age, two things happen that negatively affect their vitamin D levels. First, they stay indoors more due to decreased activity levels. This means that they get less sun and therefore produce less cholecalciferol via UVB radiation. Second, as a person ages the skin becomes less adept at producing vitamin D.

The immune system is affected by sleep and rest, and sleep deprivation is detrimental to immune function. Complex feedback loops involving cytokines, such as interleukin-1 and tumor necrosis factor-α produced in response to infection, appear to also play a role in the regulation of non-rapid eye movement sleep.

When suffering from sleep deprivation, active immunizations may have a diminished effect and may result in lower antibody production, and a lower immune response, than would be noted in a well-rested individual. Additionally, proteins such as NFIL3, which have been shown to be closely intertwined with both T-cell differentiation and our circadian rhythms, can be affected through the disturbance of natural light and dark cycles through instances of sleep deprivation, shift work, etc. As a result these disruptions can lead to an increase in chronic conditions such as heart disease, chronic pain, and asthma.

In addition to the negative consequences of sleep deprivation, sleep and the intertwined circadian system have been shown to have strong regulatory effects on immunological functions affecting both the innate and the adaptive immunity. First, during the early slow-wave-sleep stage, a sudden drop in blood levels of cortisol, epinephrine, and norepinephrine induce increased blood levels of the hormones leptin, pituitary growth hormone, and prolactin. These signals induce a pro-inflammatory state through the production of the pro-inflammatory cytokines interleukin-1, interleukin-12, TNF-alpha and IFN-gamma. These cytokines then stimulate immune functions such as immune cells activation, proliferation, and differentiation. It is during this time that undifferentiated, or less differentiated, like naïve and central memory T cells, peak. In addition to these effects, the milieu of hormones produced at this time (leptin, pituitary growth hormone, and prolactin) support the interactions between APCs and T-cells, a shift of the Th1/Th2 cytokine balance towards one that supports Th1, an increase in overall Th cell proliferation, and naïve T cell migration to lymph nodes. This milieu is also thought to support the formation of long-lasting immune memory through the initiation of Th1 immune responses.

In contrast, during wake periods differentiated effector cells, such as cytotoxic natural killer cells and CTLs, peak in order to elicit an effective response against any intruding pathogens. As well during awake active times, anti-inflammatory molecules, such as cortisol and catecholamines, peak. There are two theories as to why the pro-inflammatory state is reserved for sleep time. First, inflammation would

cause serious cognitive and physical impairments if it were to occur during wake times. Second, inflammation may occur during sleep times due to the presence of melatonin. Inflammation causes a great deal of oxidative stress and the presence of melatonin during sleep times could actively counteract free radical production during this time.

An evasion strategy used by several pathogens to avoid the innate immune system is to hide within the cells of their host. The pathogen spends most of its life-cycle inside host cells, where it is shielded from direct contact with immune cells, antibodies and complement. Some examples of intracellular pathogens include viruses, the food poisoning bacterium Salmonella and the eukaryotic parasites that cause malaria (Plasmodium falciparum) and leishmaniasis (Leishmania spp.). Other bacteria, such as Mycobacterium tuberculosis, live inside a protective capsule that prevents lysis by complement. Many pathogens secrete compounds that diminish or misdirect the host's immune response. Some bacteria form biofilms to protect themselves from the cells and proteins of the immune system. Such biofilms are present in many successful infections, e.g., the chronic Pseudomonas aeruginosa and Burkholderia cenocepacia infections characteristic of cystic fibrosis. Other bacteria generate surface proteins that bind to antibodies, rendering them ineffective; examples include Streptococcus (protein G), Staphylococcus aureus (protein A), and Peptostreptococcus magnus (protein L).

The mechanisms used to evade the adaptive immune system are more complicated. The simplest approach is to rapidly change non-essential epitopes (amino acids and/or sugars) on the surface of the pathogen, while keeping essential epitopes concealed. This is called antigenic variation. An example is HIV, which mutates rapidly, so the proteins on its viral envelope that are essential for entry into its host target cell are constantly changing. These frequent changes in antigens may explain the failures of vaccines directed at this virus. The parasite Trypanosoma brucei uses a similar strategy, constantly switching one type of surface protein for another, allowing it to stay one step ahead of the antibody response. Masking antigens with host molecules is another common strategy for avoiding detection by the immune system. In HIV, the envelope that covers the virion is formed from the outermost membrane of the host cell; such "self-cloaked" viruses make it difficult for the immune system to identify them as "non-self" structures.

The innate immune system is an important subsystem of the overall immune system that comprises the cells and mechanisms that defend the host from infection by other organisms. The cells of the innate system recognize and respond to pathogens in a generic way and it does not confer long-lasting or protective immunity to the host. Innate immune systems provide immediate defense against infection, and are found in all animals and plants. The innate immune system is an evolutionarily older defense strategy, and is the dominant immune system found in plants, fungi, insects, and primitive multicellular organisms.

All white blood cells are known as leukocytes. Leukocytes are different from other cells of the body in that they are not tightly associated with a particular organ or tissue; thus, they function similar to independent, single-cell organisms. Leukocytes are able to move freely and interact with and capture cellular debris, foreign particles, or invading microorganisms. Unlike many other cells in the body, most innate immune leukocytes cannot divide or reproduce on their own, but are the products of multipotent hematopoietic stem cells present in the bone marrow. The innate leukocytes include: natural killer cells, mast cells, eosinophils, basophils and the phagocytic cells including macrophages, neutrophils, and dendritic cells, and function within the immune system by identifying and eliminating pathogens that might cause infection.

Toll-like receptors (TLRs) are a class of proteins that play a key role in the innate immune system. They are single, membrane-spanning, non-catalytic receptors usually expressed in sentinel cells such as macrophages and dendritic cells, that recognize structurally conserved molecules derived from microbes. Once these microbes have breached physical barriers such as the skin or intestinal tract mucosa, they are recognized by TLRs, which activate immune cell responses. The TLRs include TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, TLR11, TLR12, and TLR13. TLRs are a type of pattern recognition receptor (PRR) and recognize molecules that are broadly shared by pathogens but distinguishable from host molecules, collectively referred to as pathogen-associated molecular patterns (PAMPs). TLRs together with the Interleukin-1 receptors form a receptor superfamily, known as the "interleukin-1 receptor / toll-like receptor superfamily"; all members of this family have in common a so-called TIR (toll-IL-1 receptor) domain. TLRs are present in vertebrates and invertebrates. Molecular building blocks of the TLRs are represented in bacteria and in plants, and plant pattern recognition receptors are well known to be required for host defence against infection. The TLRs thus appear to be one of the most ancient, conserved components of the immune system. TLRs are identified also in the mammalian nervous system. Members of the TLR family are detected on glia,

neurons and on neural progenitor cells in which they regulate cell-fate decision.

TLR1 is a member of the Toll-like receptor family (TLR) of pattern recognition receptors of the innate immune system. TLR1 recognizes pathogen-associated molecular pattern with a specificity for gram-positive bacteria. TLR1 has also been designated as CD281 (cluster of differentiation 281).

TLR1 recognises peptidoglycan and (triacyl) lipoproteins in concert with TLR2 (as a heterodimer). It is found on the surface of macrophages and neutrophils.

As a membrane surface receptor, TLR2 recognizes many bacterial, fungal, viral, and certain endogenous substances. In general, this results in the uptake (internalization, phagocytosis) of bound molecules by endosomes/phagosomes and in cellular activation; thus such elements of innate immunity as macrophages. Cytokines participating in this include tumor necrosis factor-alpha (TNF-α) and various interleukins (IL-1α, IL-1β, IL-6, IL-8, IL-12).

TLR2 is expressed on microglia, Schwann cells, monocytes, macrophages, dendritic cells, polymorphonuclear leukocytes (PMNs or PMLs), B cells (B1a, MZ B, B2), and T cells, including Tregs (CD4+CD25+ regulatory T cells). In some cases, it occurs in a heterodimer (combination molecule), e.g., paired with TLR-1 or TLR-6. TLR2 is also found in the epithelia of air passages, pulmonary alveoli, renal tubules, and the Bowman's capsules in renal corpuscles. In the skin, it is found on keratinocytes and sebaceous glands; spc1 is induced here, allowing a bactericidal sebum to be formed.

TLR2 resides on the plasma membrane where it responds to lipid-containing PAMPs such as lipoteichoic acid and di- and tri-acylated cysteine-containing lipopeptides. It does this by forming dimeric complexes with either TLR 1 or TLR6 on the plasma membrane. TLR2 interactions with malarial Glycophosphatidylinositols of Plasmodium falciparum was shown and a detailed structure of TLR–GPI interactions was computationally predicted.

Various single nucleotide polymorphisms (SNPs) of the TLR2 have been identified and for some of them an association with faster progression and a more severe course of sepsis in critically ill patients was reported.

Toll-like receptor 3 (TLR3) also known as CD283 (cluster of differentiation 283) is a protein that in humans is encoded by the TLR3 gene. TLR3 is a member of the Toll-like receptor family of pattern recognition receptors of the innate immune system. TLR3 is a member of the TLR family which plays a fundamental role in pathogen recognition and activation of innate immunity.

TLR3 recognizes double-stranded RNA, a form of genetic information carried by some viruses such as retroviruses. Upon recognition, TLR 3 induces the activation of IRF3 to increase production of type I interferons which signal other cells to increase their antiviral defenses. TLR3 displays a protective role in mouse models of atherosclerosis, and its activators show effects on human vascular cells.

TLR3 forms a large horseshoe shape that contacts with a neighboring horseshoe, forming a "dimer" of two horseshoes. Much of the TLR3 protein surface is covered with sugar molecules, making it a glycoprotein, but on one face (including the proposed interface between the two horseshoes), there is a large sugar-free surface. This surface also contains two distinct patches rich in positively charged amino acids, which may be a binding site for negatively charged double-stranded RNA. Despite being a glycoprotein, TLR3 crystallises readily - a prerequisite for structural analysis by x-ray crystallography.

TLR 4 is a toll-like receptor that in humans is encoded by the TLR4 gene. It detects lipopolysaccharide from Gram-negative bacteria and is thus important in the activation of the innate immune system. TLR 4 has also been designated as CD284 (cluster of differentiation 284). The molecular weight of TLR 4 is approximately 95 kDa.

TLR4 is a toll-like receptor that detects lipopolysaccharide from Gram-negative bacteria and is thus important in the activation of the innate immune system. TLR4 has also been designated as cluster of differentiation 284 (CD284). Unilateral ureteral obstruction (UUO) produces a well documented triphasic response in the renal hemodynamics (Wikipedia, 2014); (Zhang et al.). TLR4 mediates many biological effects of LPS, which has antitumoral effects on glioblastoma both in vivo and in vitro (Chicoine et al.) (2012). Lithium can inhibit LPS-induced TLR4 expression and microglial activation through the PI3K/Akt/FoxO1 signaling pathway (Dong et al.) (2012). This experiment is to observe the TLR4 expression induced by LPS in rat kidney after the urinal obstruction.

TLR4 cooperates with LY96 and CD14 to mediate in signal transduction events induced by lipopolysaccharide (LPS) found in most gram-negative bacteria. Mutations in this gene have been associated with differences in LPS responsiveness. Several transcript variants of this gene have been found, but the protein-coding potential of most of them is uncertain.

When genes responsible for the expression of TLR 4 and GABA receptors are manipulated in rodents that had been bred and trained to drink excessively, the animals showed a profound reduction in drinking behaviours. Additionally, it has been

shown that ethanol, even in the absence of LPS, can activate TLR4 signaling pathways. High levels of TLR4 molecules and M2 tumor-associated macrophages are associated with increased susceptibility to cancer growth.

TLR4 has been shown to be important for the long-term side-effects of opioid analgesic drugs. Various μ-opioid receptor ligands have been tested and found to also possess action as agonists or antagonists of TLR4, with opioid agonists such as morphine being TLR4 agonists. Activation of TLR4 leads to downstream release of inflammatory modulators including TNF-α and Interleukin-1, and constant low-level release of these modulators is thought to reduce the efficacy of opioid drug treatment with time, and be involved in both the development of tolerance to opioid analgesic drugs. Drugs that block the action of TNF-α or IL-1β have been shown to increase the analgesic effects of opioids and reduce the development of tolerance and other side-effects. Morphine causes inflammation by binding to the protein lymphocyte antigen 96, which, in turn, causes the protein to bind to TLR4). The morphine-induced TLR4 activation attenuates pain suppression by opioid and enhances the development of opioid tolerance and addiction, drug abuse, and other negative side effects such as respiratory depression. Drug candidates that target TLR4 may improve opioid-based pain management therapies.

Toll-like receptor 5, also known as TLR5, is a protein which in humans is encoded by the TLR5 gene. It is a member of the TLR family. TLR5 is expressed on both immune and non-immune cells. TLR5 recognizes bacterial flagellin, a principal component of bacterial flagella and a virulence factor. The activation of this receptor mobilizes the nuclear factor NF-κB and stimulates tumor necrosis factor-alpha production. TLR5 recognizes flagellin, which is the protein monomer that makes up the filament of bacterial flagella, found on nearly all motile bacteria. There are highly conserved regions in the flagellin protein among all bacteria, facilitating the recognition of flagellin by a germ-line encoded receptor such as TLR5.

Toll-like receptor 6 (TLR6) is a protein that in humans is encoded by the TLR6 gene. TLR6 has also been designated as CD286 (cluster of differentiation 286).

Toll-like receptor 7, also known as TLR7, is protein that in humans is encoded by the TLR7 gene. TLR7 recognises single-stranded RNA in endosomes, which is a common feature of viral genomes which are internalised by macrophages and dendritic cells.

Toll-like receptor 8 (TLR8) is a protein that in humans is encoded by the TLR8 gene. TLR8 has also been designated as CD288 (cluster of differentiation 288). It is a member of the toll-like receptor (TLR) family. TLR7 is functional both in human and mouse, but TLR8 is only functional in human. Its gene is predominantly expressed in lung and peripheral blood leukocytes, and lies in close proximity to another family member, TLR7, on chromosome X. TLR8 recognizes G-rich oligonucleotides.

Toll-like receptor 9 (TLR9) is a protein that in humans is encoded by the TLR9 gene. TLR9 has also been designated as CD289 (cluster of differentiation 289). It is a member of the toll-like receptor (TLR) family. TLR9 recognizes unmethylated CpG sequences in DNA molecules. CpG sites are relatively rare (~1%) on vertebrate genomes in comparison to bacterial genomes or viral DNA. TLR9 is expressed by numerous cells of the immune system such as B lymphocytes, monocytes, natural killer (NK) cells, and plasmacytoid dendritic cells. TLR9 is expressed intracellularly, within the endosomal compartments and functions to alert the immune system of viral and bacterial infections by binding to DNA rich in CpG motifs. TLR9 signals leads to activation of the cells initiating pro-inflammatory reactions that result in the production of cytokines such as type-I interferon and IL-12.

Toll-like receptor 10 (TLR10) is a protein that in humans is encoded by the TLR10 gene. TLR10 has also been designated as CD290 (cluster of differentiation 290). Its gene is most highly expressed in lymphoid tissues such as spleen, lymph node, thymus, and tonsil. Its exact function is not known. Multiple alternatively spliced transcript variants encoding the same protein have been found for this gene.

Toll-like receptor 11 (TLR11) is a protein that in humans is encoded by the gene TLR11. TLR11 belongs to the toll-like receptor (TLR) family and the interleukin-1 receptor/toll-like receptor superfamily. By recognizing flagellin and/or profilin present on certain microbes, it helps propagate a host immune response. TLR11 plays a fundamental role in both the innate and adaptive immune responses, through the activation of Tumor necrosis factor-alpha, the Interleukin 12 (IL-12) response, and Interferon-gamma (IFN-gamma) secretion. TLR11 mounts an immune response to multiple microbes, including Toxoplasma gondii (T. gondii), Salmonella species, and uropathogenic Escherichia coli (E. coli), and likely many other species due to the highly conserved nature of flagellin and profilin.

Every TLR has three domains that compose its overall structure: a leucine-rich repeat (LRR) region, a transmembrane domain, and a Toll/Interleukin-1 receptor (TIR) domain. The LRR region of TLR 11 interacts with the T. gondii profilin and uropathogenic E. coli. It is localized to the endosomal compartment

of the cell with the LRR region facing into the endosome. The transmembrane domain mounts TLR 11 to the endosomal membrane and connects the LRR region to the TIR domain. The TIR domain resides on the cytosolic side of the cell. Its job is to initiate a signal that will activate the Toll pathway in the cell. The ultimate end of the Toll pathway is the expression of genes by the transcription factors NF-κB and AP-1 that initiate an immune response to the pathogen.

TLR 11 is expressed in macrophages, dendritic cells, and liver, kidney, and bladder epithelial cells. Many mammals, including humans, have the TLR 11 gene. But only some species' TLR 11 can successfully code for the functional protein that is able to play an active role in the innate immune response. Human TLR 11 contains stop codons, meaning functional TLR 11 protein is not found in humans. All the collective knowledge about the function and immunopathology of TLR 11 has come from experiments in other animals, often mice.

Experiments on mouse TLR 11 both in vivo and in vitro have revealed much about the biological role of TLR 11. TLR 11 has a primary role as a "sentinel" for the innate immune system. Like all TLRs, TLR 11 distinguishes between self molecules and non-self molecules. When an infection of T. gondii or uropathogenic E. coli reaches a host cell expressing TLR 11 on its surface, the LRR region binds to the pathogen and activates the Toll pathway through the TIR domain. The transcription factor NF-kappa B at the end of the pathway transcribes pro-inflammatory cytokines (such as IL-12) and chemokines. Activation of the Toll pathway also results in the expression of co-stimulatory molecules on dendritic cells, which then go on to activate naïve CD4 cells in the lymph nodes.

T. gondii and other apicomplexan parasites rely on actin-dependent gliding motility in order to gain access to the body. This form of cellular motion requires profilin, an actin filament binding protein that helps restructure the actin cytoskeleton. Without profilin, T. gondii can still grow and replicate, but it loses the ability to pass through cell layers and biological barriers in order to carry out infection. Thus profilin is a conserved, essential protein for T. gondii infection efficacy.

Profilin from T. gondii is a critical parasite ligand for TLR 11. It preferentially induces IL-12 production in dendritic cells that communicate with natural killer cells and cytotoxic T cells. In one study, mice bred to not express TLR 11 (knock-out mice) did not mount the IL-12 response upon profilin stimulation. Dendritic cells in the knock-out mice also failed to migrate to lymph nodes, halting the initiation of the adaptive immune response.

Furthermore, mice lacking the TLR 11 gene are susceptible to pancreatitis, fat cell necrosis, and increased inflammatory reactants. Pancreatitis is also a pathological response in humans to T. gondii infection. [3] Wild-type mice are able to produce an immune response, marked by IL-12 and IFN-gamma production that is unseen in humans, who lack a functional TLR 11 protein.

TLR 11 and uropathogenic E. coli [edit] Uropathogenic E. coli is a bacterium that causes urinary tract infections. The infection begins with colonization in the urethra. The infection typically ascends and can reside primarily in the bladder or the kidneys, though the latter is more threatening due to the possibility of transmission of pathogens to the blood stream.

TLR 11 is expressed in mouse kidney and bladder epithelial cells, the cells that line the urinary tract and protect the underlying tissue. In another study of TLR 11 in mice, exposure of human uropathogenic E. coli bacteria to mouse cells expressing TLR 11 resulted in NF-kappa B activation. While the bladders from both wild-type and knockout mice were almost equally infected, the kidneys of the mice without TLR 11 had 10,000 times more bacteria and showed a greater inflammatory response than the normal mouse kidneys. TLR 11 appears to recognize a pattern on uropathogenic E. coli and can prevent ascending infection.

It is important to note that mice as a species do not grapple with urinary tract infections like humans do, unless some part of their TLR 11 immune response is made non-functional. With functional TLR 11, humans might not succumb to urinary tract infections so readily.

The activity of the immune system by interventions with specific nutrients is termed as immunonutrition. Immunonutrition has become associated most closely with attempts to improve the normal people and clinical course of critically ill and surgical patients, who will often require an exogenous supply of nutrients through the parenteral or enteral routes. Improving immune function is important for the health. Three potential targets exist for immunonutrition–mucosal barrier function, cellular defence, and local or systemic inflammation. The nutrients most often studied for immunonutrition are arginine, glutamine, branched chain amino acids, n-3 fatty acids, and nucleotides.

Many clinical trials of immunonutrition in critically ill and surgical patients have been performed that used various nutrient combinations. Three meta-analyses give a fairly consistent view of the clinical efficacy of enteral immunonutrition. All three considered only randomised controlled trials in either surgical or critically ill patients; the control was a

"standard" enteral feed in all. Most trials used a combination of arginine, n-3 fatty acids, and nucleotides, whereas some used a combination of these nutrients and glutamine and branched chain amino acids or of arginine and n-3 fatty acids. The experimental feeds were often much higher in total nitrogen content and contained greater amounts of antioxidant vitamins and minerals such as vitamins A and E and selenium.

All three meta-analyses found that immunonutrition results in notable reductions in infections and in length of stay in hospital. In general the reduced infection rate and length of hospital stay are more pronounced in surgical than critically ill patients. Despite these apparent benefits of immunonutrition, none of the meta-analyses identified a significant effect of immunonutrition on mortality either across all trials considered or within surgical or critically ill patients. This is partly because one trial showed significantly increased mortality in critically ill patients receiving immunonutrition, an effect that was more pronounced in patients with sepsis.

Trials have also shown some benefit from the "single" immunonutrient approach. For example, enteral provision of glutamine decreased the incidence of sepsis in premature neonates and the incidence of pneumonia, bacteraemia, and severe sepsis in critically ill patients. However, in the latter study the decreased rate of infection was not associated with decreased mortality. Parenteral glutamine decreased the incidence of infections in recipients of bone marrow transplantation and changed the pattern of mortality in patients in intensive care. These clinical benefits of glutamine seem to be associated with improvements in intestinal integrity and in cellular immune function.

An enteral feed that differed in lipid composition from the control was shown to decrease the requirement for supplemental oxygen, time on ventilation support, and length of stay in the intensive care unit in patients with moderate and severe acute respiratory distress syndrome. Total length of stay in hospital and mortality also tended to be decreased in the treatment group, and fewer patients developed new organ failure. Although several studies report potential immune benefits and anti-inflammatory effects of parenteral n-3 fatty acids, few trials of the effect of this approach on clinical outcomes exist. Recent trials using parenteral n-3 fatty acids in surgical patients show immune benefits and anti-inflammatory effects but no reduction in infection rate or mortality, although postoperative stay in intensive care and in hospital tended to be shorter in the fish oil group.

Trials of immunonutrients indicate several beneficial clinical effects, particularly in surgical patients. However, doubts remain about the efficacy of this approach in critically ill patients, with contradictory findings among trials. Methodological differences among trials hamper comparisons. Use of immunonutrition should be approached cautiously in the most critically ill patients. Future efforts should try and define the most effective nutrients and optimal mixes for use in different patient groups (Philip C Calder, 2003).

The systemic inflammatory response, which occurs as a result of surgery, trauma or infection, may exert high metabolic demands upon patients and lead to a depletion of essential nutrient stores. Pro-inflammatory cytokines orchestrate the host response to injury and infection and are crucial for normal immune responses. However, the high levels of inflammation induced by pro-inflammatory cytokine production may exert an immunosuppressive effect. Malnourished patients have reduced immune function.

Immunonutrition can be defined as modulation of either the activity of the immune system, or modulation of the consequences of activation of the immune system, by nutrients or specific food items fed in amounts above those normally encountered in the diet.

Immunonutrients are nutrients, which have an effect on the immune system. There are many nutrients. The ω-3 fatty acids, have anti-inflammatory actions, which will help to reverse immunosuppression by down-regulating eicosanoid production. Sulphur amino acids enhance antioxidant status by maintaining concentrations of glutathione, one of the key anti-oxidants in the body. Glutamine is an important nutrient for rapidly dividing cells, such as those of the immune system and helps to improve gut carrier function. Glutamine also enhances glutathione production thereby improving anti-oxidant status. Arginine stimulates nitric oxide synthesis, and growth hormone production. It therefore has an anabolic effect, and also increases T helper cell numbers. Nucleotides currently have a less well defined role, but it is suspected that they have important effects upon T cell function. Immunonutrition does not work in all patient groups probably due to the way in which they are fed, the amounts fed, the timing of feeding and individual genetic factors.

Oxidant molecules, produced during the inflammatory response, up-regulate cytokine production through the activation of nuclear transcription factors such as nuclear factor kappa B (NFκB), nuclear factor IL-6 (NF-IL-6) and activator protein-1 (AP-1).

The transcription factor NFκB pre-exists within the cell cytoplasm in an inactive form, by virtue of its binding to an inhibitory sub-unit, termed IκB. Cellular

signals induce dissociation of the IκB, to reveal a nuclear recognition site, which, after a series of phosphorylation steps causes the NFκB sub-unit to move into the cell nucleus and turns on gene transcription. There are large ranges of genes, which have been shown to be regulated through NFκB. Their products include, cytokines, adhesion molecules, enzymes and other inflammatory mediators. The process of dissociation and phosphorylation has a redox sensitive step, which means that oxidant molecules promote NFκB activation and antioxidants inhibit it.

Up-regulation of NFκB controls many of the cytokines implicated in the inflammatory responses that seen during infection and injury. Indeed, three separate investigators have shown that increased NFκB activation in patients with sepsis is associated with increased mortality rates.

The body has a complex array of interacting antioxidant defences to provide protection from oxidant damage. These antioxidants are present in body fluids and within various compartments of the cell, including cell membranes. Within plasma several antioxidant molecules are derived directly from the diet are found, such as tocopherols (vitamin E), ascorbic acid (vitamin C), carotenoids – β-carotene and lycopene, catechins. In addition, proteins and peptides, that are important in antioxidant defence, such as glutathione, caeruloplasmin, albumin, and metallothionein, are present, which are synthesised endogenously. Many of these substances act as antioxidants within aqueous compartments of the cell, although vitamin E and carotene are the predominant antioxidants within the cell membranes. Superoxide dismutase, catalase, glutathione peroxidase/reductase, convert oxidant molecules to harmless by-products. Nutrients with anti-oxidant properties and those which are precursors for the molecules described above contribute to the body's antioxidant defences and thereby limit the ability of oxidants, released during inflammation, to activate NFκB directly or damage host tissue.

These nutrients therefore may be able to limit pathological aspects of the cytokine-mediated responses to infection and injury. Many of the antioxidants act in a complementary fashion in oxidation/reduction cycling. Micronutrients also influence antioxidant defences since some of these trace elements are present in antioxidant enzymes: caeruloplasmin (copper), superoxide dismutases (copper, zinc, manganese), and glutathione peroxidase (selenium).

Given the interaction of antioxidant defences and the dependence within the system on oxidant cycling, it is important to consider that what happens if one component of these antioxidant defences decreases in concentration. A study, which investigated this, gave rats diethylmaleate, a drug, which binds onto glutathione and blocks normal function. Both treated and untreated animals then received similar doses of TNF-α. Animals, who did not receive diethylmaleate and hence had adequate antioxidant defences, experienced no mortality, however, the rats which had impaired glutathione function, experienced high mortality rates. Glutathione concentrations in a wide range of tissues decrease after surgery, during infection and have been shown to be sub-optimal in a wide range of clinical conditions including human immunodeficiency virus infection, hepatitis C infection, cirrhosis, type II diabetes, ulcerative colitis and myocardial infarction. It therefore seems that the normal response to trauma of any sort, and infection results in depletion of antioxidant defences.

There are many ways of boosting glutathione synthesis. It can be achieved simply by supplying patients with the 3 amino acids need to make glutathione, i.e. glycine, glutamic acid and cysteine. Glutamine is easily converted to glutamic acid. This may be one of the ways in which glutamine produces its beneficial effect by providing glutamic acid for glutathione synthesis. It is very difficult to give cysteine and methionine to patients since these amino acids are not easily taken up by cells. However, cysteine can be supplied as *n*-acetylcysteine (NAC) or pro-cysteine.

A number of studies have shown beneficial effects of glutamine supplementation on patient outcome with decreased infection rates and reduced hospital length of stay observed. It may be that glutamine is exerting its effects by helping to maintain glutathione status as well as nourishing the gut and immune system.

Fatty acids may influence the ability of cells to produce cytokines and the ability of target tissues to respond to cytokines. The fatty acids in dietary fat consist of three main types according to chemical composition, namely saturated, monounsaturated and polyunsaturated fatty acids (PUFA). PUFA can be sub-divided into two types according to the position of the double bonds in the molecule. The classification of ω-3 and ω-6 (or *n*−3 and *n*−6, respectively) results.

There have been many studies, mostly in animal models, using several of fats. The studies have examined the effects of dietary fat on burn injury, cytokine-, and endotoxin-induced anorexia and fever, cytokine- and endotoxin-induced changes in visceral protein metabolism, and cytokine production from macrophages. In summary, fats rich in ω-3 fatty acids, or monounsaturated fatty acids, or poor in ω-6 fatty acids reduce responsiveness to cytokines and inflammation. Fats rich in ω-6-fatty acids exert the opposite effect. The exception to this rule is evening

primrose oil, which, although rich in the ω-6-fatty acid linolenic acid, has an anti-inflammatory effect.

The mechanism of action whereby lipids modulate the immune system is fairly straightforward. Our dietary intake of monounsaturated fatty acids or different types of polyunsaturated fatty acids dictates the fatty acid composition of membrane phospholipids in the immune cells and target tissue cells upon which cytokines act. Under the action of phospholipases, which are activated as a part of the response to trauma or infection, prostaglandins and leukotrienes are produced. Wide ranges of physiological and metabolic changes ensue. Feeding different fatty acids will result in different profiles of released prostaglandin and leukotriene, which will have some impact on the strength of the inflammatory response. A number of studies in particular have looked at fish oil (rich in ω-3 fatty acids) as an anti-inflammatory agent. All of these studies were performed in patients with chronic inflammatory disease rather than the acute inflammation. Inflammatory symptoms were improved by fish oil in diseases such as rheumatoid arthritis, psoriasis, asthma, multiple sclerosis, Crohn's disease, and ulcerative colitis. Fish oil reduces the ability of leucocytes from healthy subjects and rheumatoid patients to produce several pro-inflammatory cytokines and may partly explain the anti-inflammatory effects of fish oil. Fish oil also confers a degree protection in animals against the lethal effects of endotoxin, burn injury, and bacterial infection.

Feeding SMOF reduced the ratio of leukotrienes B4 to leukotrienes B5 produced by peripheral blood mononuclear cells in the patients. Leukotriene B5 is a much less potent form of leukotrienes, than LTB4. Hospital length of stay was reduced by 2 days in patients treated with SMOF.

Nutrient status has the potential to modulate cytokine biology and immune function. Inflammation may inhibit T lymphocyte function. Thus any nutrient, which has an anti-inflammatory effect, may enhance T lymphocyte function by removing this inhibitory influence. Nutrients may act at many cellular locations, affecting cytokine production and altering the response of target tissues to cytokines. Fatty acids can exert a direct influence by changing membrane phospholipid fatty acid composition. Nutrients, which influence antioxidant defences, may alter cytokine production indirectly by modulating the extent of activation of transcription factors by oxidant molecules that are produced during the inflammatory response.

Patients undergoing salvage surgery for recurrent head and neck squamous cell carcinoma are at high risk of postoperative complications due to the adverse effects of radiotherapy on wound healing. Malnutrition is an additional risk factor and Mueller et al tested the hypothesis that preoperative administration of immunonutrition would decrease complications in this high risk population. This single armed study with historical control included consecutive patients undergoing salvage surgery for recurrent head and neck squamous cell carcinoma. They compared outcomes before and after implementation of preoperative immunonutrition and adjusted the regression analysis for gender, age, body mass index, Nutritional Risk Screening (NRS 2002), tobacco and alcohol consumption, tumor localization, tumor stage, and type of surgery. The primary endpoint was overall complications from surgery within a follow-up of 30 days. Ninety-six patients were included (intervention group: 51, control group: 45). Use of preoperative immunonutrition was associated with a significant reduction in overall complications (35% vs. 58%, fully-adjusted odds ratio 0.30 (95%CI 0.10-0.91, p = 0.034). Length of hospital stay was also significantly reduced (17 days vs. 6 days, p = < 0.001). No differences in mortality and hospital readmission were found. These results remained robust in multivariate analysis. As a conclusion, in patients undergoing salvage surgery for recurrent head and neck squamous cell carcinoma, preoperative immunonutrition exhibited favorable effects on the complication rate and consequently reduced the length of hospital stay. By improving both tissue regeneration and immune response, immunonutrition may help to improve surgical outcomes in this high-risk population (Mueller et al., 2019).

Plant-based dietary patterns, functional foods, dietary supplements, and bioactive compounds such as the Mediterranean Diet, berries, polyunsaturated fatty acids, omega-3 and omega-6, vitamins E, A, C, and D, coenzyme Q10, as well as phytochemicals including isoflavones, stilbenes, and sterols have been associated with improvement in atheroma plaque at an inflammatory level (Ruiz-Leon et al., 2019).

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

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