VITAL FORCE TECHNOLOGY™

Immune System Response

Ways to Approach Autoimmunity*

Introduction

In this chapter we do our best to describe the immune system as a set of mechanisms designed to preserve the integrity of the organism when it is affected by various homeostatic disturbances as well as to use our understanding of the pathogenesis of autoimmune diseases for developing strategies in reestablishing the healthy balance between the effector and regulatory immune responses.

While pathogens represent the primary source of homeostatic stress, and immune responses retain complex cellular and molecular mediators to fight viruses and microbes, the elimination or suppression of such pathogens may not always be compatible with the ultimate goal, which is the preservation of self. From this point of view, the maintenance of a suboptimal state, such as chronic infection, that still allows survival, may be preferable in comparison with the ultimate pathogen extermination associated with extensive damage to self.

Components of the organism have developed various protective mechanisms against immune responses, and in most cases the immune response itself seems to follow the path of minimal harm. When these regulatory modules are lost or damaged, however considerable pathology ensues. Understanding the principles and mechanisms of these regulatory modules is essential for the prevention and treatment of diseases.

Also, in this chapter we will be concentrating on the presentation of autoimmunity mechanisms and different ways of prevention or better control of the body's autoimmune response that include herbal and nutritional information, as well as Energy Tools International (ETI) formulas to support and/or balance the immune system function.

We provided a glossary to help you better understand the text (Appendix 1).

1. Immune System Structure

The immune system has two anatomical components: cells responsible for the immune response and lymphoid tissue.

1.1. Cells level

The immune system consists of billions of cells of different types, that interact with the infection units and with each other to fight the infection. All cells of the immune system are produced in

the bone marrow, then they go to the bloodstream, enter other tissues, and create a part of the specific lymphoid tissues (Fig 1) (1).

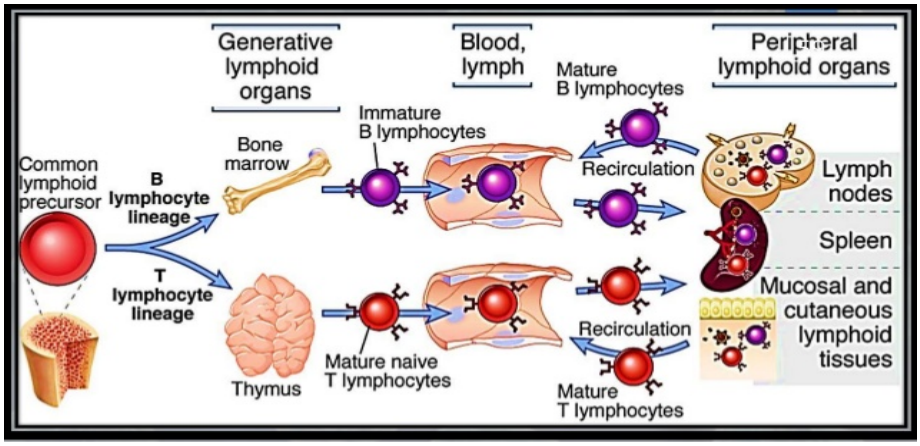

Fig. 1. From https://www.slideshare.net/vartika1428/cells-of-immune-system-37288603

In the bone marrow, the pluripotent stem cell divides and differentiates into more specialized progenitor cells that give rise to three specific lineages, called the lymphoid, the myeloid, and the erythroid progenitors (2). The common lymphoid progenitor divides and differentiates into B cells, T cells, and NK cells. Activated by infection, B cells divide and differentiate into plasma cells; T cells differentiate into various types of effector T cells. The myeloid progenitor cell divides and differentiates to produce at least six cell types. There are three types of granulocytes – the neutrophil, the eosinophil, and the basophil; the mast cells, that reside in connective and mucosal tissue; the circulating monocyte, that gives rise to the macrophages resident in tissues; and the dendritic cells. The erythroid progenitor gives rise to erythrocytes and megakaryocytes (Fig. 2) (3). For more details, see Appendix 2.

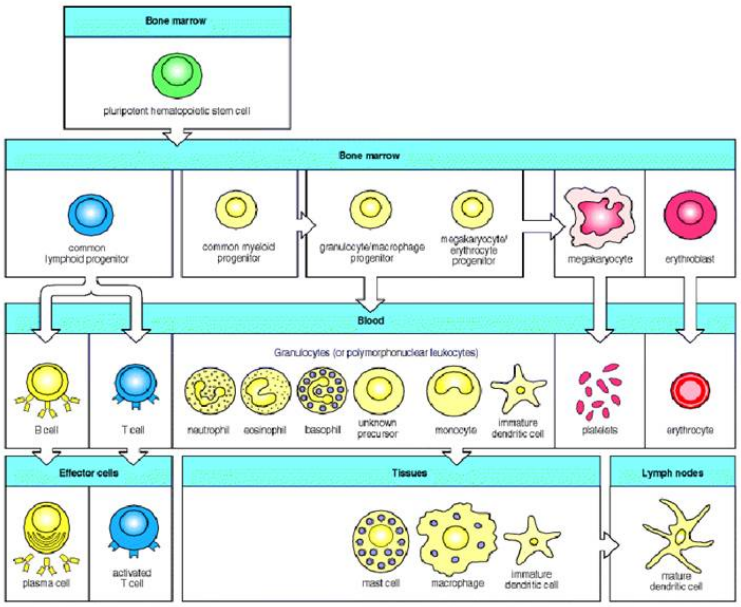

Fig. 2. From http://intranet.tdmu.edu.ua

1.2. The lymphoid tissues

B cells complete their maturation in the bone marrow. T cells leave it at an immature stage and complete their development in the thymus. The bone marrow and thymus are the primary lymphoid tissues. The secondary lymphoid tissues are adenoids, tonsils, lymphatic vessels, lymph nodes, appendix, spleen and Peyer's patch in the small intestine (Fig. 3.) (4).

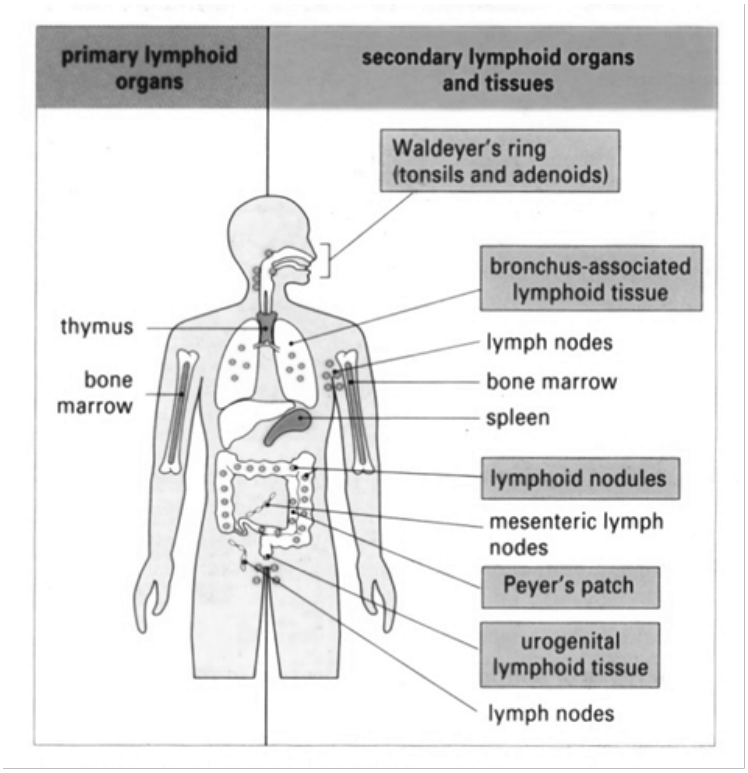

Fig 3. From http://intranet.tdmu.edu.ua

1.3. The complement system

The complement system is a part of the immune system that consists of more than 30 proteins produced in the liver. These proteins help in killing of pathogens by antibodies. The complement system activates biochemical pathways in which foreign cells are opsonized (coated) with complement proteins which weakenes or brakes their cell walls (5-6). The action of the complement system also attracts other immune cells such as *macrophages* and *neutrophils*, along with antibodies, to the site of infection (7).

2. Immune System Response

Through the evolutionary history, multicellular organisms have been infected by microorganisms. In response, animals and humans evolved to have a series of defenses

(Appendix 3). The mechanisms enabling recognition of microbial, toxic, or allergenic structures "can be broken down into two general categories: responses that are encoded by genes in the host's germ line and recognize molecular patterns shared both by many microbes and toxins that are not present in the mammalian host; and responses that are encoded by gene elements that somatically rearrange to assemble antigen-binding molecules with exquisite specificity for individual unique foreign structures." (8). The first set of responses represent the innate immune response; the second set works as an adaptive response.

In responding to microbial or viral attack, the immune system starts with innate immunity, whose mechanisms are fast and effective in stopping most infections at the early stage (9-11). The mechanisms of adaptive immunity are slow to start, but eventually become powerful enough to terminate almost all of the infections that escaped innate immunity (12). Adaptive immunity is an evolving process within a person's lifetime, in which each infection changes the make-up of that individual's lymphocyte population (13-15).

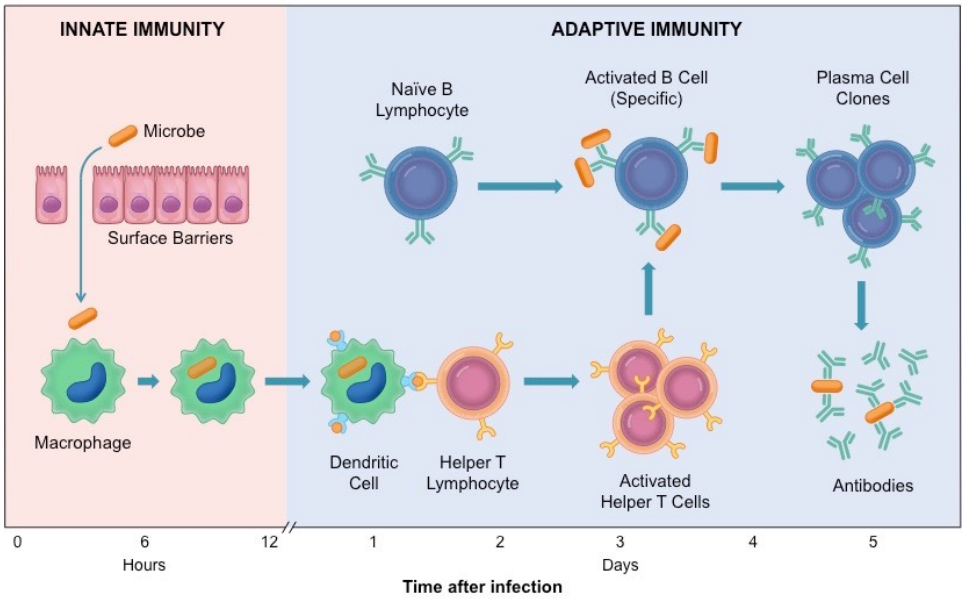

Fig 4. From https://ib.bioninja.com.au/standard-level/topic-6-human-physiology/63-defence-against-infectio/lymphocytes.html

Because the adaptive system is composed of small numbers of cells with the specificity for any individual pathogen, toxin or allergen, the responding cells must proliferate after encountering the antigen in order to attain sufficient numbers to mount an effective response against the microbe or the toxin (16). A key feature of the adaptive response is that it produces long-lived cells that persist in an inactive state, but that can re-express effector functions rapidly after another encounter with their specific antigen. This provides the adaptive response with the ability to manifest immune memory, permitting it to contribute prominently to a more effective host response against particular pathogens or toxins when they are encountered a second time (17).

At the same time when the immune system is eliminating pathological microbes and toxic or allergenic proteins, it must avoid responses that produce excessive damage of self-tissues or that

might eliminate beneficial, commensal microbes and sustaining tolerance toward human macromolecules (18, 19).

The innate and adaptive immune systems are often described as contrasting, separate arms of the host response; however, they usually act together, with the innate response representing the first line of host defense, and with the adaptive response becoming prominent after several days, as antigen-specific T and B cells have undergone clonal expansion. Components of the innate system contribute to activation of the antigen-specific cells. Additionally, the antigen-specific cells amplify their responses by recruiting innate effector mechanisms to bring about the complete control of invading microbes (20-22).

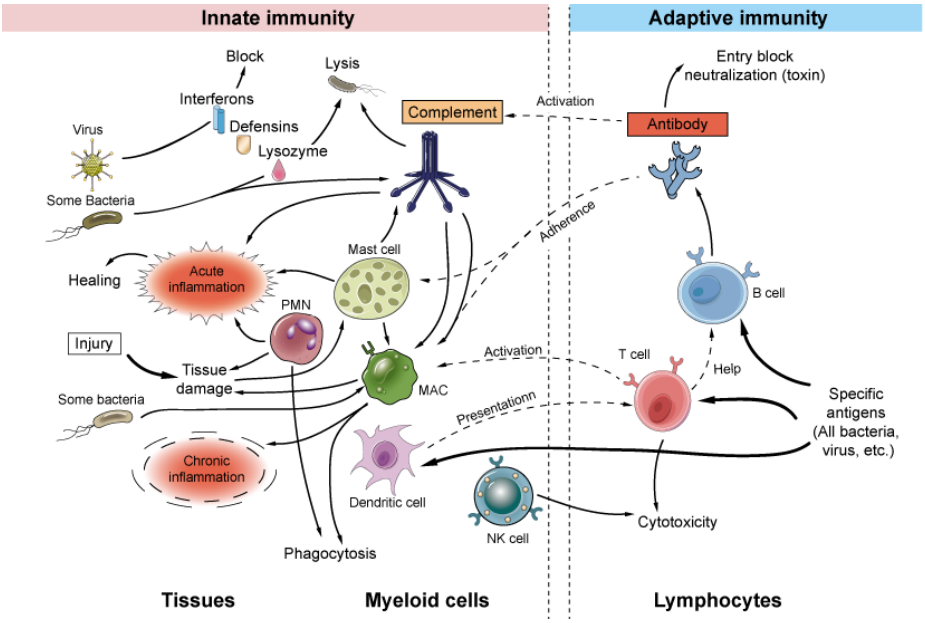

Fig. 5. From https://www.creative-diagnostics.com/innate-and-adaptive-immunity.htm

While the innate and adaptive immune responses are fundamentally different in their mechanisms of action, synergy between them is essential for a complete and effective immune response.

2.1. Innate immunity

Generally defined, the innate immune system includes all aspects of the host's immune defense mechanisms that are encoded in their mature functional forms by the germ-line genes of the host and allow to prevent entry of pathogens into the body through physical and chemical barriers (23); to avoid the spread of infections through the complement system and to remove pathogens through phagocytosis and cytotoxicity mechanisms (24); and to activate the adaptive immune response through the synthesis of several cytokines and antigen presentation mechanism to T and B cells of the adaptive immune system (25).

The successful defense mechanisms largely depend on its early interactions with innate immune cells, such as macrophages, dendritic cells (DCs), neutrophils and natural killer (NK) cells (26, 27). These immune cells express a variety of pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), Nod-like receptors (NLRs) and C-type lectin receptors (CLRs). These receptors are also involved in the initiation of various innate immune defense-associated cellular functions, such as phagocytosis, autophagy, apoptosis and inflammasome activation (Fig 6). (28-30).

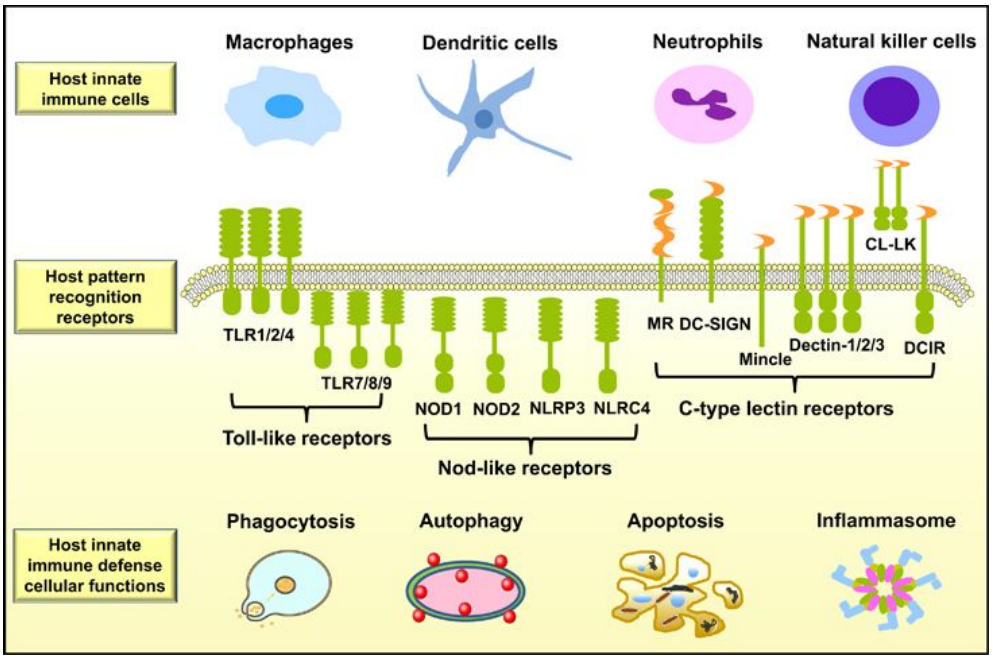

Fig. 6. From https://www.nature.com/articles/cmi201788#ref2

Another subgroup of white blood cells are natural killer cells (NK). NK cells are generally considered to be components of the innate immune defense because they lack antigen-specific cell surface receptors. NK cells have been shown in humans and mice to participate in the early control against virus infections, especially herpes virus infection (31), and in tumor suppression (32).

The complement system is an ancient and critical effector mechanism of the innate immune system, composed of >30 proteins found in the circulation and tissue, as it senses, kills, and clears infectious and/or dangerous particles and alerts the immune system to the presence of the infection and/or danger (33).

Upon activation, a series of proteolytic and protein-protein interactions occurs, resulting in the opsonization of invading pathogens or dangerous particles, recruitment of leukocytes to the site of infection or injury, and/or lysis of the pathogens (Fig. 7) (34, 35). Interestingly, an increasing number of reports have demonstrated a clear role for the complement system in the adaptive immune system as well (36, 37).

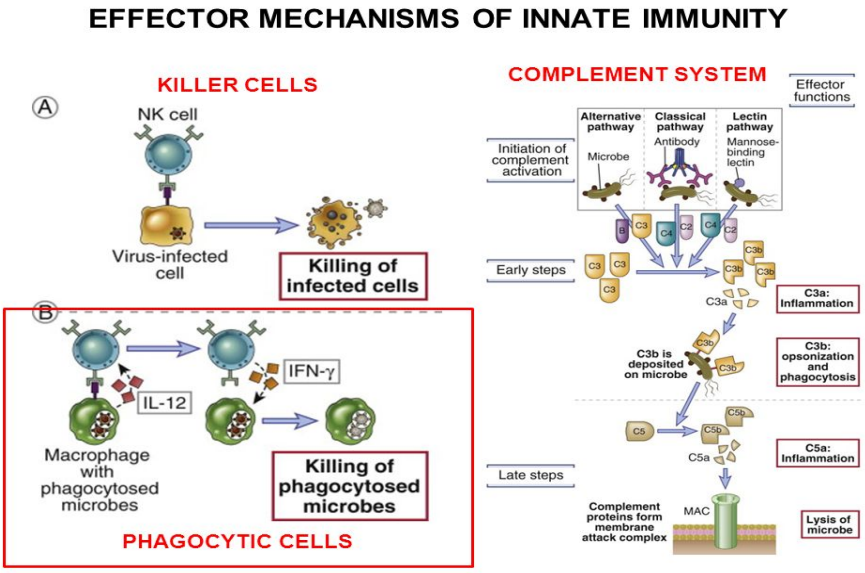

Fig 7. From https://slideplayer.com/slide/3430784/

2.2. Adaptive immunity

The adaptive immune response will utilize the ability of specific lymphocytes, that are generally the T and B lymphocytes, and their products (immunoglobulins and cytokines) to generate a response against the invaders and its typical features are:

- Specificity: as the triggering mechanism is a particular pathogen, or antigen (38)
- Heterogeneity: signifies the production of millions of different effectors of the immune response (antibodies) against millions of intruders (39)
- Memory: the immune system has the ability not only to recognize the pathogen on its second contact but to generate a faster and stronger response (40).

Adaptive responses are established primarily on the antigen-specific receptors expressed on the surfaces of T- and B-lymphocytes. Unlike the germ-line-encoded recognition molecules of the innate immune response, the antigen-specific receptors of the adaptive response are encoded by genes that are assembled by somatic rearrangement of germ-line gene elements to form intact T cell receptor (TCR) and immunoglobulin (B cell antigen receptor; Ig) genes (41). The assembly of antigen receptors from a collection of a few hundred germ-line-encoded gene elements permits the formation of millions of different antigen receptors, each with potentially unique specificity for a different antigen (Fig. 8).

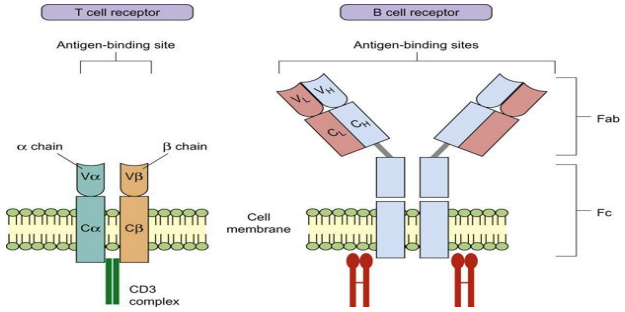

Fig 8. From https://doctorlib.info/medical/biochemistry/40.html

T cells

T cells recognize processed antigen via their antigen receptors, interacting with the antigen presented by MHC-bearing cells (42) (Fig. 9).

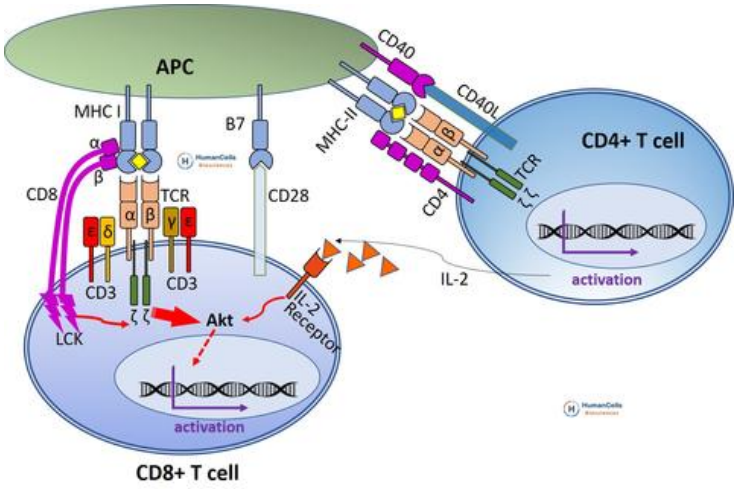

Fig. 9. https://humancellsbio.com/products/human-normal-peripheral-blood-cd8-cytotoxic-t-cells

This leads to the secretion of additional cytokines and the generation of effector functions such as the T cell help and the T cell-mediated cytotoxicity, brought about by the T helper and T cytotoxic subsets, respectively. Historically, T cell responses have been termed the cellular immune response (Fig. 10) (43, 44).

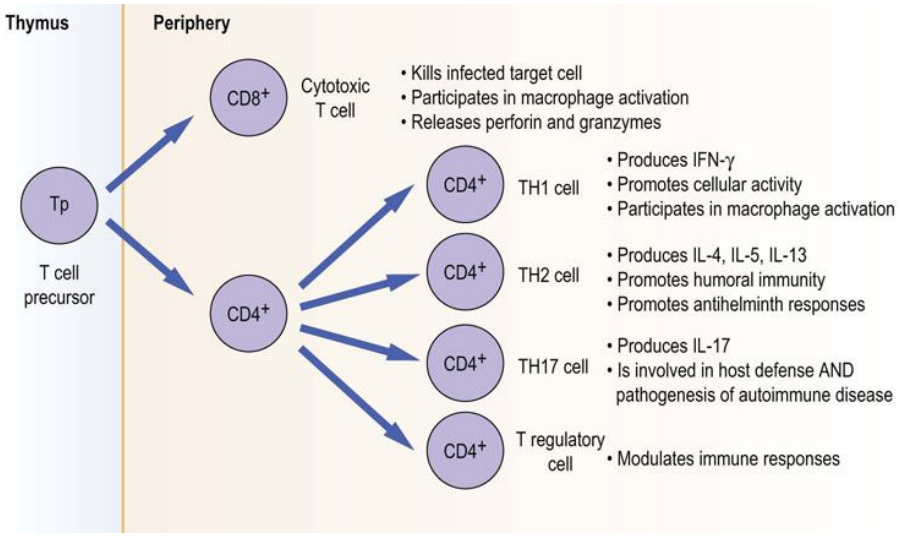

Fig 10. From https://doctorlib.info/medical/biochemistry/40.html

B cells

B cells recognize native antigen and secrete proteins, termed antibodies, which can bind directly to the antigen (45, 46). Historically, B cells and their antibody products have been termed the humoral immune response (Fig. 11).

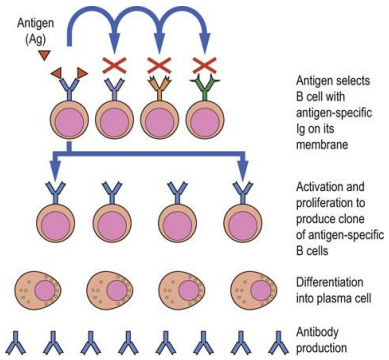

Fig 11. From https://doctorlib.info/medical/biochemistry/40.html

Summary of the adaptive immune response is presented in Fig. 12. APCs activate naive CD4 T cells, that in turn can activate B cells. Cytotoxic T cells kill infected target cells.

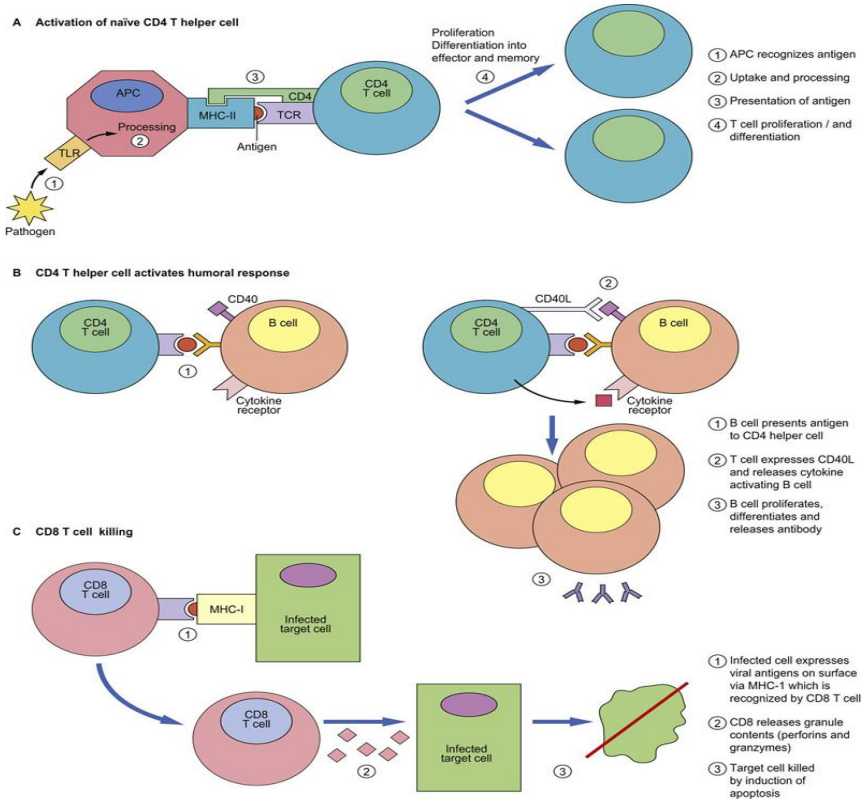

Fig 12. From https://doctorlib.info/medical/biochemistry/40.html

3. Autoimmune Response

Epidemiological studies provide increasing evidence for the rise in the prevalence of immune-related disorders including autoimmune and allergic diseases in Western countries (47). It is predicted that the incidence of chronic inflammatory disorders, particularly autoimmune diseases, such as type 1 diabetes, Crohn's disease, rheumatoid arthritis and multiple sclerosis, will grow even more rapidly during the next several decades (47-49).

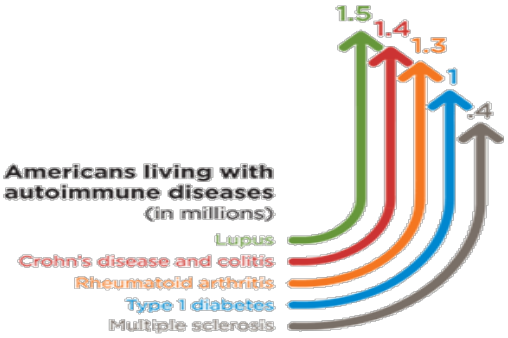

Fig. 13. From https://www.benaroyaresearch.org/what-is-bri/disease-information/autoimmune-diseases

More than 80 have been identified, a considerable number with similar symptoms, as the presence of autoreactive T and B cells, and a complex pathogenesis of multifactorial etiology, whereas genetics and environmental factors together are responsible for disease onset (50-52). Because failure of self-tolerance underlies the broad class of autoimmune diseases, this process has been extensively studied (53). Inflammation is the classic sign of autoimmunity although how this impacts an individual is determined by which part of the body is affected (52).

Simply, the process of autoimmunity is as follows: first, the self-antigens drive the reaction that obviously cannot be eliminated. This problem is compounded by the emergence of new antigenic epitopes as a result of tissue damage and alterations in self-proteins, the phenomenon known as epitope spreading. Epitope spreading sets up a vicious cycle in which newly created antigenic epitopes activate more lymphocytes of different specificities and recruit these cells into the reaction, leading to more tissue damage and the emergence of even more novel epitopes targeted by autoreactive lymphocytes. Second, the autoimmune response creates an inflammatory environment in which multiple immune cells interact to produce cytokines and other mediators that amplify the reaction, creating an inflammatory loop (54).

3.1. Causes of autoimmunity

Autoimmune diseases, like many other complex disorders, are believed to arise from a combination of genetic and environmental factors. Also, "one potential answer is that vulnerability to immune-mediated disease is simply the price we must pay for the potent and

rapid defense against infection." (Andrea Graham, an evolutionary biologist at Princeton University) (55).

A simple hypothesis is that polymorphisms in various genes result in the defective regulation or reduced threshold for lymphocyte activation, and environmental factors initiate or enhance activation of self-reactive lymphocytes that have escaped control and reacted against self-constituents.

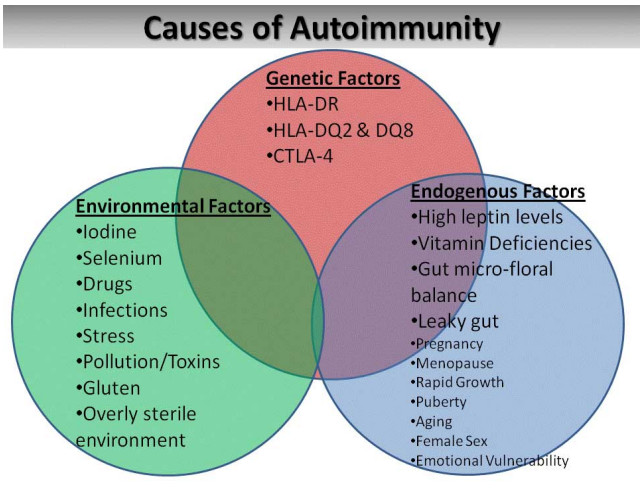

Fig 14.

Genetic factors

It is difficult to define the role of most of the polymorphisms in the breakdown of tolerance to self-antigens and the development of autoimmunity. For instance, of all the genes associated with autoimmune diseases, the strongest associations, and the ones that have been known for the longest time, are with the particular HLA complex (The major histocompatibility complex (MHC) is a set of cell surface proteins essential for the acquired immune system to recognize foreign molecules in vertebrates. The human MHC is also called the HLA (human leukocyte antigen)). (56). However, it is still not definitively known how different HLA alleles contribute to any autoimmune disease. It is unlikely that a disease-associated allele is especially efficient at displaying the autoantigens targeted by self-reactive T cells because most HLA alleles are capable of presenting self-antigens even in healthy individuals. Additionally, most healthy individuals have autoreactive T cells that escape thymus deletion (57, 58). Explaining gene involvement of the pathogenesis of autoimmune diseases is much more overwhelming for other polymorphisms than those for HLA alleles.

Environmental triggers

For almost every autoimmune disease there are clinical observations suggesting that autoimmunity is triggered by some sort of infection and the immune response that it provokes (59, 60). Multiple theories have been proposed to explain this association, including epitope spreading, antigenic complementarity, and excessive innate/pattern recognition receptor activation (61). Additionally, systemic infections have been reported to trigger relapses in

patients with relapsing-remitting MS through enhancement of myelin-specific T cell responses (61). Another example of the association of infections with autoimmunity is that of periodontal infections and rheumatoid arthritis (62).

A well-recognized nonmicrobial environmental trigger is UV irradiation for cutaneous lupus. A possible explanation for this connection is that UV radiation induces apoptotic death of many cell types and increases the burden of nuclear antigens, especially if the dead cells cannot be efficiently cleared (63).

Vaccination and autoimmunity

The first report on a fundamental correlation between several vaccines (e.g., diphtheria, tetanus toxoids, oral polio vaccines) and autoimmune disorders (e.g., Guillain–Barre syndrome, type 1 diabetes, and multiple sclerosis) was published in 1994 (64).

Many autoimmune disorders (rheumatic, endocrinological, and gastrointestinal diseases) have increased significantly over the last 30 years and affect more than 5% of individuals worldwide at the age of vaccination programs, which is quite different compared to the spontaneous autoimmune disease incidence (65-68). These observations raise the problem whether vaccination should be recommended or avoided in autoimmune risk patients (69).

Several studies suggest that a vaccine component (inactive viral/bacterial agent or attenuated living microorganism) or a wild superimposed infectious agent can induce autoimmune diseases in people with genetic predispositions (70-74).

For more information regarding underlying mechanism following vaccination and review cases of autoimmune diseases that have been correlated with vaccination" see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5607155/.

3.2. Autoimmune mechanisms

Understanding the autoimmune mechanism continues to be a significant challenge. One problem is that various types of autoimmunity are evident in healthy people; a second is that once cell and tissue distraction has begun, it will often initiate further autoimmune responses that are consequences, but not causes, of the disease (54, 65, 78).

The adaptive immune system's T cells and B cells usually keep the balance between reacting toward foreign antigens and avoiding the attack on "self" (75, 76). Both T cells and B cells contain subsets of regulatory cells with an immunoregulatory cytokine profile on the one hand and effector cells that produce antibodies or secrete pro-inflammatory cytokines on the other (86-88).

Several mechanisms were proposed (59, 60, 75, 78), but it is unknown whether a specific dysfunction of the immune regulatory mechanism or all these dysfunctions (Fig. 15) are needed simultaneously to develop an autoimmune response (80, 83, 84). Let us look closely at each of the factors presented below.

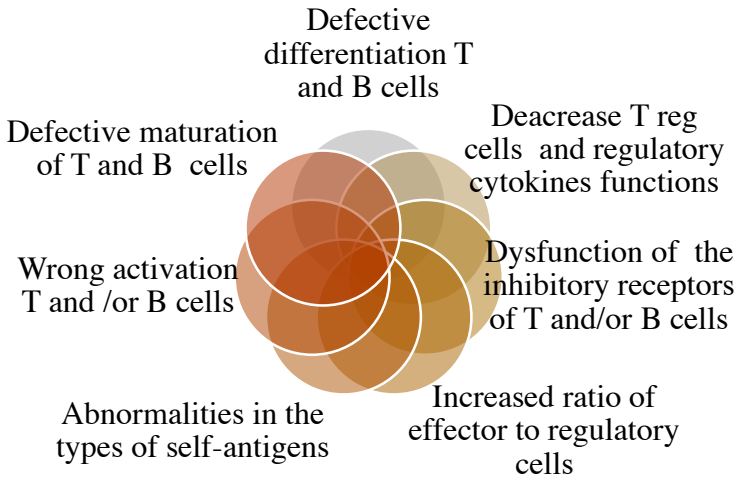

Fig. 15.

Autoreactive T cells

Thymus selection of T-cell range provides the foundation for immunological self-tolerance. With age, the healthy thymus tissue is first replaced by tissue containing mature T cells and subsequently by fat. By age 50 the capacity to produce new T cells is reduced by 20%, and by age 60 it is practically gone. When the thymus can no longer satisfy the need for T cells, the immune system compensates by expanding the population of existing T-cell clones and altering the properties of some T cells so they become less susceptible to apoptosis (80, 84).

During T-cell development, negative selection removes T cells that respond to self-peptides presented by the MHC molecules of thymus cells. Even when the negative selection in the thymus is working normally, some autoreactive T cells escape deletion and enter the peripheral circulation (Fig. 16.) (75, 76, 80).

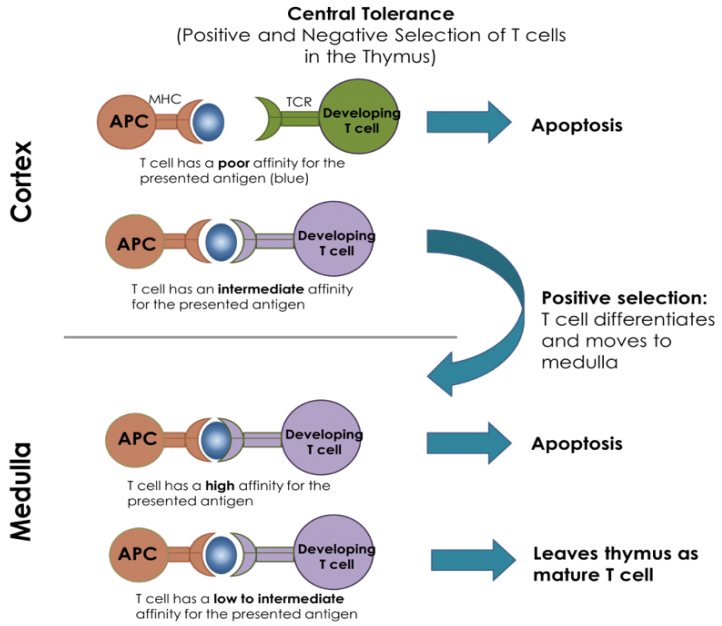

Fig. 16. From https://sites.tufts.edu/transplants/answer/

If these cells encounter healthy tissue expressing the MHC complex at the surface, they usually will not be activated, because tissue cells do not regularly express the specific B7 co-stimulators that are essential for the activation of naive T-cells. On the the other hand, this matter of presentation can lead to tolerance and can induce T cells activation (80, 84).

Autoreactive B cells

During B cells maturation in the bone marrow, clonal deletion and inactivation of self-reactive B cells prevent the emergence of cells with antigen receptors that bind common molecules of human cells surfaces of plasma. This process does not prevent the appearance of B cells with specificity for numerous other self-antigens that are not present in the bone marrow or plasma (90-92). There is also the mechanism of arrest and death of autoreactive B cells in the secondary lymphatic tissue via recognition of abnormal B cells by contact with CD4 T cells that lead to apoptosis and elimination of the autoreactive B cells. The lack of normal function of this mechanism can also be cause of the B cells tolerance (93-96).

Defective differentiation of T and B cells

Current data shows that autoimmune responses have abnormalities in a structure or function of Th1-type or Th17-type CD4 T cells, suggesting that defective regulation of either T cell differentiation or activation is an underlying response (77, 78).

Decrease T regulatory (Treg) cells functions

The central role of Treg cells in controlling all aspects of the CD4 T cell response, and the observation that the genetic absence of T_{reg} cells leads to the development of an autoimmune state suggests that disturbed Treg function may be underlying in all autoimmune and atopic diseases (80).

Studies have shown that patients with autoimmune diseases have a dysfunction of Treg cells (80, 81). Usually, Treg cells that have a high surface expression of a particular type of receptor on the surface of the cell what is known as CD25+ and Foxp3. (80, 82), and mutation or deletion of Foxp3 lead to autoimmunity in humans and mice. (85, 86).

The primary function of Tregs is to inhibit activated T cells and dendritic (DCs) (72, 83, 84). The current mechanism for Treg-mediated inhibition (83, 87) can be divided into three main classes: (1) cell-cell contact; (2) inhibitory cytokine secretion; and (3) competition. Tregs can inhibit DCs through mechanisms 1 and 2, and T effector (Teff) cells through mechanisms 1, 2, and 3. In the cell-cell contact model, Tregs directly bind to the DCs or effector T cells through receptor-ligand interactions, such as peptide-major histocompatibility complex MHCII-TCR and CTLA4/B7-1, and mediate inhibition, cytolysis, or apoptosis of the cells by delivering suppressive factors, such as cyclic adenosine monophosphate and transforming growth factor-beta (TGFβ)1 via gap junctions (83, 88, 89) or by membrane-bound TGFβ. Next, in the inhibitory cytokine secretion model, Tregs upon activation can directly secrete IL-10, TGFβ, and IL-35 that mediate suppression of DCs and Teff cells (97-99). Last, in the competition model, Tregs either compete for cytokines (such as IL-2), which leads to cytokine-deprived cell apoptosis (100-102) or may

bind to DCs through CTLA4/B7-1 interaction, thereby decreasing the amount of co-stimulatory molecule (B7-1/2) available to bind CD28 on naive T cells, thus inhibiting T cell activation. It is not known whether all these mechanisms are needed simultaneously to apply Treg-mediated inhibition (103).

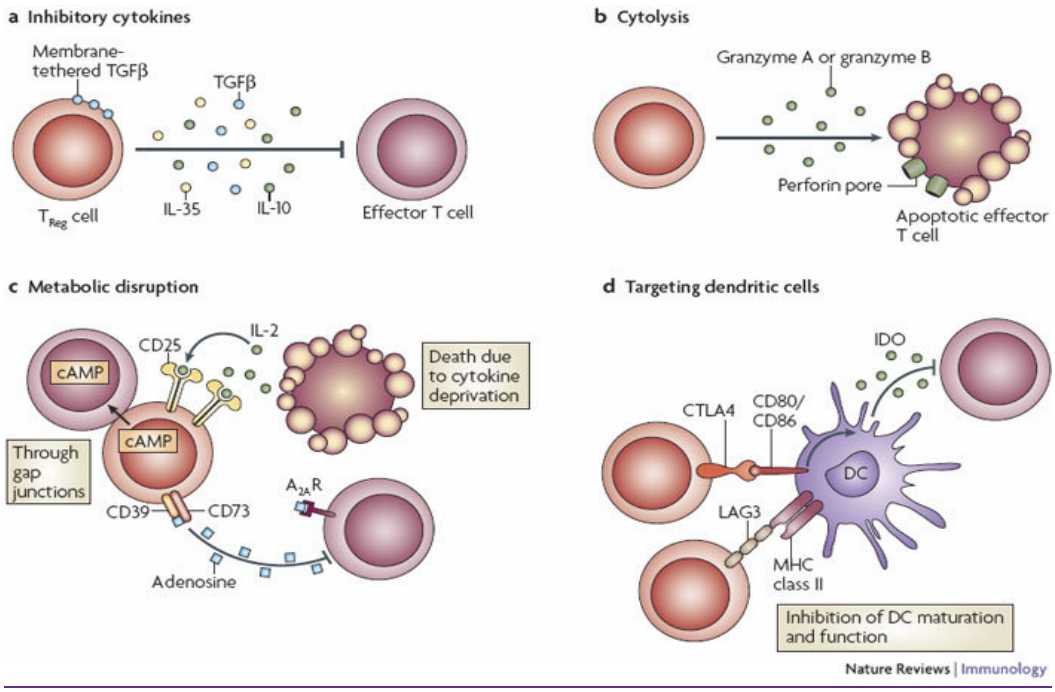

Fig. 17. From https://www.researchgate.net/

Tregs also inhibit B cell antibody production by secreting inhibitory factors IL-10, TGFβ, and granzymes, or by binding through CTLA4/B7-1 interaction (88). It has been shown that increased presence of Tregs decrease the production of antibodies, whereas their absence increases production (104-106). Recently, a new subset of Tregs called T-follicular regulatory cells (Tfregs) has also been shown to inhibit B cell activity by directly entering the germinal center and secreting inhibitory cytokines (107,108). Tfregs may also inhibit B cell activity by disrupting the interaction between T cells and B cells (108).

Dysfunction of the inhibitory receptors of T and/or B cells

In addition to Tregs, other mechanisms that have been proposed to limit autoimmune reactions include the activation of various inhibitory receptors. For example, following activation, T cells begin to express two receptors of the CD28 family, CTLA-4 and PD-1, which function to suppress various immune responses (109, 110).

B lymphocytes also express inhibitory receptors, notably CD22 and FcγRII (111, 112). To what extent these pathways and their deficiencies contribute to B cell autoimmunity in humans has also not been established yet.

Increased ratio of effector to regulatory cells

It also appears that a decrease in the number of functional Tregs, or resistance of effector T cells to regulation, play a role in the initiation of human autoimmune diseases (113). Once a pathologic immune reaction starts, there is an increased accumulation of effector T cells in the tissues that are the main drivers of the autoimmune response. This may be accompanied by a relative decline in Treg numbers, or increased amounts of dysfunctional Tregs (114-116). This data leads us to believe that therapeutic strategies to reset the effector T cell/Treg balance are an exciting new approach to treat autoimmune diseases.

Abnormalities in the types of self-antigens

There is experimental evidence that autoimmune reactions are associated with abnormalities in the types of self-antigens that are displayed in the immune system. For instance, abnormal presentation of extracellular derived peptides or denatured proteins by antigen-presenting cells (APCs) can give rise to peptide/MHC complexes that are distinct from those generated typically inside APCs and are thus capable of activating potentially pathogenic T cells (117). This unconventional activation of potentially self-reactive T cells may arise from either the recognition of conformational isomers of peptide/MHC or from a differential binding register of a peptide within the groove of the MHC molecule (118, 119).

Receptors dysregulations

After an immune response is completed, the majority of antigen-responsive cells must be removed in order to prepare for the next immune challenge faced by the organism. Removal of effector cells without causing inflammation and tissue damage is best achieved by inducing the unwanted cells to undergo apoptosis. Molecules of the TNF family provide strong signals for the apoptotic programmed cell death pathway. TNF, signaling through the type I TNF receptor, induces death in tumor cells and at sites of ongoing inflammation. An alternative apoptosis-inducing receptor, Fas, is more specifically involved in regulatory apoptotic events. Fas, for example, transmits necessary apoptotic signals during thymus T cell selection (120). It also contributes to the regulation of autoreactive cells in the periphery. Defects in Fas or in its ligand, FasL, result in autoimmune disorders with prominent lymph proliferation (121).

4. Approach to Autoimmunity

4.1. Decrease the exposure to environmental factors

One approach to decrease accidental autoimmune reactions is to diminish the exposure to environmental factors (122-124) that are known to contribute to autoimmunity. Some of those are listed below:

- exposure to solvents, which are used in thousands of products, including paint thinners, cleaning supplies, and nail polish (125, 126)
- smoking (127)
- exposure to fine particles of crystalline silica, a primary component of quartz, granite, and many other minerals (128)
- eating gluten, present in wheat and some other grains (129-132)
- taking certain supplements containing L-tryptophan, an essential amino acid used as a dietary supplement (eosinophilia-myalgia syndrome) (133-136)
- consumption of diets rich in fat and salt (137-141).

4.2. Use a specific dietary protocol

Research data indicate that nutritional factors, such as vitamin D (142, 143), vitamin E (144-148) and omega-3 fatty acids (149-151) have the capability to potentially modulate autoimmune responses and inflammation. But the 'single nutriant' approach has so far prevailed in experiments on nutrition and autoimmunity. Recent advances in nutritional physiology suggest that this approach may be simplistic and a more effective influence might be achieved by a food-oriented intervention (152-158) and normalizing intestinal microbiota (159-170).

Dr. Sarah Ballantyne developed a compelling autoimmune protocol that helps maximize the potential therapeutic value of healthy foods, as a positive influence on immune regulation, gut health, hormone regulation and removing proinflammatory stimuli from the diet: https://www.thepaleomom.com/start-here/the-autoimmune-protocol/.

4.3. Use of certain herbs and nutrients

There is a growing interest to use herbal medicines as multi-component agents to modulate the complex immune system in the prevention and treatment of immune-related diseases (171). Some of these herbs include: Astragalus, Artemisia, Reishi, Ashwagandha, Nettle, Rehmannia, Chinese Skullcap, Boswellia. Phytochemicals such as flavonoids, polysaccharides, lactones, alkaloids, diterpenoids and glycosides have been reported to be responsible for the plants immunomodulation properties (172, 173).

- **Astragalus** (*Astragalus spp.*). *Astragalus* could affect the adaptive immune response. An aqueous extract of *astragalus* activated $CD4^+$ and $CD8^+$ T cells of humans without influencing proliferation (174). In addition, the ethanol extracts of *astragalus* selectively alter Th1/Th2 cytokine secretion patterns of $CD4^+$ T cells through enhancing the IL-4 and IL-10 levels in Th2 cells and reducing the levels of IL-2 and IFN-γ in Th1 cells (175 -177).
- **Sweet Anni** *(Artemisia annua)*. In traditional Chinese medicine, *Artemisia annua* has been widely used to treat autoimmune diseases such as Systemic Lupus Erythematosus (SLE) and RA. Artemisia may be useful in the treatment of autoimmune diseases via an immune-modulatory effect. In addition, many healthcare practitioners are using Sweet Anni as adjunctive care for borreliosis due to the spirochete that is linked to the development of Lyme disease, and several other co-infections accompanying Lyme and other tick-borne illnesses (178, 179).

- **Licorice** (*Glycyrrhiza glabra*). Current studies demonstrate that licorice, widely used in the herbal medicine for ages (180), could increase the induction of T regulatory cells *in vitro* and *in vivo* (181, 182). These findings suggested that the promotion of regulatory T cell induction could be an underlying mechanism of licorice to modulate an immune response. It is an immune amphoteric (both stimulating immune response in low immune states and exerting an immunosuppressive in hyper-immune/autoimmune states) and can be useful for autoimmune disorders (Lupus, Scleroderma, Crohn's disease, R.A.) as well as immune deficiency conditions (cancer, HIV) (183).
- **Reishi** (*Ganoderma spp*.). Reishi mushroom is a true "amphoteric" herb, which can upregulate or downregulate the immune system as needed. Reishi mushroom is rich in polysaccharides, immune-modulating proteins, and steroidal saponin glycosides that influence the adrenal-hypothalamic-pituitary axis feedback loop, which regulates inflammation (184, 185). An amphoteric protein isolated from Reishi (called Ling Zhi-8) was shown to be both mutagenic (causing white blood cells to multiply) and immunosuppressive (reducing TNF-alpha and the formation of antibodies) in autoimmune diseases (186).
- **Ashwagandha** (*Withania somnifera*). In one study, the extract was shown to significantly suppress lipopolysaccharide-induced production of pro-inflammatory cytokines TNF-alpha, IL-1beta and IL-12p40, but had no effect on IL-6 production at the protein and transcript level (187). Ashwagandha is an immune amphoteric, both stimulating the immune response in low immune states and exerting an immunosuppressive action on B and T cell activity in hyper-immune/autoimmune states (188, 189).
- **Rehmannia** (*Rehmannia glutinosa*). Rehmannia has shown promise in bringing balance to aggressive autoimmune states. Studies have shown that this herb possesses both immune-enhancing and immune-suppressant effects. Modern pharmacological research has isolated various components in *Rehmannia*, which may be responsible for its adrenal tonifying, immune-modulatory, and anti-inflammatory effects (190-192).
- **Chinese skullcap** (*Scutellaria baicalensis*). Chinese skullcap is one of the most widely used herbs in oriental medicine. It has a wide range of therapeutic effects (including anti-inflammatory, anti-cancer, antiviral, anti-bacterial and amphoteric effects) on the immune system. It shows anti-inflammatory effects by reducing the expression of nitric oxide (NO), NOS (iNOS), Cyclooxygenase2 (COX-2), Prostaglandin E2, NFkB, as well as inflammatory cytokines, such as IL-1, IL-2, IL-6, IL-12 and TNF-alpha (193, 194).
- **Boswellia** (*Boswellia serrata*). Boswellia extract has been shown to inhibit Th1 cytokines and promotes Th2 cytokines, which helps to reverse the imbalance of Th1 and Th2 that increases inflammation (195).
- **Green tea** (Camellia sinensis). One of the most active polyphenol of green tea is epigallocatechin-3-gallate (EGCG). It has been widely reported for its *in vitro* and *in vivo* chemopreventive, anti-angiogenic, anti-invasive, anti-proliferative, anti-inflammatory, and antioxidant effects (196-198) and it has been associated with increased Treg populations in lymphoid tissues and in the central nervous system, as well as impacting the development of CD4+ T cell subpopulations differently (199). This may explain it's beneficial anti-inflammatory effects for patients with autoimmune disease.
- **Nettle** (*Urtica dioica*). Data has shown that nettle leaf has the ability to alter the genetic transcription of nuclear factor kappa beta (NFkB), thereby decreasing inflammation of synovial tissue in the joints. Nettle leaf extract also had a suppressive effect on the

development of dendritic cells that stimulate T-cells to release inflammatory chemicals (200, 201).

- **Vitamin D** – Multiple studies have found that having proper levels of Vitamin D will support healthy T regulatory cell function with functional CD25+ expression (142, 143).
- **Curcumin extract** – Curcumin is an active component of the spice, turmeric *(Curcuma longa)*. It has a remarkable anti-inflammatory profile and has been shown to significantly increase T regulatory populations (202-204).
- **Specific Strains of Probiotics** – This is a complicated topic, and different strains of probiotics appear to have different effects when it comes to stimulating the immune system. A highly detailed study found that S. thermophilus 1342, Lb. casei 290, Lb paracasei 292, S. thermophilus M5, Lb. delbrueckii ssp. bulgaricus 11842, B. lactis BB12, Lb. rhamnosus G5434, Lb. rhamnosus 5434, Lc. lactis , Bifidobacterium spp. (BL1941, BB12 and BB99), and Lb. salivarius 5248, all demonstrated a significant ability to induce CD25+ T regulatory cells, potentially beneficial for those with autoimmune diseases (205).

5. ETI Formulations to Support Immune System Homeostasis and Increase Self Healing Opportunities

The following specific combinations of ETI formulas are suggested for different immune system-related conditions, with the understanding that practitioners should take the liberty to fine-tune dosages and periodicity of the client's intake, as well as to combine different formulas to create a personalized approach to the individual client to support his/her immune system.

5.1. Support the immune system during temporary acquired immune deficiencies

Formulation and Dosage:
Combine Chronic Immune (5 drops), Longevity (5 drops) and Detox (5 drops) in 2-4 oz. of water. Drink 2-3 times per day up to 2-3 weeks.
Description:
Might be helpful with immune weakness due to drug intake, chronic illness, after multiple infections, as well as deficiencies caused by smoking, alcohol, poor nutrition or due to the body's increased toxic load.
Precautions:
No precautions or side effects, if used within the recommended dosages.

5.2. Support the immune system during stressful conditions

Formulation and Dosage:
Combine Chronic Immune (10 drops), Stress Relief (5 drops) and Adrenal Support (5 drops) in 2-4 oz. of water. Drink 2-3 times per day up to 10 -15 days.
Description:
Maybe helpful with prolonged stressful conditions and frequent cold or flu infections.
Precautions:

No precautions or side effects, if used with the recommended dosages.

5.3. Support the immune system with compromised GI functions

Formulation and Dosage:
Combine Chronic Immune (10 drops), GI Aid (5 drops), Detox (5 drops) and Healthy Mouth (5 drops) in 2-4 oz. of water. Drink 3 times per day after food intake up to 2 weeks.
Description:
May support immune system when malabsorption and maldigestion symptoms are present.
Precautions:
Increase the amount of water up to 4-6 oz. preparing the formula for individuals with GI sensitivity to minerals.

5.4. For immune dysfunctions associated with unresolved inflammatory states

Formulation and Dosage:
Combine Chronic Immune (5 drops), Acute Immune (5 drops) and Vital360 (5 drops) in 2-4 oz. of water. Drink 3 times per day and continue up to 2 weeks.
Description:
May be helpful with the spectrum of the immune system functions related to an inappropriate inflammatory response.
Precautions:
Increase the amount of water up to 4-6 oz. preparing the formula for individuals with GI sensitivity to minerals.

5.5. Support healthy teeth and gums

Formulation and Dosage:
Combine Healthy Mouth (10 drops) and Vital360 (10 drops). Add several drops to your toothbrush and gently apply to your gums and teeth.
Description:
The following combination effectively supports your dental cavity against pain and inflammation after dental procedures, as well as with a variety of conditions associated with gum problems. You may want to add it to your personal dental-care regiment, too.
Safety:
Safe within the recommended dosages.

5.6. A formulation against common allergic reactions

Formulation and Dosage:
Combine Rose Absolute (5 drops), Acute Immune (5 drops), Stress Relief (5 drops), and GI Aid (5 drops) in 2-4 oz. of water. Drink 3 times per day after food intake up to 1 week or whenever it seems necessary.
Description:

May be helpful with allergic reactions such as sneezing,run ny nose, sniffling, and swelling of your nasal passages from indoor allergens such as home dust or dust associated with pets, or outdoor allergens such as pollens or molds.

Precautions:

No precautions or side effects if used within the recommended dosages.

5.7. Support health of bones and joints

Formulation and Dosage:

Combine Vital360 (10 drops), Chronic Immune (10 drops), and Rejuvenation (3-5 drops). Drink 2-3 times per up to 1 week or whenever it seems necessary.

Description:

The following combination might effectively support against pain and inflammation of the joints.

Safety:

Safe within the recommended dosages.

5.8. Formulation against seasonal allergies

Formulation and Dosage:

Combine Seasonal Calm (10 drops) and Chronic Immune (5-10 drops) in 2-4 oz. of water. Drink 3 times per day up to 1 week or whenever it seems necessary.

Description:

Maybe helpful with seasonal allergic reactions to pollens and other substances.

Precautions:

No precautions or side effects if used within the recommended dosages.

5.9. Systemic support in decreasing a low-level state of inflammation

Formulation and Dosage: Combine Master Brain (5-10 drops), Vital360 (5 -10 drops), Adrenal Support (3 drops) and Stress Relief (3-5 drops) in 4-6 oz. of water. Drink 2-3 times per day up to 2 weeks.

Description:

Relaxation and pleasant experiences appear to reduce inflammatory responses, promote normalization of neuroendocrine status and allow humoral and cellular elements of the immune system to function correctly, as well as to decrease susceptibility to allergy, infection and neurogenic inflammation.

Precautions:

No precautions or side effects, if used within the recommended dosages.

5.10. Support aging of the immune system

Formulation and Dosage:

Combine Chronic Immune (5 drops), Anti-Aging (5 drops) and Thymus (5 drops) in 2-4 oz. of water. Drink 2-3 times per day up to 2-3 weeks.

Description:

Recommended to use after the age of 50-55 when the immune system decreases its strength and precision of functioning.

Precautions:

No precautions or side effects, if used within the recommended dosages.

5.11. Future ETI Formulas to Balance the Immune System Response

ETI and VFT are continually working to improve and/or bring new formulas to our customers' that show effectiveness in supporting the body's energy field, as well as of the immune systems homeostasis. Our new Autoimmune Modulator formula will be presented in September-October 2019.

Appendix 1. Glossary of items

- **Affinity** The strength of binding between two biomolecules.
- **Affinity maturation** The process by which sequential rounds of mutation and selection increase the affinity in which antibodies bind free antigen.
- **Alleles** Different structural variants of the same gene; produces slightly different versions of a protein.
- **Amino acid** Fundamental building block of protein. Our genes can code for 20 amino acids.
- **Antibodies** Soluble proteins, produced from B-cells by rearrangement of their B-cell receptor. Antibodies bind to their targets with very high affinity and therefore specificity.
- **Antigen** A structure recognized by the adaptive immune system.
- **Antigen-presenting cell (APC)** A cell that presents antigen to T-cells.
- **Apoptosis** Process of cell suicide. Carried out by a proteolytic cascade.
- **Autoimmune disease** Disease caused by the immune system attacking normal tissues as if they were infected.
- **Autoinflammatory** Disease state that arises through the uncontrolled activation of the innate immune system.
- **Autoreactive** Reactivity to a component of the self.
- **B-cell** Lymphocyte that develops in the bone marrow (hence B) and then moves to secondary lymphoid tissue, where it may become an antibody-producing cell.

- **B-cell receptor (BCR)** The receptor on B-cells that binds free antigen. Incorporated into secreted antibodies that therefore have the same binding specificity as the BCR.
- **Basophils** Granulocyte cells that are stained by basic dyes.
- **Biologics** Complex molecular structures (such as antibodies) adapted to use as drugs.
- **Bone marrow** Found inside bones. In adults, most cells of the immune system start life in the bone marrow, going through a number of different stages before they are released into the blood.
- **Caspases** Family of enzymes that digest proteins.
- **CD4** Cell-surface protein marking T-helper cells.
- **CD8** Cell-surface protein marking cytotoxic T-cells.
- **Cell membranes** Cell membranes contain the internal cellular environment. They control signals in and out of the cell. Many specific structures (receptors) that span the membrane are devoted to these processes.
- **Clotting** Complex biochemical process that arrests the flow of blood in the event of vessel injury.
- **Complement** Part of the innate immune response, a family of proteins that amplify immune responses and kill bacteria.
- **Co-stimulation/co-inhibition** Signals that modulate the response of lymphocytes triggered through their antigen-recognizing receptors.
- **Cytokines** Cytokines are a family of ligands (usually soluble), produced from one cell and signaling to another. The information that they provide to receiving cells regulates growth and effector function.
- **Cytoplasm** The internal environment of the cell.
- **Cytotoxic** Cell killing.
- **DNA** Deoxyribonucleic acid. Used to store the genetic code in the nucleus.
- **Effector function** A process by which cells alter the environment around them.
- **Enzymes** Proteins that work as catalysts, speeding up chemical reactions without themselves being altered.
- **Eosinophils** Granulocyte cells that are stained by acidic dyes.
- ***Escherichia coli*** Bacterium found in the normal microbiome and widely used in molecular biology.
- **Fab fragment** The head of the antibody containing the antigen recognizing parts of the immunoglobulin.
- **Fas/FasL** Receptor-ligand pair that induces cell suicide (apoptosis).

- **Fc fragment** The tail of an antibody. It defines how the antibody functions.
- **Gain-of-function mutations** A usually dominant mutation that exaggerates the normal activity of the affected gene, causing a new cellular phenotype.
- **Gene** The genetic instructions that specify the amino acid sequence of an individual protein.
- **Granulocytes** White blood cells containing granules of chemicals such as histamines that can be released rapidly on stimulation.
- **Granzyme** Enzyme that induces cell suicide (apoptosis).
- **Histamines** Soluble inducer of an inflammatory response. Derived from the amino acid histidine.
- **HIV** Human immunodeficiency virus. Produces the infection that causes AIDS.
- **Human leucocyte antigen (HLA)** Alternative name for MHC in humans. Matching is essential for organ transplantation.
- **Humoral** Referring to antibody/B-cell-mediated immunity.
- **Hybridomas** Immune cells immortalized by fusion with a tumorous cell line, which provides self-replicating source of cells that, for example, secreted a single type of antibody.
- **IL-1, IL-6, IL-17** Cytokines that cause inflammation.
- **Immunoglobulin (Ig)** Antibody proteins found in tissue fluids and the circulation.
- **Immunoglobulin superfamily** Large family of proteins related structurally by containing one or more Ig domains or folds.
- **Immunosuppression** A reduction in immune responses. Associated with an increased risk of infection.
- **Inflammasome** Cytoplasmic complex whose assembly stimulates the release of inflammatory cytokines.
- **Innate immune system** Immune system using receptors that recognize early signs of infection and respond rapidly to limit spread and promote adaptive immune responses.
- **Interferon γ** A cytokine that stimulates macrophage activation.
- **Isotype** Types of antibody; defined by the antibody tail (the Fc fragment).
- **Leucocytes** White blood cells.
- **Leukotrienes** Soluble inducers of an inflammatory response.
- **Ligands** Ligands are the partners of receptors. They bind specifically, commonly initiating the transmission of signals across cell membranes. They can be soluble or bound to the cell surface.

- **Lymph node** Specialized structure that coordinates interactions between APCs, T-cells and B-cells. They form a widely distributed network throughout the body, close to sites of potential antigen entry.
- **Lymphocytes** Immune cells that provide adaptive immunity. T-lymphocytes recognize antigen processed from infections; B-lymphocytes produce antibodies that bind free antigens.
- **Lysosome** Intracellular organelle containing proteolytic (protein-cutting) enzymes.
- **Lysozyme** Enzyme that damages bacterial cell walls.
- **Macrophages** White blood cells that engulf and digest invading micro-organisms.
- **Major histocompatibility (MHC) determinants** Polymorphic molecules that bind peptides processed from proteins. Class I (MHC I) binds peptides typically eight or nine amino acids long, class II (MHC II) accommodates peptides of 10 to 30 residues).
- **Measles virus** The RNA virus that causes measles.
- **Microbiome** The microbial ecology that normal healthy individuals carry with them.
- **Monoclonal antibodies** Antibodies of a single specificity secreted in large amounts by hybridomas.
- **Myasthenia gravis** Autoimmune disease that leads to weakness because of the presence of antibodies that inhibit normal muscle function.
- **Natural killer cells** Innate immune system cells that kill cells infected by virus or transformed into cancers.
- **Neutrophils** White blood cells that fight infection by phagocytosis and by releasing sterilizing chemicals that kill invading micro-organisms.
- **Nucleic acid** Chemical used in genes.
- **Nucleus** Cell organelle containing the genetic code (DNA).
- **Opsonization** Process by which antibodies coat a structure, to stimulate phagocytosis.
- **Passive immunity** The transfer of immune function by transfusion of specific antisera, for example anti-venoms from horse serum.
- **Pathogen** A living organism that causes disease.
- **Peptides** Short stretches of amino acids.
- **Perforins** Secreted proteins, released from cytotoxic cells, which produce holes in cell membranes.
- **Plasma cells** Antibody-secreting B-cells.
- **Phagocytosis** The process by which a cell engulfs material in its local environment.
- **Phagosome** A membrane-bound structure inside a cell created by phagocytosis.

- **Proteolytic cascade** A sequence of enzymes that activate each other, allowing a rapidly amplification in response. Widely used, for example in blood clotting, activation of complement and apoptosis.
- **Protein** Protein molecules are made from chains of amino acids. They have a wide range of different functions.
- **Rabies virus** The RNA virus that causes rabies. Symptomatic infection with rabies virus is almost always fatal.
- **Receptors** Receptors bind specific ligands and produce signals that reflect the local concentration of the ligand at the cell surface.
- **Rheumatoid arthritis** Autoimmune disease that attacks the small joints of the hands and feet.
- **RNA** Ribonucleic acid. Genetic material used by all cells when producing proteins and by some viruses to store genetic information.
- **Self-antigens** Antigens derived from normal proteins. Targeted in autoimmune disease.
- **Sepsis** The clinical state that develops in severe systemic infection. Often life-threatening.
- **Serum** Liquid component of blood, lacking cells and clotting factors, but containing antibodies and other soluble proteins.
- **Spirochaete** Spiral-shaped bacterium. The pathogen that causes syphilis is a spirochaete.
- **Spleen** Organ that coordinates interactions between APCs, T-cells and B-cells. Found in the abdomen. Also responsible for digesting red blood cells and recycling iron.
- **T-cell** Lymphocyte that is programmed in the thymus (hence T) and which recognizes antigen bound to MHC molecules.
- **T-cell receptor (TCR) complex** The receptor on T-cells that binds peptide MHC molecules, and signals into the cell.
- **Thymus** The organ, found in the chest, in which T-cells bearing useful TCRs are selected.
- **Thyrotropin receptor** Receptor on thyroid cells. Stimulation leads to the release of hormones that increase the metabolic rate.
- **Tissue type** The tissue antigens (mainly MHC molecules) possessed by a single individual that are recognized by the immune system and which stimulate the rejection of transplants.
- **Toll-like receptor (TLR)** Receptor belonging to the Toll-like family of proteins first described in insects. One of many families of receptor that activate the innate immune system.
- **Toxins** Poisons.

- **Tumour necrosis factor (TNF)** Cytokine released by macrophages that stimulates immune cell effector functions that promote inflammation.
- **Vaccination** The deliberate recruitment of the adaptive immune response to develop memory of a specific infection in a therapeutic setting.
- **Viruses** The smallest organisms, viruses need to co-opt the protein-producing machinery of larger cells to reproduce.

Appendix 2. Cells of the Immune System

Granulocytes are white blood cells (i.e., leukocytes) characterized by the presence of granules in their cytoplasm. Granulocytes include the following cell types:

Neutrophils are the most abundant granulocytes and also the most abundant type of white blood cell, reaching concentrations of up to 5 million cells per milliliter in the blood. Neutrophils normally circulate in the blood and, upon injury or infection, quickly move to the affected site. They thereby follow chemical signals consisting of *cytokines* and *chemokines* to the site where they are among the first immune cells to arrive. Neutrophils detect pathogens via TLRs and directly attack them, for example, through phagocytosis. Neutrophils also release extracellular traps composed of DNA and antimicrobial peptides that ensnare and kill microbes. Thus, neutrophils represent an important first-line defense against invading microbes.

Basophils originate from bone marrow and circulate in the blood; they are the least abundant white blood cells. Upon activation by proteins, they move to an injured or infected site. Similar to *mast cells*, basophils also sometimes cause inflammatory responses such as allergic reactions. Basophils release the anticoagulant heparin and the vasoactive compounds histamine and serotonin, which reduce blood clotting and contribute to wound swelling typical of inflammations, respectively.

Eosinophils develop and mature in bone marrow and then also circulate in the blood. They are activated, for example, by lymphocytes of the adaptive immune systems, and they are crucial for combating larger parasites that cannot be phagocytized, such as protozoans. Eosinophils also help fight other types of infections.

Mast cells reside in connective tissues and mucous membranes and aid in wound healing and also in defending against pathogens. When activated by pathogens or allergens such as pollen, mast cells rapidly release protein-carrying granules rich in both histamine and heparin, molecules involved in inflammation. Mast cell activation often underlies adverse immune responses such as allergies, arthritis, and anaphylactic shock.

Monocytes are the largest cells of the innate immune system. They mature in bone marrow and then circulate through the blood. Half of them are stored in the spleen and the other half in other locations throughout the body. Monocytes are precursors for two other innate immune system cells: *macrophages* and *dendritic cells*.

Macrophages are cells that search for and phagocytize pathogens. Upon exiting blood and entering tissues, *monocytes* develop into macrophages. They help remove excess, damaged, or

dead cells marked by surface proteins for elimination. “Resident” macrophages inhabit specific locations or organs that are prone to infections, such as the lungs and liver, or serve in hubs, such as the spleen, for rapid deployment to injured or infected sites. Examples include Kupffer cells, macrophages residing in the liver, and microglia, residing in the central nervous system. Macrophages carry several TLRs on their surface, that are activated by pathogen- or damage-associated molecular patterns—this activation stimulates the macrophages to phagocytose pathogens or damaged cells or to secrete *cytokines* to activate and recruit additional immune cells. Macrophages contribute to wound healing, help control immune responses and other cells of the innate immune system, and also stimulate adaptive immunity.

Dendritic cells act as messengers between the innate and adaptive immune systems. They reside in tissues exposed to the external environment, including the skin and the linings of the nose, lungs, stomach, and colon. Like *neutrophils* and *macrophages*, they detect foreign invaders via TLRs. Upon encountering a pathogen, dendritic cells ingest (i.e., endocytose) it or its products and attach pieces of the pathogen (i.e., antigens) to their cell surface on a protein assembly called the major histocompatibility complex II (MHC II). The dendritic cells then migrate to the lymph nodes where they activate *T cells* and *B cells* by presenting the pathogen’s antigens to them. Dendritic cells are the most potent of several types of antigen-presenting cells, which effectively jumpstart the adaptive immune response.

Natural killer cells (NK cells) rapidly respond to the presence of virus-infected and tumor cells and destroy them with proteolytic enzymes and cytotoxic proteins that destabilize the cells’ membranes and induce apoptosis. NK cells recognize stressed cells in the absence of the chemical triggers other immune cells need to mount an immune response. Although traditionally classified along with innate immune cells, some evidence of immunological memory in NK cells suggests that these cells are also affiliated with adaptive immunity.

T-Lymphocytes

The T-cells are a type of white blood cell that matures in the thymus (a gland located behind the sternum) and tonsils. There are several different types of T cells including T helper cells (assist other cells by secreting cytokines that activate different killing mechanisms in the immune system), Cytotoxic T Cells (secrete toxic substances to destroy virally infected cells and cancer cells, Memory T Cells (keep within them a memory of past infections so if reinfection occurs, the action of the immune system is rapid), Natural Killer T Cells (perform actions similar to the T helper and the Cytotoxic T cells), and Regulatory T Cells. *Regulatory T cells are the cells that keep everything in the immune system under control*. Regulatory T Cells shut off the immune response once it has finished its work, and are required for something known as immunological tolerance.

B Cells

B-lymphocytes are generated in the bone marrow after which they mature into fully competent B cells in the spleen and other secondary lymphoid tissues such as the cervical lymph nodes. Their activation requires antigen recognition by B cell receptors (BCRs) followed by a secondary activation signal, typically in the context of antigen-presenting cells. Upon activation B cells proliferate, form germinal centers, and differentiate into memory B cells or plasma cells. The primary function of plasma cells is the secretion of clone-specific antibodies.

Appendix 3. The Immune System Response to Different Microorganisms

Immune response to bacteria - Response often depends on the pathogenicity of the bacteria:

Neutralizing antibodies are synthesized if the bacterial pathogenicity is due to a toxin

- *Opsonizing antibodies* - produced as they are essential in destroying extracellular bacteria
- The *complement system* is activated especially by gram-negative bacterial lipid layers
- Phagocytes kill most bacteria utilizing positive chemotaxis, attachment, uptake and finally engulfing the bacteria
- CD8+ T cells can kill cells infected by bacteria

Immune response to fungi:

- The innate immunity to fungi includes defensins and phagocytes
- CD4+ T helper cells are responsible for the adaptive immune response against fungi
- Dendritic cells secrete IL-12 after ingesting fungi, and IL-12 activates the synthesis of gamma interferon which activates the cell-mediated immunity

Immune response to viruses:

- Interferon, NK cells, and phagocytes prevent the spread of viruses in the early stage
- Specific antibodies and complement proteins participate in viral neutralization and can limit spread and reinfection
- The adaptive immunity is of foremost importance in the protection against viruses - these include CD8+ T cells that kill them and CD4+ T cells as the dominant effector cell population in response to many virus infections

Immune response to parasites (9):

- Parasitic infection stimulates various mechanisms of immunity due to their complex life cycle
- Both CD4+ and CD8+ Cells protect against parasites
- Macrophages, eosinophils, neutrophils, and platelets can kill protozoa and worms by releasing reactive oxygen radicals and nitric oxide
- Increased eosinophil number and the stimulation of IgE by Th-2 CD4+ T cells are necessary for the killing of intestinal worms
- Inflammatory responses also combat parasitic infections

Despite Immune response(s) generated by intact and functional Immune system we still fall sick, and this is often due to evasive mechanisms employed by these microbes. Here are some of those.

Strategies of viruses to evade the immune system

Antigenic variation: It is a mutation in proteins that are typically recognized by antibodies and lymphocytes. HIV continually mutates, thus making it difficult for either the immune system to protect against it and also hinders the development of a vaccine.

By disrupting 2',5'-oligoadenylate synthetase activity or by the production of soluble interferon receptors viruses disrupt the Interferon response.

By several mechanisms, Viruses affects the expression of MHC molecules.

A virus can infect immune cells: Normal T and B cells are also sites of virus persistence. HIV hides in CD4+T cells and EBV in B cells.

Strategies of bacteria to evade the immune system

Intracellular pathogens may hide in cells: Bacteria can live inside metabolically damaged host leukocytes, and escaping from phagolysosomes (*Shigella spp).*

Other mechanisms:

- Production of toxins that inhibit the phagocytosis
- They are preventing killing by encapsulation
- The release of catalase inactivates hydrogen peroxide
- They infect cells and then cause impaired antigenic presentation
- The organism may kill the phagocyte by apoptosis or necrosis

Strategies of fungi to evade the immune system

- Fungi produce a polysaccharide capsule, which inhibits the process of phagocytosis and overcoming opsonization, complement, and antibodies
- Some fungi inhibit the activities of host T cells from delaying cell-mediated killing
- Other organisms (e.g., *Histoplasma capsulatum*) evade macrophage killing by entering the cells via CR3 and them escape from phagosome formation

Strategies of parasites to evade the immune system

- Parasites can resist destruction by complement complex
- Intracellular parasites can avoid being killed by lysosomal enzymes and oxygen metabolites
- Parasites disguise themselves as a protection mechanism
- Antigenic variation (e.g., African trypanosome) is an essential mechanism to evade the immune system
- Parasites release molecules that interfere with immune system normal function

* **Disclaimer** (i) The information is provided for educational purposes only. (ii) These statements have not been evaluated by the Food and Drug Administration (FDA). The provided information is not intended to diagnose, treat, cure or prevent any diseases or, medical problems.

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