IMMUNEBALANCE

White Paper

IMMUNE SYSTEM EQUILIBRIUM

Chemical and biological agents, together with trauma, continuously threaten health. Fortunately, the organism is equipped with a powerful weapon to counteract them: the immune system.

Two kinds of immunity work side by side to defend it. **Innate immunity** (e.g. monocytes and Natural Killer – NK – cells) provides a fast protection, representing body's first line of defense. This protection is unspecific and incomplete but is needed until the second kind of immunity (the **adaptive immunity**) is established. Adaptive immunity takes longer to respond to health insults, but is highly specific and permanent. Its cells (T and B cells) respond to the inflammatory environment generated by the innate immunity, proliferating and differentiating to eliminate the health insult. Upon terminating their work, the majority of these cells die, leaving memory cells able to mediate a rapid and protective response in case of reinfection.

Based on actual knowledge, it is possible to outline what should happen after microbe invasion in the presence of an ideal immune response. Infection is initially contained by the recruitment of cells able to phagocytize foreign substances and release cytotoxic and proinflammatory molecules, such as monocytes. Meanwhile, antigen presenting cells (whose functions are processing and presenting antigens for recognition by other immune cells) are activated at the site of infection by the local inflammatory response, acquire antigen, and migrate to secondary lymphoid organs. During transit, they process the antigen and upregulate cell surface molecules and cytokines. In the secondary lymphoid organs, antigen presenting cells stimulate T cells, which collaborate with B cell to promote antibody production and memory B cell formation. Then, T cells proliferate and migrate into the infection site, where they exert their effector function, contributing to pathogen elimination.

Several factors, such as sex, diet, and exercise, influence the immune system. **Age** has an effect on its efficiency too. First, immune system stimulation and oxidative stress exposure occurring in the course of life promote a state called **inflammaging**, that is inflammation associated with aging. This low-grade inflammation status is associated with almost all the health problems typical of aging, such as cardiometabolic and neurodegenerative diseases. It is due to chronic immune system stimulation, which induces the increase of both activated immune cells and pro-inflammatory lymphokines production, contributing to the imbalance between inflammatory and anti-inflammatory mechanisms. Moreover, during the course of life, **oxidative stress** damages cell lipids, proteins, and nucleic acids, triggering protective mechanisms; however, as oxidative insult goes on, such

protective mechanisms become less effective. The consequent accumulation of senescent, dysfunctional, and mutated cells leads to a reduction of immune response and to an increased risk of infections, cancer, and degenerative disorders.

Besides the increased tendency for inflammation, aging comes with **immune defense decay** too. This phenomenon, known as immunosenescence, is associated with the reduction of adaptive immune response, the enhancement of the susceptibility to infections, the increase in the production of autoantibodies (that is, antibodies directed against structures of the organism), and increased mortality. This is though to explain why some diseases involving the immune system (such as autoimmune diseases, malignancies, and infections) develop during aging.

Actually, **the immune system is thought to play an active role in aging**, and physiological events such as the involution of thymus gland (which in the first years of life participates in immune cell maturation) support this theory. In general, the ability of constantly renewing immune system cells declines with age, and hematopoietic tissue that produce them decreases.

The aging of the immune system compromises the healthspan, that is the period of life free from chronic diseases and disability. In fact, immunosenescence reduces the ability to respond to new antigens (with the accumulation of memory T cells) and the inflammaging is associated with several health risks. However, aging differs from one individual to another, and the hallmarks of immunosenescence are affected by the history of individual exposure to pathogens.

Thymus involution starts early in life, and it almost completes between 40 and 50 years. Both innate and adaptive immune response progressively decrease during aging, with a significant decrease in the absolute frequencies of CD45+ Peripheral Blood Mononuclear Cells (PBMCs, including lymphocytes and monocytes). However, adaptive immunity is more extensively affected. Its effectiveness diminishes because of changes in both the quality and the quantity of the T and B cell responses. As a consequence, the reaction against newly encountered antigens becomes inadequate, and older individuals are more susceptible to infection and to the development of age-related diseases, including cancer.

AGE EFFECT ON IMMUNE SYSTEM	
inflammaging	. increased activated immune cells . increased pro-inflammatory lymphokines production . association with age-related pathologies
reduced oxidative stress response	. accumulation of senescent, dysfunctional, and mutated cells . reduced immune response . increased risk of infections, cancer, and degenerative disorders
immunosenescence	. reduced adaptive and innate immune response . enhanced infection susceptibility . increased antibody production . increased mortality

T cells in aging

T cells are a type of lymphocytes generated in the thymus. Based on their co-receptor molecules, they can be distinguished in CD4+ and CD8+ cells.

Among **CD4+ lymphocytes** are T helper cells, which are the immune cells leading the fight against infections. CD4+ cells are involved in the identification and destruction of bacteria, fungi, and viruses. By releasing cytokines, they activate neighboring cells; by chemokines secretion, they recruit new immune cells.

Among **CD8+ lymphocytes** are cytotoxic T cells. These lymphocytes identify and kill cells infected by viruses and cancer cells by delivering cytotoxic granules into them. As CD4+ cells, CD8+ cells produce cytokines too.

Typically, a T cell response peaks in 7-15 days, after which the vast majority of antigen-specific T cells die off, leaving a pool of memory cells. Both CD4+ and CD8+ lymphocytes can leave central-memory and effector-memory cells. The former can extensively proliferate after antigen reencounter, while the latter are characterized by limited proliferative potential but rapid effector, cytolitic, function. Effector-memory cells are thus considered first responders to peripheral reinfection

controlling the initial re-exposure to a pathogen, allowing central-memory cells the time to proliferate and create new effectors.

Memory cells can survive for decades, with a half-life of 8-15 years. That is why overexuberant exposure to antigens can compromise immune memory: overdifferentiation of T cells can limit the **immunological space** available for new memory cells. In fact, the immune system works to maintain the number of peripheral T cells at almost constant level. As a consequence, the increase in differentiated T cells reduces the space for new T cells. For example, chronic viral infections lead to continuous stimulation of T cells, increasing the risk of clonal exhaustion and overdifferentiation of all the viral-specific T cells into effectors.

In general, both inflammatory and immune-modulating signals are required for proper effector and memory function. However, the overcommitment to one or the other can lead to dysfunctional immune response.

Unfortunately, the increase in life expectancy does not always coincide with the increase in healthy, free-of-disease, years to be lived. For example, the elderly is characterized by a decrease in the ability to resist new infections. Changes in T cell population are in part responsible for phenomena like this.

In the elderly, reduction in total T cell number has been reported, and the decreased ability to resist new infections is associated with the reduction of naïve T cells – that is, newly produced, resting cells that can be activated by the interaction with an antigen. This decrease is a consequence of both thymic involution and chronic antigenic stimulation. Moreover, elderly naïve T cells show multiple alterations, including the reduced production of IL-2 and the diminished ability to differentiate into effector cells. Finally, senescent cell reduced sensitivity to damaged-induced apoptosis reduces the immunological space; as a consequence, depleted CD4+ cells cannot be replaced with either CD4+ or CD8+ cells. In fact, aging-associated reduced sensitivity to damaged-induced apoptosis promotes the accumulation of dysfunctional cells, CD8+, and memory cells, reducing the space for other immune cells, in particular CD4+ cells. This is why the accumulation of these cells increases the risk of both infections and neoplastic or degenerative disorders even without significant changes in the total CD3+ (T) cell level.

Factors affecting the elderly can progressively influence **CD4+/CD8+ ratio**, a parameter telling how strong the immune system is. CD4+/CD8+ ratio is considered as a component of the increased risk of death. In very old individuals the combination of high CD8+ and low CD4+ percentages and poor T cell proliferation in peripheral blood lymphocytes is associated with higher mortality, and the mortality rate above the age of 60 is significantly increased when CD4+/CD8+ ratio is inverted. That is why CD4+/CD8+ inversion evaluation is crucial for individuals suspected of having a compromised immunity.

CD4+/CD8+ ratio is high in neonates, and declines to adult values by 4 years of age. **Its inversion is a feature of the so-called immune risk phenotype** (IRP), a condition typical of the elderly characterized by memory-effector cells increase. Interestingly, IRP is independent of the overall health status, not being exclusive of frail individuals. Moreover, there is a significant lowering of T cells (CD3+), CD4+ and CD8+ cells across the adult life-span, and the prevalence of CD4+/CD8+ ratio inversion increases with aging, shifting from about 8% in 20-59 year old individuals to 16% in 60-94 year old individuals. Finally, CD4+/CD8+ inversion was reported to be significantly more frequent among men. This phenomenon was suggested to contribute for the differences in longevity between sexes.

CD4+/CD8+ inversion might represent a step toward a progressive CD4+ lymphocytopenia, a not unusually rare condition in aged people. In this case, factors affecting the CD4+ population could be the cause of the inversion. However, aging-associated CD8+ cells changes are more important. In particular, healthy elderly clonal expansion has been reported and has been associated with a CD28-

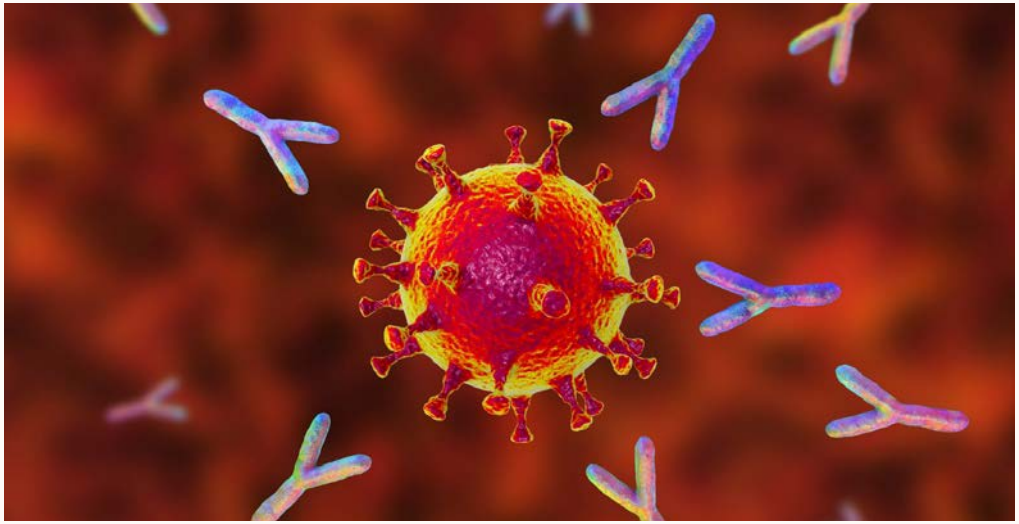
T CELLS IN AGING	
REDUCED IMMUNOLOGICAL SPACE	IMMUNE RISK PHENOTYPE (IRP)
accumulation of: dysfunctional cells CD8+ cells memory cells	CD4+/CD8+ ratio inversion high CD8+ low CD4+ poor T cell proliferation in peripheral blood increase in memory-effector cells

subpopulation, lacking in proliferative responses to T cell receptor stimuli.

Moreover, CD4+/CD8+ balance may be altered by some conditions, particularly viral infections. Cytomegalovirus (CMV) positivity, a leading cause of immune system senescence, is closely related to the inversion of the CD4+/CD8+ ratio. CMV infection, that persists lifelong after the first exposure, chronically stimulates CD8+ cells, which expand and show a memory-effector phenotype. CD4+ cells decrease in a compensatory way. In the IRP, marked seropositivity for cytomegalovirus is associated with reversal of CD4+/CD8+ ratio, the increase in CD8+CD28- memory-effector cells and in proinflammatory cytokines such as IL-6, and the reduction of B cells (CD19+). This condition is predictive of the development of cognitive deficits, and of mortality rate over the next 4 years in 58% of cases. Even if a significant number of adults are positive to CMV, only a minor part of them is aware of its seropositivity; as a consequence, they are unaware of their possible compromised immune defenses.

Other conditions associated with CD4+/CD8+ inversion are transplantation, hemophilia treatment, acute illness, and malnutrition. In many cases, T cell subpopulations are only temporarily affected; however, CD4+/CD8+ ratio can remain altered in the long term. In general, both microbial agents and environmental stressors can initiate T cell changes; an immune system lacking the required resilience might foster a progressive change in CD4+/CD8+ ratio toward unhealthy values.

In the elderly, CD4+/CD8+ ratio values greater than 2 where reported to. It must be noted that, beside strong immunity, such values can be associated with specific pathologies, such as infections and blood cancers. Moreover, as opposed to the mean, the median elderly CD4+/CD8+ ratio tends towards lower values, indicating a tendency towards inversion.



B cells in aging

B cells are immune cells responsible for the production of antibodies, antigen presentation and cytokine secretion. They are released as immature cells by the bone marrow, and their total number, as well as the composition of the B cell population circulating in peripheral blood, dynamically changes during the course of life.

Immediately after birth total B cell count increases 2-fold. This increase is due to an active production and release of B cells by the bone marrow, that reaches a maximum between 0 and 12 months of age. Then B cell count remains high until 2 years, when a gradual decrease starts, leading to approximately 6.5-fold lower numbers in the adulthood. Starting from 2 months of life memory B cells increase too. Their number remains high until age 5 years, when it starts decreasing to adult-like values.

In the adulthood, total B cell number remains relatively stable until aging. However, **aging is associated with the reduction of B cell production** by the bone marrow. Recent analyses suggest that this age-related declines is due to the increased production of inflammatory cytokines that can inhibit their creation, such as IL-1, IL-6 and TNF-α. In young people, short-term inflammation may stimulate the production of myeloid cells, such as monocytes, that help to promptly respond to infections; instead, the chronic inflammation associated with aging may translate in a continuous inhibition of B cell production.

Moreover, memory B cells and new plasma cells (that is, the more advanced differentiation step of mature B cells, able to secrete large amounts of antibodies) gradually decrease after 60 years of age.

MONOCYTES	MARKERS	FEATURES
classical	CD14++/CD16-	. phagocytic capacity . innate sensing/immune responses and migration . ROS production . active against fungi
non-classical	CD14+/CD16+	. wound healing . anti-viral responses . TNF-α production . reduced migration
intermediate	CD14++/CD16+	. phagocytic and differentiation capacity . reduced adhesion capacity . higher class II molecules expression . cytokine synthesis (higher IL-2 production) . apoptosis regulation

Monocytes in aging

Monocytes are white blood cells developing in the bone marrow that are involved in both the innate immune response, and processes such as tissue repair. They circulate in the blood, migrating to sites of injury or infection after the engagement of chemokine and pathogen recognition receptors. They can perform pro-inflammatory and pro-resolving functions, take up cells and toxic molecules, and differentiate into inflammatory dendritic cells or macrophages. Two major monocytes subsets in the peripheral blood can be distinguished based on the differential expression of two molecules: CD14 and CD16. **CD14++CD16-** cells are known as "classical monocytes", whereas **CD14+CD16+** cells are known as "non-classical monocytes". A third subset of monocytes is represented by **CD14++CD16+** cells, or "intermediate monocytes".

CD14++CD16- cells represent up to 95% monocytes in healthy individuals. They are characterized by a high phagocytic capacity, innate sensing/immune responses and migration, and can be somewhat more efficient than CD14++CD16+ monocytes in producing reactive oxygen species (ROS) and constraining fungi. They can differentiate into monocyte-derived macrophages and dendritic cells, immune cells playing a pivotal role in tissue inflammation development and resolution.

Compared to them, CD14++CD16+ cells display similar phagocytosis potential, but lower adhesion capacity, and higher class II molecule expression and IL-2 production. They are well-suited for antigen presentation, cytokine production (TNF-α, IL-1β, and IL-6), apoptosis regulation, and differentiation. Their blood number is expanded in case of systemic infection, so they must play an important role in the rapid response to pathogens.

CD14+CD16+ monocytes are instead associated with wound healing and anti-viral responses, and promote neutrophil adhesion at the endothelial interface via TNF-α production. However, they do not produce the same levels of pro-inflammatory cytokines as classical monocytes. Moreover, compared to classical CD14++CD16- cells, non-classical CD14+CD16+ monocytes express lower levels of chemokine receptors involved in monocyte migration.

CD16+ subsets correlate with chronic inflammation-associated pathologies, such as coronary artery disease, obesity, diabetes, arthritis, and intestinal inflammatory diseases, and with cardiovascular disease progression. For example, increased levels

of both intermediate and non-classical monocytes have been associated with proatherogenic lipoprotein profiles. Intermediate monocytes number negatively correlates with plaque thickness and plays a pivotal role in cardiac attack and plaque growth and stability. They showed an association also with cardiovascular outcomes in patients with chronic kidney disease.

The absolute number and the relative contribution to the circulating monocyte pool of non-classical cells increase also during aging. In fact, in healthy adults total monocytes levels do not change **with age**, but after the age of 50 **there is a shift from classical CD14++CD16- monocytes to CD14+CD16+ cells**. This could represent a physiological trick to preserve the overall functionality of the monocyte pool, but it does not necessarily correspond to enhanced monocyte availability and functionality in aging.

In fact, after the age of 50 **the functionality of CD14+CD16+ monocytes seems to decrease**. They express lower levels of activation markers and display a potentially reduced capacity to migrate to inflammatory sites and to the spleen. Moreover, the half-life of monocyte-derived tissue macrophages is lower too.

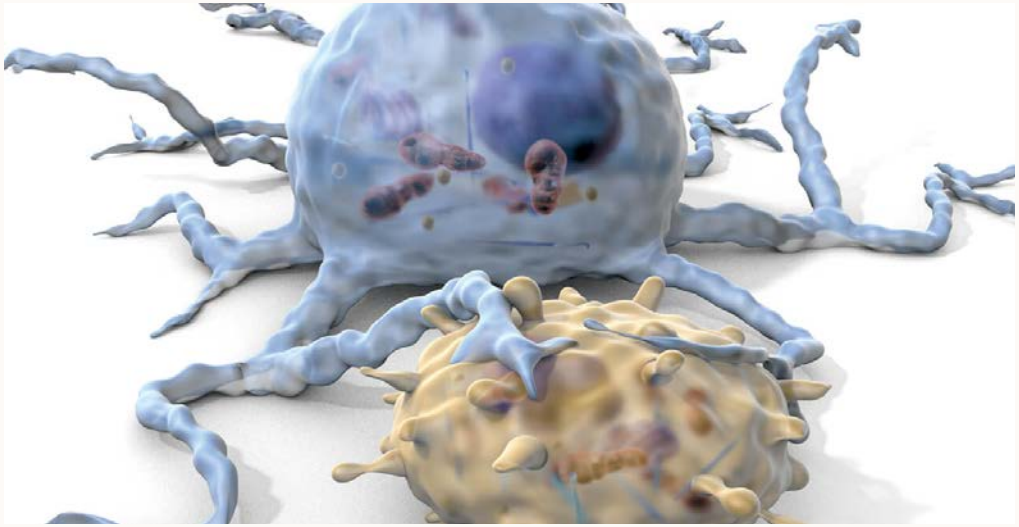
Finally, **CD14+CD16+ monocytes that are expanded after the age of 50 are generally believed to have the capacity to produce higher levels of pro-inflammatory cytokines.** In particular, advanced-age, frail elderly showed a higher production of TNF-α, and to a lesser extent IL-8. Pro-inflammatory cytokines production is constitutively higher, suggesting a predisposition to chronic disease development.

Looking at the differences between adults (19-59 years), seniors (61-76 years), and the advanced-aged, frail elderly (81-100 years), the latter showed a significant reduction in CD14++CD16- and CD14+CD16+ monocytes, and an increase in CD14++CD16+ cells.

Overall, data in the scientific literature indicate a decrease in CD14++CD16- monocytes starting from 61 years of age, and an increase in CD16+ subpopulations. CD14+CD16+ cells seem to increase after the age of 50, but their functionality is compromised; starting from the age of 81, frailty is associated with their reduction, whereas CD14++CD16+ monocytes increase.

CD16+ cells, in particular **non-classical monocytes, seem to account for the increase in plasma TNF-α levels and inflammatory conditions in aged individuals**. Monocyte frequency, phenotype, and functional changes observed in the advanced-age, frail elderly correlate with chronic diseases associated with a chronic inflammatory state, such as coronary artery disease, arthritis, and inflammatory diseases of the intestinal tract. Moreover, monocyte frequency and the classical to intermediate monocyte ratio were positively associated with the likelihood of having dementia.

Interestingly, reversal of CD16+ cell increase seem to be possible. In obese individuals, for example, both dietary intervention and gastric bypass surgery result in the decrease of these subsets of monocytes.



NK cells in aging

NK cells are versatile lymphocytes involved in both innate and adaptive immunity

that can destroy virus-infected and tumor cells. Their cytotoxicity relies on the fine balance between activating and inhibitory surface receptors. They can secrete cytokines, regulate dendritic cell maturation and act as antigen presenting cells.

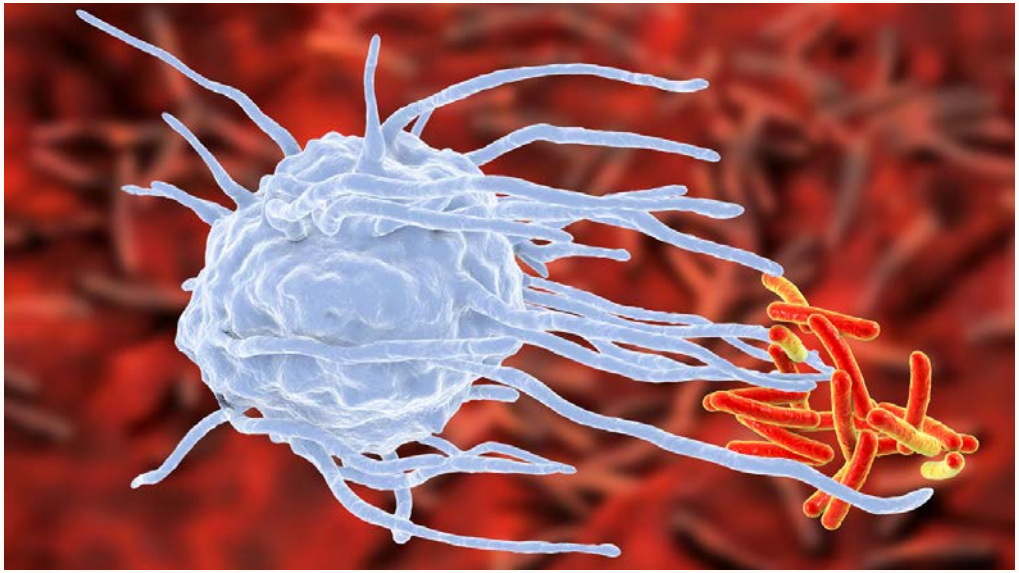
NK cells can be divided in subsets based on CD56 and CD16 expression. **$CD56^{dim}CD16+$ cells** are mature cytotoxic cells with a poor capacity to proliferate in response to cytokines. They represent up to 90% of NK cells circulating in peripheral blood cells, and directly kill target cells via exocytosis of granules, activation of cell death, or antibody-dependent cytotoxicity. After direct contact with target cells, $CD56^{dim}CD16+$ cells secrete cytokines such as IFN-γ. CD56bright cells are less mature and are concentrated mostly in lymph nodes. They produce and are responsive to cytokines; in particular, **$CD56^{bright}CD16-$ cells** produce high levels of cytokines and chemokines in response to IL-2, IL-12 and IL-18.

Although some conflicting evidence, several data suggest that **during aging** absolute peripheral blood NK cell number tend to increase. However, starting from the age of 50 the production of new NK cells is reduced, indicating **a high proportion of "old" NK cells** in the elderly. **$CD56^{bright}$ cells decrease**, probably because of the age-associated changes in the hematopoietic stem cells in the bone marrow. As a consequence, in the elderly cytokine and chemokine production by NK cells is impaired. Instead, the production of IFN-γ increases, probably as a compensatory mechanism to maintain CD56bright immunoregulatory role.

On the contrary, **the subset of CD56-CD16+ NK cells increase**s. These cells are characterized by **low replicative capacities and reduced cytokine production**. CD57+$CD56^{dim}CD16+$ cells increase too. This subpopulation, characterized by high cytotoxic capacity and reduced sensitivity to cytokines and replicative potential, is absent at birth and increases with age.

However, CD57 seems to be a marker of NK cells expansion in response to CMV infection; in CMV-positive people, it would accumulate during aging to maintain NK cell homeostasis. On the contrary, the redistribution of NK cell subsets, with $CD56^{bright}$ decreasing and CD56-CD16+ cells increasing, is associated with aging but not with CMV infection.

In general, **a low NK cytotoxicity is associated with an increase in morbidity** (e.g. infections and mechanisms of atherosclerotic and neurodegenerative diseases) **and mortality**. On the contrary, high NK function is associated with longevity and good health.



Vitamin D and the immune system

Immune system efficiency depends also on vitamin D status. This peculiar micronutrient (in effect, a prohormone) is a potent immunomodulator. Before the advent of efficient antibiotics therapies, it has been used to treat serious infections, such as tuberculosis. Nowadays, **the association between its deficiency and the increased susceptibility to infection** (both respiratory and oral, gastrointestinal, genitourinary tract, and ocular) **is well-known**. Moreover, the link between inadequate vitamin D status and the prevalence of autoimmune disorders has been unveiled too. In general, avoidance of vitamin D deficiency is associated

with better immune system functioning.

In human, it is synthesized in the skin by the action of ultraviolet (UV) rays on its precursor, 7-dehydrocholesterol. Its active form is then obtained by hydroxylation taking place in the liver and in the kidney. In the circulation, vitamin D and its metabolites are bound to the vitamin D-Binding Protein (DBP), which functions as inflammation and immune response regulator too.

Immune cells possess the necessary machinery to synthesize its active form too. Moreover, they express the vitamin D receptor (VDR). Thus, immune system can both produce and respond to vitamin D, and vitamin D can act on immune cells both in a paracrine and autocrine manner. It exerts a complex effect, promoting a more tolerogenic immune status.

First, **vitamin D plays an important role in the innate response** to microbes. Its antimicrobial role is mediated by monocytes. In these cells, vitamin D exerts an anti-oxidative effect. Moreover, it inhibits the production of cytokines such as IL-1, IL-6, IL-8, IL-12 and TNF-α. Finally, recent studies suggest an epigenetic effect during antigen encounter and differentiation.

In macrophages, the activation of toll like receptors (TLRs) by microbial components leads to the increase of the expression of both the vitamin D synthesizing enzyme and the VDR. This results in the production of antimicrobial proteins. Moreover, the active form of vitamin D exerts an anti-inflammatory action on these immune cells. It increases IL-10 and decreases inflammatory stimuli, such as IL-1β, IL-6, TNF-α, and cyclo-oxygenase-2 (COX-2). VDR expression levels are reduced comparing to monocytes.

The enzyme responsible for vitamin D synthesis is dependent on 25-hydroxyvitamin D3 (25-(OH)D3) produced in the liver, and may be induced by cytokines such as IFN-γ, IL-1 or TNF-α.

The active form vitamin D induces changes in dendritic cells morphology, cytokine production and surface markers, promoting a less mature and more tolerogenic phenotype. IL-6 and IL-12 are reduced, whereas IL-10 is increased, together with molecules that regulates T cell activity, such as TNF.

Finally, vitamin D regulates NK cells and neutrophils too. In particular, by modulating the activity of neutrophils, this vitamin helps to minimize damage by pathogens and to reduce the risk of autoimmunity.

Vitamin D affects also adaptive immunity. First, it seems to directly act on B cells, inducing the apoptosis of activated lymphocytes and impeding the generation of plasma cells (that is, antibodies producing cells) and memory B lymphocytes. Moreover, it upregulates B cell IL-10 production.

Secondly, acting on antigen presenting cells (that is, immune cells that collect antigens and communicate with lymphocytes to orchestrate the adaptive immune response), vitamin D influences T cell activity. In particular, it modulate T cell response reducing T cell autoreactive proliferation, inducing the apoptosis of autoreactive T cells, and increasing T lymphocytes that downregulate the immune response.

Vitamin D can also directly influence T cell activity, promoting the reduction of inflammatory cytokines (IL-2, IL-9, IL-17, IL-21, and IFN-γ) and the increase of anti-inflammatory cytokines (such as IL-10). Its effect is dependent on the state of activation of T cells; in fact, T cell VDR concentration increase upon their activation.

Unfortunately, **up to 40% of adults suffer from low serum vitamin D level**. This widespread vitamin D deficiency is caused by a combination of vitamin D-rich foods scarcity and poor UV-synthesis.

Salmon, rainbow trout, swordfish, mackerel, herrings, eggs, tuna, milk, and bovine liver are the richest sources in the diet. However, most of the dose of this peculiar nutrient required to fulfill daily organism requirement is synthesized in the skin by the action of sunbeam UV-rays.

People spend less time in the open air than in the past, and they need to protect their skin from cancer risk by blocking UV-rays with adequate sunscreens. Moreover,

latitude, season and skin pigmentation influence skin vitamin D synthesis. All these factors can limit the exposure to UV-rays.

Aging comes with an even greater risk of severe vitamin D deficiency. In a study involving 75-year and older men and women, French and Canadian researchers found the recommended vitamin D level only in 15% of the participants, and classified more than a quarter of them (27%) as affected by a "very sever vitamin D deficiency". Severe, moderate, and minor vitamin D deficiency were found, respectively, in 16%, 27% and 15% of the participants. No significant difference was observed between age subgroups, suggesting that all old people might be at high risk of deficiency.

Other studies showed even smaller percentages of normal vitamin D concentration in the elderly (6-7,5%). In general, available data demonstrate that vitamin D deficiency in the elderly is a public health problem. Reasons behind it includes the already cited low sun exposure and scarce availability of dietary sources, the lack of physical activity, and the reported decrease in skin vitamin D synthesis.

This deficiency is traditionally associated with bone fracture, but not only. In fact, low serum vitamin D level was reported to be associated with frailty syndrome and, as stated before, several infections. Vitamin D status correlates with cardiovascular disorders, diabetic retinopathy, migraine, and cancer (in particular bladder carcinoma and colorectal cancer) too. What is more, vitamin D supplementation has been associated with a significant improvement in senile dementia-associated cognitive performance decline and type 2 diabetes fasting blood glucose. In summary, there is plenty of reasons to warrant the organism adequate vitamin D level in the adulthood.

The nutritional vitamin D status is reflected by 25-(OH)D3 levels. To warrant immune system efficiency, all deficiencies must be corrected. Supplementation represents an effective strategy. For example, both vitamin D2 and vitamin D3 have been associated with protection against acute respiratory tract infections in 25-(OH)D3 deficient adults, especially with a daily or weekly supplementation.

Why IMMUNEBALANCE

Monitoring immune system balance allows intercepting immune function aging, and enables counteracting it to reach old age without disability. The adequate modulation of immune responses and the counterbalance of a pro-inflammatory cytokine profile with an anti-inflammatory profile can help reduce age-related degenerative, inflammatory and neoplastic diseases.

IMMUNEBALANCE by Bioscience Institute enables immune balance monitoring in healthy people, regardless of age, by the simultaneous analysis of total leukocytes, T and B cells, CD4+/CD8+ T cell ratio, monocytes CD14 and CD16 expression, NK cells, and vitamin D levels. It intercepts deviation from healthy values before the onset of health problems. The imbalance status eventually detected can be counteracted via lifestyle-based solutions, such as the use of food supplements specifically studied to promote immune system functioning.

PARAMETER	DISEQUILIBRIUM
Total lymphocytes	↓
T cells	↓
CD4+ T cells	↓
CD8+ T cells	↓ or ↑
CD4+/CD8+	↓ or ↑
Monocytes	
non-classical	↓ or ↑
intermediate	↑
classical	↓
classical/intermediate	↓
intermediate/non-classical	↑
NK cells	↑
CD56bright	↓
CD56-CD16+	↑
Vitamin D	< 30 ng/ml (insufficiency) < 20 ng/ml (deficiency)

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