Theories of Immunosenescence and Infection

Cytomegalovirus, Inflammation, and Homotoxicology

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Introduction

Aging is generally a complex process which forms part of the cycle of physiological cell growth where living organisms going through one of the phases of tissue evolution undergo the hardest and most irreversible processes of tissue deterioration. This is based on cell wear and tear (increase in chromosomal and telomeric alterations)[1] and matrix wear and tear (protein and lymphatic deterioration), accelerated catabolism (increase in post-transductional protein changes and in oxidation with increased apoptosis), and loss of the regenerative capacity of tissues over time (loss of mitochondrial function and stem cell reparation).

This progressive deterioration, considered to be physiological, affects not only the internal organs but also the skin, the central nervous system, and the immune system. The involvement of the immune system affects the ability to attack microbes, tumors, chemical or physical agents, or toxins (by slowing it down, diminishing it, down-regulating it, or preventing it altogether), compromising the organism's general immunity. This immune aging is known as immunosenescence, and it is particularly important in current clinical practice, since an understanding of these subtle biological changes can provide us with the tools to carry out suitable immunotherapy in the clinical field.

Changes in the immune system with aging

The immune system consists of a complex network of cell subtypes, membrane receptors, chemical communication signals (cytokines and chemokines), and humoral defense elements (antibodies, complement, immune peptides) which together enable the defenses to work in harmony, and other tissues such as the extracellular matrix, and the lymphatic, neuroendrocrine, and metabolic systems to remain in homeostasis. The main features recognized to date in immunosenescence[2] are shown in Table 1. For example, it has been observed that young individuals have an adequate population of T lymphocytes producing interleukin (IL) 2, responsible for the clonal expansion of other T lymphocytes. However, elderly individuals have T cells with low IL-2 production and consequently far slower T cell clonal expansion which gives rise to incomplete or reduced immune responses.[3] These incomplete immune responses generally result in diseases: autoinflammation, autoimmunity, neoplastic processes (leukemias/lymphomas, cancer), or degenerative processes (Alzheimer's disease).

There are many factors which affect the TCD3+ cells in the elderly, but it is clear that one of the main types of damage to TCD3+ cells is caused by oxygen free radicals resulting from oxidative stress. It is important to mention that despite having high levels of free radicals, elderly individuals also appear to have high antioxidant levels in plasma.[4] Repeated accumulation and the increasingly chronic nature of the oxidative process therefore seem to cause the TCD3+ cells to become destabilized.

Chronic inflammation and chronic infection in the elderly

The most important impact of immune dysfunction in old age is, however, chronic inflammation (inflamm-aging).[5] New theories and studies demonstrate how persistent, chronic inflammation throughout life (including that related to birth) is responsible for morbidity in old age.[6] The slow and on occasion imperceptible production of inflammatory mediators such as C-reactive protein, fibrinogen, amyloid protein, and cytokines such as platelet-derived growth factor, IL-6, IL-10, tumor necrosis factor (TNF) α, and transforming growth factor β alters the vascular epithelium and causes tissues to become chronically inflamed and to degenerate. The most important cause of this persistent inflammation is infectious diseases which contribute to a chronic state of immune activation and, over time, immunodeficiency. Some of the key microorganisms that produce chronic inflammation in humans are:

Table 1:
Main defects in immunosenescence

Immune component	Abnormality in immunosenescence
Hematopoietic stem cells	Increase in hematopoietic progenitor cell counts CD34+
T lymphocytes	Increase in circulating cytotoxic TCD8+/CD28+ lymphocytes Reduction in the quantity of naïve TCD3+/CD45RA+ cells Reduction in TCD3+/CD8+/CD45RO+ memory lymphocytes Reduction in CD4/CD8 ratio < 1.2
B lymphocytes	Increase in B lymphocyte polyreactivity Reduction in specificity and quantity in antibody production
NK cells	Increase in the expression of receptor activators of NKCD16+/CD56+ and NKT CD16+/CD56+CD3
Macrophages	Reduction in lipopolysaccharide recognition and activity Reduction in the production of TNF-α Phagocyte deficiencies
Lymph nodes	Reduction in the cellular and functional structure of lymph nodes

- viruses: cytomegalovirus (CMV), hepatitis B virus,[7] hepatitis C virus, virus G, herpes virus type 6, -7, -8;
- bacteria: *Chlamydia, Toxoplasma, Helicobacter pylori, Mycobacteria, Mycoplasma, Listeria, Brucella,* and *Borrelia.*[8]

Several recent studies have shown that populations of elderly patients have excess TCD8+ (cytotoxic) lymphocytes in their peripheral blood, compared to a healthy young or adult population, and these cell groups are linked by serological markers positive for CMV.[9] Although the risk of infection is higher than 70% according to study groups, this lentivirus has been shown to be capable of producing asymptomatic, persistent viral replications, causing chronic, undiagnosed, and untreated infections.[10] It is not known whether the loss of TCD3+/CD4+ lymphocytes in old age is caused directly by CMV (as has been seen in other diseases) or whether it is simply an opportunistic pathogen, but it is known that the reduction in the CD4/CD8 ratio, with increased cytotoxic TCD8+ expansion and being seropositive for CMV increases mortality in the first 4 years in more than 90%.[11] The formulation of anti-CMV antiviral protocols should therefore be considered in patients with a suspected viral infection, and immunostimulant products specific to the cytotoxic functions of T cells should be considered in patients with a CD4/CD8 ratio below 1.2 (normal value 1.5 ± 0.3). CMV is thus directly concerned and is one of the main agents involved in immune deterioration, and from this point of view immunosenescence, with the loss of T cells, could be highly infectious in nature.[9]

Supportive therapy in immunosenescence

Given these severe defects of immunity in the elderly and the important infectious link with CMV, it is essential to consider maintenance therapies adjusted to the individual's condition, with low toxicity, good tolerance, and within reach of all. It is in this type of situation that homotoxicology has a vital role: in immunological regulation, inflammation regulation, detoxification and lymphatic, gastrohepatic, and renal drainage of toxins. Combination medications exist with proven antiviral activity and with the ability to increase IFN-γ levels (Engystol), or involved in cellular phagocyte recovery (Echinacea compositum), which are undoubtedly an indisputable replacement therapy in immunosenescence. Inflammation-regulating products (Traumeel) with the ability to inhibit proinflammatory cytokines (Il-1, IL-8, TNF-α) and therefore systemic chronic inflammation are essential as blockers of inflamm-aging. Tables 2 and 3 show several antihomotoxic measures useful in immunosenescence. According to the course, detoxification and drainage cycles may be repeated. If treatment starts with immunostimulation, the patient may experience changes counter to the therapeutic aims, owing to the high levels of inflammatory molecules. The nutritional status of the elderly patient must be improved at the same time as antihomotoxic medication is administered. In some cases, antioxidative supplementation (vitamin C, vitamin E, glutathione, N-acetylcysteine, and S-adenosyl methionine), which tends to improve phagocyte migration, phagocytosis, production of TNF-α, and production of IL-1 and IL-2 in T lymphocytes, is also necessary.

We can conclude from the above that the aging process has a major

DET-phase	Basic and/or symptomatic		Regulation therapy*	Optional
Impregnation, degeneration	• Ginseng compositum	D&D	• Advanced supportive detoxification and drainage	• Arnica-Heel (if the inflammation is more severe)
		IM	• Traumeel	
		OR	• Coenzyme compositum • Ubichinon compositum • Tonsilla compositum	
Notes: Advanced supportive detoxification and drainage consists of Hepar compositum (liver), Solidago compositum (kidneys), and Thyreoidea compositum (connective tissue).				
Dosages: Detoxification and drainage: 1 ampoule of each medication 3 times per week. Immunomodulation: Traumeel, 1 tablet 3 times per day for 6 weeks. Organ regulation: Coenzyme compositum, Ubichinon compositum, and Tonsilla compositum, 1 ampoule of each 3 times per week.				

Table 2:
Immunosenescence: therapy scheme for weeks 1-5

DET-phase	Basic and/or symptomatic		Regulation therapy*	Optional
Impregnation, degeneration	• Ginseng compositum	D&D	• Basic detoxification and drainage: Detox-Kit	• Echinacea compositum (if there is a suspicion of a bacterial infection)
		IM	• Engystol	
		OR	• Pulsatilla compositum • Glyoxal compositum	
Notes: The Detox-Kit consists of Lymphomyosot, Nux vomica-Homaccord, and Berberis-Homaccord.				
Dosages: Detoxification and drainage: 30 drops of each medication in 1.5 l of water, drink over the day. Immunomodulation: Engystol, 1 tablet 3 times per day for 5 days, then break for 5, then take for 5 days (continue in this fashion for 6 weeks). Organ regulation: Pulsatilla compositum, 1 ampoule 3 times per week for 6 weeks; Glyoxal compositum, 1 ampoule only in the entire 6 weeks.				

Table 3:
Immunosenescence: therapy schemes for weeks 6-12

* Antihomotoxic regulation therapy consists of a three-pillar approach:
– Detoxification & Drainage (D&D)
– Immunomodulation (IM)
– Organ regulation (OR)

inflammatory component, triggered by infectious activators (principally viral) which give rise to profound defects in the immunity of elderly individuals which must be corrected in a natural and biological manner.[12]

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