Autoimmunity in the Elderly: Insights from Basic Science and Clinics – A Mini-Review

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Keywords

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Abstract

Advancements in the field of biomedicine, including the control of infectious diseases through antibiotics and vaccination practices and the prevention of chronic disorders, have led to reduced mortality, increased life expectancy and, as such, growth of the older population. Ageing is accompanied by profound morphological and physiological alterations. In particular, the immune system undergoes a complex series of remodeling/restructuring events, involving almost all compartments – both the innate and the adaptive system. This process is termed immunosenescence or immune dysregulation and, basically, includes 3 events: a reduction in immune response, an increase in the inflammatory and oxidation background (inflammaging and oxi-inflammaging), and a production of autoantibodies. While

there is an increase in autoimmunity in the elderly, this does not always translate into an increase in autoimmune diseases, which represent an important cause of morbidity and mortality and affect 5–10% of the world population. Each disease involves a specific age group. Generally speaking, most autoimmune diseases have a decreased peak age of onset, except for very few diseases such as giant cell arteritis and primary biliary cirrhosis, which are more prevalent among the elderly, or inflammatory bowel disease, which has 2 peaks of onset, the first one in young subjects and the other in those older than 60 years. Autoimmune disorders in the elderly have unique clinical presentations, and insidious and atypical symptoms may constitute a challenge for the physician. They are generally milder than in adults and can be controlled by a proper therapeutic treatment. However, despite advancements both in basic and clinical sciences, further studies and investigations are warranted and should be carried out in order to dissect the molecular framework induced by ageing.

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The Epidemiology and Impact of Ageing

Ageing can be defined as “a progressive, generalized impairment of function resulting in a loss of adaptive response to stress and an increasing probability of death” [1]. The last decades have been characterized by remarkable advancements in the field of biomedicine, including the control of infectious diseases through antibiotics and vaccination practices, as well as the prevention and the improved management and treatment of chronic-degenerative disorders, such as cancer, through the achievements of higher life standards and the delivery of better health care.

These changes have led to reduced mortality, increased life expectancy and, as such, growth of the older population, among others. According to some estimates, 1 in 4 Europeans is projected to be aged 65 years or older by 2030 [2]. Worldwide, the old population is expected to reach 1.5 billion subjects in 2050, the increase being particularly relevant in developing countries [3]. Therefore, understanding the physiological and physiopathological mechanisms underlying ageing is of crucial importance, given both the societal and clinical impact of ageing.

The Physiology and Physiopathology of Ageing

Ageing is accompanied by profound morphological and physiological alterations, concerning cellularity, hormonal profile, and, in particular, insulin responsiveness, cognitive functions, and immune system, among others. If not properly counteracted, the decline in these domains can lead to frailty, physical limitations, development of chronic-degenerative diseases, and mortality [4].

Since ageing is a complex, multifactorial process, different theories of ageing have been formulated, which vary according to the perspective used – biological, sociological, or psychological. The major ones are biological and belong to the family of damage or error theories and include the Dr. August Weismann’s wear and tear theory (“human body wears out due to use and time”). Another conceptual framework is given by Dr. Johan Bjorksten’s cross-linking theory, according to which senescence is a process characterized by an impairment of proteostasis (a portmanteau of the words “protein” and “homeostasis”) and accumulation of cross-linked proteins and structural molecules. Dr. Max Rubner, Dr. Raymond Pearl, and Dr. Rollo’s rate of living theory states that “larger animals outlive smaller ones, and the larger animals have slower metabolisms” or, in other words, “the faster an organ-

ism’s metabolism, the shorter its lifespan.” The idea of a putative correlation between the size of animals and their lifespan has been pioneered by Dr. Andrzej Bartke [5]. Dr. Alexander, Dr. Gensler, and Dr. Bernstein’s somatic DNA damage theory attributes a major role to the accumulation of genetic mutations, which the human body fails to repair. In conclusion, Dr. Rebeca Gerschman and Dr. Denham Harman’s free-radical and mitochondrial theories claim that ageing is characterized, respectively, by free radical-induced DNA damages and mutations, as well as by impairment and disruption of cellular processes, and by the loss of the mitochondrial ability to produce and stock energy [6, 7].

The other competing family of theories described ageing as a programmed series of biological events, which are regulated by a fine tuning of genes, being switched on and off, and by the existence of “endocrinological clocks” that modulate the hormonal release [6, 7].

For further details concerning these and further ageing theories, including the psychosocial ones, the reader is referred to Table 1.

Of particular importance for us, given the specific topic of the current mini-review, is the immunological theory. Cellular senescence, with the immune cell infiltration and the subsequent release of proinflammatory cytokines and chemokines and chronic sterile inflammation, results in senescence-associated secretory phenotype [8]. Immunological theory claims to explain not only the increased rate of infectious diseases and vulnerability among elderly people, but also a variety of disorders, including cardiovascular diseases, Alzheimer disease and chronic-degenerative disorders, such as atherosclerosis and cancer.

The Immune System and Ageing

During ageing, the immune system undergoes a complex series of remodeling/restructuring events involving almost all compartments – both the innate and the adaptive system, even though the latter is affected to a greater extent [9]. This process is termed as “immunosenescence,” “immunopause,” or “immune dysregulation” and, basically, includes 3 events: (a) a reduction in immune response, (b) an increase in the inflammatory and oxidation background (inflammaging – a term coined by Dr. Claudio Franceschi [10] – and oxi-inflammaging), and (c) a production and release of autoantibodies [11, 12].

For example, among the elderly, immunosenescence has been associated with an increased incidence of blood

Table 1. An overview of the main theories of ageing

Theory	Details	Theory	Details
<i>Biological theories</i>		Insulin resistance theory	Ageing is characterized by insulin resistance and impairment in glucose homeostasis
Accumulation theory	Ageing is characterized by accumulation of aberrant materials	Integrative theory	Since many biological theories are conceptually overlapping, this theory aims at integrating some of them into a coherent framework
Advanced glycation theory	Ageing is characterized by accumulation of advanced glycation end products	Membrane theory	Senescent cell membranes lose lipids and therefore ability to transfer chemicals, heat, electrical/ biophysical processes and other molecules, leading to toxic accumulation and reduced efficiency and functioning
Antagonistic pleiotropy theory	Genes with antagonistic pleiotropic effects may have benefiting effects early in life but detrimental effects in later age	Mitochondrial theory	Mitochondria lose their ability to produce and stock energy
Cellular theory	Ageing is characterized by cell senescence and telomere shortening	Mutation theory	This theory postulates that ageing is caused by mutations of different structural components of the human body
Circadian regulation theory	Ageing is characterized by an impairment and disruption of mechanisms regulating circadian rhythms	Neuroendocrine theory	This theory postulates the existence of a hypothalamic clock/timer of ageing
Cross-linking theory (known also as collagen theory)	Ageing is characterized by the accumulation of cross-linked proteins and structural molecules	Physical/biophysical theory	Ageing is modeled as a physical process and described as a loss of complexity, an increase in entropy or a failure of information transmission
Damage (fault)-accumulation theory	Ageing derives from the accumulation of faults and damages at a molecular/cellular level	Programmed longevity theory	Ageing is an essential part of the program of the human biology
Developmental theory	Ageing is the result and consequent of development; ageing and development are strictly related	Rate of living theory	"The faster an organism's metabolism, the shorter its lifespan"
Disposable soma theory	Available energy is limited and it is preferable to save energy for reproduction purposes rather than for preserving and maintaining a senescent body	Somatic DNA damage theory	This theory, being a mutation theory, attributes a major role to DNA mutations and accumulations of faults
Endocrine theory	It is a programmed theory and postulates the existence of biological endocrinological clocks that finely tune the hormonal release	Wear and tear theory	"The human body wears out due to use and time"
Endotomy/marginotomy theory	Ageing is characterized by DNA shortening during replication or in postmitotic cells	<i>Psychosocial theories</i>	
Error catastrophe theory	"Too many mutations cause the extinction of an organism"	Activity theory	Active engagement in social activities and leisure contribute to greater satisfaction and quality of life
Evolutionary theory	Old people "sacrifice" themselves for group benefit; this theory is known (with some variants) also as population-benefit theory, group selection theory, kin selection theory, selfish gene theory, and evolvability theories ("ageing as an adaptive program")	Continuity theory	Old people continue the activities and leisure preferred in early life, adapting to new situations and stimuli using learned patterns and approaches
Free radical theory	Free radicals interact with healthy molecules in a destructive way	Cumulative advantage/ disadvantage theory	Inequalities become more pronounced during ageing ("the rich get richer and the poor get poorer")
Gene-controlling theory	A set of genes controls and finely tunes the ageing processes and events, in a complete, independent way	Disengagement theory	Old people naturally withdraw from society
General imbalance theory	This theory postulates a general decline of body functions	Ecological theory	Environmental resources can contribute to ageing – in a positive or negative sense
Genetic/epigenetic theory	Genetic clocks (programmed cell death or apoptosis) and epigenetic clocks	Gerotranscendence theory	Old people develop new ways of viewing and experiencing the world
Hayflick's limit	Ageing is explained at a cellular level, given that cells are not immortal but are characterized by a limited number of cell divisions	Psychosocial stage theory	Generativity, ego-integration
Immunological theory/ autoimmune theory	It is a programmed theory and postulates a programmed immunosenescence, leading to increased vulnerability and frailty	Selective optimization with compensation theory	Selection of the most meaningful activities, strategic compensation of limitations for preserving involvement in a restricted number of preferred activities
		Socioemotional selectivity theory	Activities are reduced to those most meaningful from a socioemotional point of view

tumors and lymphomas due to immune deficiency and immune surveillance changes. Age-related changes at the level of the immune system are summarized in Table 2. It should be emphasized that changes in lymphoid

populations with age are selective; in other words, not all subpopulations are equally affected: the degree of changes can vary between people and can occur at different ages.

Table 2. Overview of the main biological changes of immunosenescence at the level of the human immune system

Immune cell type	Age-related changes	Immune cell type	Age-related changes
B cells	<ul style="list-style-type: none"> ↓ B cell development ↓ pre-B cells number (impaired pro-B/pre-B transition) ↓ naïve B cell number ↓ B cell repertoire diversity (skewed VH repertoire) ↑ CD19+ CD5+ cells which produce monoclonal, low-affinity immunoglobulins, with no involvement of T cells ↑ memory B cells with reduced diversity and affinity of antibodies ↑ serum levels of IgG1, IgG2, and IgG4 ↓ response to new antigens 	Neutrophils	<ul style="list-style-type: none"> ↓ phagocytosis ↓ chemotaxis ↓ release of superoxide anion radical ↓ signaling transduction cascades and pathways ↓ GM-CSF-induced activation ↓ LPS and fMLP activation
Dendritic cells	<ul style="list-style-type: none"> ↓ cell number ↓ antigen processing and presentation ↓ IL-12 and IFN-α production and release ↓ ability to stimulate lymphocytes ↓ chemotaxis ↓ endocytosis and micropinocytosis ↓ migration ↓ TLR functioning 	NK cells	<ul style="list-style-type: none"> ↑ cell number ↑ CD56dim CD57+ subset ↓ CD56bright subset ↓ HLA-DR, CD57, CD95, DNAM-1 (CD226), NKp30 (CD337), NKp46 (CD335) expression ↑ NKG2A, NKG2C, KIR expression ↓ cytokines and IFN-α production and release ↓ responsiveness to cytokines = ADCC
Macrophages	<ul style="list-style-type: none"> ↓ apoptosis ↓ phagocytosis ↓ chemotaxis ↓ polarization ↓ differentiation ↓ TLR function (↓ TLR1 and TLR4) ↓ MHC-II expression ↑ PGE2 production ↓ ROS production and release 	T cells	<ul style="list-style-type: none"> ↓ naïve cell CD45RA+ number ↓ proliferative capacity ↓ CD4/CD8 ratio ↓ T cell repertoire diversity ↑ surface expression of NK-associated receptors (KIR, NKG2D) ↓ CD28+ T cells ↑ CD28– T cells, in particular CD8+ CD28– ↑ (non functional) memory T cells ↓ or ↑ CD4+ CD25+ Treg ↓ Th1 function = Th2 function

Adapted and modified from [32]. ↓, decreased/down-regulated; =, unchanged; ↑, increased/up-regulated; ADCC, antibody-dependent cell-mediated cytotoxicity; CD, cluster of differentiation; DNAM-1, DNAX accessory molecule-1; fMLP, N-formylmethionyl-leucyl-phenylalanine or N-formyl-met-leu-phe; GM-CSF, granulocyte-macrophage colony-stimulating factor; HLA-DR, human leukocyte antigen – antigen D related; IFN, interferon; IgG, immunoglobulin G; KIR, killer cell immunoglobulin-like receptor; LPS, lipopolysaccharide; MHC, major histocompatibility complex; NK, natural killer; NKG2D, natural-killer activating receptor group 2, member D; PGE2, prostaglandin E2; ROS, reactive oxygen species; Th1, T help cell type 1; Th2, T help cell type 2; TLR, Toll-like receptor; Treg, T regulatory cells.

Ageing, T Cells, and Autoimmunity

T lymphocytes represent an important subset of the adaptive immunity compartment. Ageing is characterized by an absolute decrease in CD3+ T cells. Basically, this is due to 2 main events: (a) thymus atrophy and (b) alterations at the level of hematopoietic stem cells (HSCs).

The supply of T cell progenitors from bone marrow to thymus is compromised by genetic/epigenetic modifications of HSCs, including telomere shortening and impaired enzymes. Further, it seems that a depletion in lym-

phoid-biased HSC pool with an enrichment of the myeloid-biased HSC compartment occurs [13].

Thymic involution involving reduction in the size of the organ and increase in adipocyte content leads to a decrease in naïve CD45RA+ CD45RO– T cell output and, therefore, to a reduced T cell diversity, a restricted T cell repertoire and a shrinkage of peripheral T cell pool [14, 15]. The molecular bases of thymic involution are still unclear in details: however, it seems that molecules, like IL-6, leukemia inhibitory factor, oncostatin M, stem cell factor, and some hormones, including corticosteroids,

could play a role [16]. Ageing, as such, causes the accumulation of terminally differentiated $\alpha\beta$ CD8⁺ T cells, which can quickly act as effectors, despite their limited proliferative potential, acquiring the phenotype of innate-like T cells or natural killer (NK) cells receptors and losing co-stimulatory receptors [17]. In this way, a peculiar convergence between innate and adaptive immunity is realized [17]. Moreover, age-related FoxN1 (transcription factor) decline causes disruption of medullary thymic epithelial cells (mTECs), which are fundamental for the generation of a proper central tolerance. mTECs, indeed, eliminate self-reactive T cell clones together with thymic dendritic cells (via expression of the autoimmune regulator gene and thymic negative selection) and contribute to the development of natural regulatory T cells. An impairment of these biological processes could result in autoimmune phenotypes [18].

Thymic involution represents only one of the factors, impacting on T output, since thymic T cell generation only contributes to approximately 15% of T cell generation even in young adults. T cell generation in the adult tends to occur through homeostatic proliferation.

Another effect of ageing impacting on T cells is the loss of CD28, a molecule responsible for the proper activation of T cells: this event, indeed, requires the proper interaction between molecules such as the T cell receptor, IL-2R, and CD28. While the loss of CD28 is a typical feature of effector cells, during ageing the loss of the CD28 is accompanied with an impairment of biochemical pathways and cascades, as well as with the formation of altered second messengers, such as the nuclear factor of activated T cells and the nuclear factor kappa-light-chain-enhancer of activated B cells. Further, altered lipid rafts accumulate, leading to the formation of an improper immunological synapse (interface between antigen-presenting cell, APC, or target cell and T lymphocyte). The major biochemical pathways and cascades are altered too, leading to an alteration of phosphorylation mechanisms, kinase activation, chromatin remodeling and proteasome functioning, among others [19]. Age-related loss of CD28 occurs both in CD4⁺ and CD8⁺ T cells; however, it seems that this biological event happens more commonly and rapidly among CD8⁺ T cells. Moreover, CD4 as well as CD8 effector senescent T cells begin to de novo express receptors such as the killer immunoglobulin-like receptor, the natural-killer activating receptor group 2, member D, as well as other inhibitory receptors, whilst senescent T cells begin to mount the lymphocyte function-associated antigen 1. These molecules are usually not found on nonsenescent T cells.

They, then, acquire cytolytic capability, become resistant to apoptosis, release high titers of interleukins and cytokines, have shorter telomeres and reduced proliferative capacity, and may expand to large clonal populations, including also autoreactive T cells [20–22]. Autoreactivity can be explained considering loss of CD28 and de novo receptors (most of which inhibitory) expression: the first molecular event results in an accumulation of self-reactive cells in secondary lymphoid organs, whilst the second molecular event leads to an impaired threshold for antigen-specific activation and the ability to be activated independently of the antigen. However, it should be noticed that loss of CD28 seems to occur in humans but not in murine models.

Ageing causes a shift in the predominance of activated naïve CD4⁺ T-cell pools, too. For example, there is an expansion of the Th17 subset. These cells produce and release IL-17; in more detail, they are able to produce only IL-17A and IL-17F, 2 of the 6 IL-17 isoforms (A–F) currently known [23]. There is also impairment in the differentiation of T CD4⁺ cells in Th1 and Th2 pools [19].

The compartment of regulatory CD4⁺ CD25⁺ T cells (Tregs) tends to decrease, even though studies show contrasting findings in this regard. Treg cells have suppressive functions, and, as such, are able to counteract the insurgence of autoimmune events. A decline in their number could favor the insurgence of autoimmune disorders. However, other studies have failed to replicate such results [24].

Finally, another age-related relevant change is given by the increase in memory T cells, CD4⁺ CD45RO⁺ and CD8⁺ CD45RO⁺, which are, in the elderly people, preferentially located in tissues [19].

Besides thymic involution, chronic antigenic stimulation contributes to the above-mentioned changes. Persistent viral infections, including cytomegalovirus (CMV), human papillomavirus, varicella-zoster virus, herpes-simplex virus type 1, herpes-simplex virus type 2, Epstein-Barr virus, and measles virus, among others, can cause chronic stress and exhaust the human immune system over time.

Finally, the role of CD4⁺ CD28[–] T cells in atherosclerosis should be stressed since they are commonly found in patients with chronic inflammatory diseases including systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis (RA), progressive systemic sclerosis, multiple sclerosis, ankylosing spondylitis, Crohn disease, granulomatosis with polyangiitis (Wegener's), Graves' disease, and autoimmune myopathies, among others. CD4⁺ CD28[–] T cells grow and develop in a majority of

people as they age. Importantly, they invade atherosclerotic plaques and contribute to their growth and rupture.

Ageing, B Cells, and Autoimmunity

Ageing causes deep transformations of bone marrow, leading to reduced B cell generation. In more detail, this is due to several factors, including defects in HSCs, such as altered telomeres or epigenetic modifications, reduced transition of pro-B cells into pre-B cells, decreased IL7 production and release, and impairment in V-DJ rearrangements, which consists in heavy chain gene recombination [25, 26], as can be inferred from murine models.

Ageing can cause alterations in activation-induced cytidine deaminase and E2A/E47 concentration, reduced activation and expression of phosphotyrosine kinases and protein kinase C, resulting in impairment of immunoglobulin class switching (isotype switching or class-switch recombination) [27, 28]. Further, a reduction in the number and/or an impairment of the function of immature transitional B cells with a CD19⁺ CD24^{hi} CD38^{hi} phenotype is accompanied by an increased concentration of autoantibodies [29].

A subset of B cells with unique phenotypic and functional features termed age-associated B cells (ABCs), bearing CD11b and CD11c, but not CD21, has recently been identified in both mice and humans. These cells are characterized by a T-BET-driven transcriptional program, a robust responsiveness to Toll-like receptor 7 (TLR7) and TLR9 ligands, and a propensity for immunoglobulin G 2a/2c (IgG2a/c) allotype production [30, 31]. The evidence for a role of ABCs in the etiopathogenesis of autoimmune diseases comes from the observation that ABCs depletion in animal models leads to a reduced autoantibody titer [32]. However, further research is needed to shed light on the precise role of ABCs and their molecular mechanisms.

Ageing, NK Cells, and Autoimmunity

NKs are crucial in the defense against tumor and virus-infected cells. While ageing seems not to alter the antibody-dependent cell-mediated cytotoxicity, which remains relatively preserved, a decline in NK-mediated direct cytotoxicity and IL-2- and IL-12-mediated secretion of immunoregulatory cytokines and chemokines, such as interferon- γ (IFN- γ), has been described [33]. Expression of important molecules, such as CD69, which represents one of the earliest inducible cell surface glycoproteins mounted during lymphoid activation, and which is involved in tissue retention interacting with sphingosine

1-phosphate receptor-1 (S1P1), or HLA-DR, DNAM-1 (CD226), CD57, CD95, NKp30 (CD337), and NKp46 (CD335), seems to be decreased [19, 34]. Conversely, production and release of IL-1, IL-4, IL-6, IL-8, and TNF- α are increased [34]. Further, ageing causes an increase in absolute NK cell number; while remodeling NK population, there is, indeed, an age-related redistribution of NK subsets. In particular, there is a decrease in the CD56^{bright} pool, and an increase in the CD56^{dim} CD57⁺ population [34].

Ageing, Monocytes/Macrophages, and Autoimmunity

Age-related impairment in macrophage activity and functioning results in alterations in the TLR biochemical cascade (in particular, TLR1 and TLR4), expression of MHC class II following IFN- γ stimulation, polarization, differentiation, phagocytosis, release of reactive oxygen species and of IL-6 and TNF- α , wound healing, and tissue regeneration, among others [35]. Further, the decline in the proteasome-mediated autophagy and mitophagy pathways progressively leads to accumulation of altered molecules, resulting into an autoreactive/autoimmune profile [35]. However, most human studies focus on monocytes, and further research on macrophages is warranted.

Ageing, Neutrophils, and Autoimmunity

Neutrophils, an important part of the innate immune system, represent the largest pool of granulocytes. While not changing the total number of polymorphonuclear leukocytes, ageing, in contrast, causes several alterations in neutrophil functioning and activities, impairing calcium mobilization, actin polymerization, granulocyte-macrophage colony-stimulating factor (GM-CSF) release, oxidative burst, and the ability to develop a proper antioxidant shield (for example, releasing superoxide anion radical), microbicidal capacity, phagocytosis, and chemotaxis, among others. Also, adhesion and responses to soluble factors (including GM-CSF), bacteria – N-formylmethionyl-leucyl-phenylalanine, lipopolysaccharide, or endotoxin – or to phorbol 12-myristate 13-acetate are altered. Molecule recruitment into lipid raft, apoptosis, and signal transduction are impaired, too [36].

However, there is a dearth of information concerning the relationship between senescent neutrophils and autoimmunity [36]. The major function of neutrophils in autoimmunity is net formation. Further, it could be speculated that since polymorphonuclear leukocytes act as APCs to lymphocytes via major histocompatibility complex class I and release important mediators like IFN- γ ,

Table 3. Comparison of the age-related onset of autoimmune diseases among the elderly and young to middle-aged subjects

Autoimmune disease	Young to middle-aged (20–60 years)	Elderly (>60 years)	Ref.
Systemic lupus erythematosus	↑	↓	40
Rheumatoid arthritis	↑	↓, with ↑ disease burden	41, 42
Pemphigus vulgaris	↑	↓	43
Giant cell arteritis	↓	↑	39
Myasthenia gravis	↑	↓	44
Systemic sclerosis	↑	↓	48
Inflammatory bowel disease	↑ (20–40 years)	↑ (>65 years)	49
Graves' disease	↑	↓	46
Hashimoto's disease	↑	↓	46
Multiple sclerosis	↑	↓	47
Primary biliary cirrhosis	(50–65) ↔	(50–65) ↔	50

IL-12, and IL-18, their impairment could result in an inappropriate T cell response. Further, neutrophils act also as accessory cells in superantigen-mediated T cell activation [36]. Potentially, also this factor could play a role in the formation of autoantibodies.

Ageing, Dendritic Cells, and Autoimmunity

Dendritic cells, being APCs, are fundamental for ensuring self-tolerance. With ageing, they exhibit decreased propensity to migration, impaired production and release of IL-12 and of IFN- α [19]. Moreover, antigen processing and presenting capacity, micropinocytosis, endocytosis, phagocytosis, and TLR functioning seem to be impaired [19]. Further, dendritic cells can react to apoptotic cells and intracellular self-antigens, leading to autoimmune events [13].

Protective Factors

However, there are also factors and mechanisms that may exert an antiageing effect. For example, some studies found that the increased production of peripheral T-regulatory cells, such as CD4⁺ CD25^{high} FoxP3⁺ Treg cells, can counteract the formation of autoantibodies, protecting against the insurgence of autoimmune diseases [30].

The existence of these protective factors is very important in that it can explain, at least partially, the apparent paradoxes, i.e. an autoimmune disorder occurs despite the weakened immune system and the epidemiological/clinical incidence rate among elders, which is lower than expected, taking into account the high autoantibody levels [37]. On the other hand, the incidence and, above all, the burden of autoimmune disorders appear to be higher

in the elderly, with some diseases, like polymyalgia rheumatica and temporal arteritis, being practically nonexistent in younger people [37].

Epidemiology and Clinical Presentations of Some Relevant Autoimmune Diseases in the Elderly

Autoimmune diseases are a considerable cause of morbidity and mortality, and affect 5–10% of the world population. However, each disease involves a specific age group (Table 3) [38].

Giant cell arteritis (GCA) is a rare disease with an incidence of 200 cases per 100,000 people [39]. GCA often affects individuals aged >50 years differently from most autoimmune diseases. Its prevalence is approximately 0.2%, with a peak incidence occurring among subjects aged 70–80 years.

Systemic lupus erythematosus affects more often women in the range of 30–40 years [38]. Its age-specific incidence rate among males has a maximum of 2.2 (95% CI 1.0–3.4) per 100,000 person-years at the age of 65–70 years, while in women, the incidence is peaking at the rate of 3.6 cases per 100,000 person-years at the age of 20–25 years, having also a second local maximum of 2.6 cases per 100,000 at menopausal age [40]. RA is highly prevalent among women aged between 40 and 60 years. Its overall prevalence in adults is of 0.81% (1.16% for women and 0.44% for men, with a female:male ratio of 2.7:1) [41]. Estimates from the “Global Burden of Disease 2010” study suggest that, while the global prevalence of RA of 0.24% did not substantially change from 1990 to 2010, the overall burden as measured in disability-adjusted life years in-

creased from 3.3 million in 1990 to 4.8 million. This increase was due to both a growth in population and increase in ageing [42]. Pemphigus vulgaris (PV) is an autoimmune blistering disease that involves the skin and mucous membranes with a mortality rate of 5–15%. The mean age at onset of PV is usually between 40 and 60 years, with an incidence that varies from 0.5 to 3.2 cases per 100,000 population [43]. Myasthenia gravis (MG) has a prevalence of about 20 cases per 100,000 subjects [44]. The mean age at onset of MG is between 20 and 40 years, involving females in 60% of cases, whilst in late-onset MG, the female:male ratio is 1:1 [45]. Worldwide incidence of autoimmune hypothyroidism ranges from 27 to 448 cases per 100,000 subjects with the peak age at onset for women being between 30 and 50 years [46]. The incidence of Graves' disease is 21–120 cases per 100,000 people, with a peak age at onset usually before the age of 40 years [46]. Multiple sclerosis incidence is 3.6 and 2 cases per 100,000 subjects in females and males, respectively, and usually affects the ages between 20 and 50 years [47]. Systemic sclerosis has an incidence ranging from 3.7 to 22.8 cases per million subjects and a prevalence from 31 to 658.6 cases per million people, with a peak age at onset between 20 and 50 years [48]. Concerning the inflammatory bowel diseases (IBDs), the incidence of ulcerative colitis ranges from 0 to 24.3 cases per 100,000 subjects, with a prevalence varying from 4.9 to 505 cases per 100,000 subjects. The incidence of Crohn disease varies from 0 to 20.2 cases per 100,000 population [49]. The age at onset of IBD has 2 peaks, the first and the largest peak among subjects of 20–40 years old and the other among those >60 years old. Another disease is primary biliary cirrhosis (PBC) which affects mainly women aged 50–65 years. However, it has been reported that antimitochondrial antibodies, which are very sensitive and specific for PBC, may appear many years before the clinical presentation [50]. The fact that there is a very long period of incubation in some autoimmune diseases, such as PBC, gives rise to the hypothesis that also other autoimmune diseases may start many years before the clinical presentation. However, in GCA sub-

jects, the lack of specific autoantibodies makes this hypothesis very difficult to be proven.

Autoimmune disorders in the elderly have unique clinical presentations. As already mentioned, serological profiles are characterized by high auto-antibody (including rheumatoid factor or RF, antinuclear antibodies, antiphospholipid antibodies, antithyroglobulins, and anti-parietal cell antibodies) levels. However, while there is an increase in autoimmunity in the elderly, this does not always translate into an increase in autoimmune diseases. Moreover, insidious and atypical symptoms may constitute a challenge for the physician [51].

Conclusions

Ageing implies a complex array of changes and remodeling in homeostatic mechanisms that control the immune system, both in terms of numbers and functions of the different cellular subsets. Rather than being a mere process of immunosenescence, age-related transformations redesign the immune architecture and the balance between proinflammatory and anti-inflammatory protective factors, as well as between proapoptotic and antiapoptotic signals.

However, despite advancements in both basic and clinical sciences, further studies and investigations are warranted and should be carried out in order to dissect the molecular framework induced by ageing. Some details still remain unclear or overlooked in the extant literature, such as, for example, the role of senescent neutrophils in autoimmunity. Scholars, like Dr. Sergio Guinta, have postulated some specific mechanisms at the base of the so-called auto-innate-immunity syndromes [52]. Also, the role of gender differences in autoimmune disorders should be better explored.

Even though some notable longitudinal studies, such as the Swedish OCTO and the NONA trials [53], have contributed to a better understanding of age-related immune transformations, future research in the field of immunogeriatrics is warranted.

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