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INTRODUCTION

# The complex relationship between Immunosenescence and Inflammaging: Special issue on the New Biomedical Perspectives

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The present issue of Seminar in Immunopathology "Immunosenescence: New Biomedical Perspectives" is devoted to a hot topic, i.e., immunosenescence and inflammaging, and their complex relationship with the pathogenesis of age-related diseases (ARDs). Hereafter, we will summarize the main concepts and findings to put this issue in frame of the present knowledge.

The phenotype of old people is the result of the capability of the body to respond/adapt to cellular and molecular insults continuously occurring in all tissues and organs (damaging stimuli) we are exposed to lifelong, which are sensed as danger signals recognized by a limited number of evolutionary conserved receptors. This adaptation has been conceptualized as "remodeling," which can be considered a general theory of aging [1–3].

This remodeling is the result of the immunological history of the organism, a concept that has been dubbed "immunobiography" [4, 5]. According to this scenario, the immune system adapts (contemporarily both "negatively" and "positively") to the continuous challenges occurring throughout life, and immunosenescence represents the final result of this continuous remodeling/adaptation process.

An integral ingredient of immunosenescence is inflammaging [6]. A variety of molecules, such as stress hormones, mitokines, DAMPs, and garbage accumulation (garbaging), are able to modulate the acceleration or the deceleration of aging process loading on the inflammaging tone [7]. Immunosenescence (and inflammaging) have usually a negative connotation, but, according to a variety of recent observations, the changes of the immune system with age are much more complex, personalized, and dynamic than previously thought, being characterized by homeodynamic features balanced between "adaptive" and "maladaptive aspects" (discussed by [8] in this issue).

It is well known that with increasing age, the health status variability increases undergoing a progressive large divergence. Thus, old people are characterized by a large heterogeneity, suggesting that the basic/simple parameter "chronological age" becomes progressively less informative, according to the most recent finding suggesting that "biological age" (measured for example by whole genome DNA methylation) can be more accurate and predictive of incoming morbidity and mortality [9]. Accordingly, everyone has his/her own "immunobiography" [4], and consequently his/her own type/rate of inflammaging/immunosenescence trajectory. It will also be interesting to merge/compare immunobiography data with DNA methylation data, to pick up/measure the aging status/rate at the level of single old individual, and to check the informative value of such an approach starting at younger ages.

In this scenario, "good" and "bad" aging, ARDs, and longevity represent a continuum without precise boundaries, the extremes being represented by the wide range of relatively "younger" people affected by overt mild or severe ARDs, where inflammation plays a major pathogenic role, and by centenarians—the best example of successful aging [10, 11]—where inflammaging is present but at much lower level than younger people [12, 13].

In centenarians inflammaging appears to be balanced (at least in part) by the upregulation of a variety of anti-inflammaging parameters [14], and their "biological age" is significantly lower than their chronological age [13]. Moreover, centenarians show, at least in part, many

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characteristics similar to individuals who followed a calorie-restricted diet, one of the best practices to delay aging [15].

Never more than today, the acquired knowledge of the sophisticated mechanisms regulating the immune system activity and its aging are still only partially understood, and our knowledge of the mechanisms underpinning the immunosenescence processes at population and individual level are still largely unexplored ([16] in this issue), as shown by the Covid-19 able to provoke a pandemic attack with devastating health effects, particularly severe in the elderly previously affected by one or more ARDs. Such a peculiar susceptibility is likely substantially caused by the hyperactivity of the inflammatory component of the immune system, within a scenario of inflammaging, common in old people, and particularly in those affected by one or more ARDs and more vulnerable to the Covid-19 infection [17].

On the whole, these considerations can explain the relative lack of consensus about a "universal"/"comprehensive" definition of aging itself [18], and particularly of immunosenescence, which appears to be dominated by population-specific and individual trajectories (see [16] this issue), in agreement with the concept of immunobiography.

Within this larger perspective, the current special issue of Seminar in Immunopathology sheds light on additional new aspects of immunosenescence/inflammaging with the support of outstanding scientists, who have been working in the immunology and aging since many years. The reviewing approach has figured out emerging concepts as follows:

1. The tight local and systemic interconnection between the dynamic process of human aging and immunosenescence/inflammaging, at both site-specific (tissue/organs) and systems levels. This molecular and cellular relationship makes them master regulators and the gear of aging rate. Immunosenescence and inflammaging are key phenomena to understand the onset of ARDs which in turn accelerate the aging process and inflammaging and shortness of life span ([9, 19, 20] this issue). Within this scenario, particular attention has been devoted to major ARDs, such as neurodegenerative diseases, rheumatoid arthritis, cancer, and cardiovascular and metabolic diseases [19]. Along with this interconnection, Xu et al. focus on the complex interplay among senescence of immune cells, their different replicative capacity, and cellular turnover, stressing that several types of stimuli and signaling pathways may lead to senescence in the same cell type ([20] in this issue). The authors conclude that it is imperative to better define commonalities and differences in the process of senescence across various immune and non-immune cells. To complete the scenario, Frasca et al. focus on the senescence of a rather neglected body component, i.e., the adipose tissue (AT). AT and obesity play an essential role in both immunosenescence and inflammaging. A senescent-associated secretory phenotype accumulates in AT where adipocytes and pre-adipocytes, but also immune cells, show a senescent phenotype contributing to inflammaging with their SASP (senescent-associated secretory phenotype). The authors conclude that it is important to identify strategies of intervention to target senescent cells in the AT to reduce local and systemic inflammation and the development of ARDs ([21] in this issue).
2. The pervasive role of microbiomes. Microbiomes have a major role, not yet fully understood and appreciated, as major potential drivers of aging rate and inflammaging, being coevolved with the human genome and body microenvironment [22]. The age-related dysbiosis may indeed contribute to inflammaging because of a long-term immune system stimulation. This inflammatory condition might make the host more prone to potentially dangerous bacteria and thus contribute to various pathological conditions in older adults. Here Santoro et al. address the possible role of microbiomes from the different body sites (other than the gut) in aging and ARDs ([22] in this issue).
3. Aging, mitochondria, and mitokines. The research on role of mitokines in modulating immune response and inflammation in the elderly is still in its infancy. Here, Conte et al. focus on three important molecules, i.e., GDF15, FGF21, and humanin and their possible involvement in inflammaging. Although many aspects of mitokine biology are still controversial, the authors discuss the data showing that these mitokines and their immune-metabolic involvement and mechanisms activated by mitochondrial dysfunction have a basic anti-inflammatory role and increase with age. The hypothesis put forward by Conte et al. is that these mitokines can be considered part of the abovementioned adaptive and integrated scenario of the aging process that acts within the framework of a larger anti-inflammatory network aimed at controlling both acute inflammation and inflammaging ([23] in this issue).
4. The refined but weak equilibrium of immune response. The innate and acquired immunological responses are usually appropriate, but with aging, they significantly change becoming "hypo-" or "hyperactive." These dysregulations are at the basis of ARD pathogenesis and also sustain inflammaging. Accordingly, the effect of coronavirus SARS-CoV-2 and its interaction with the aging immune system are likely the result of an age-/disease-dependent maladaptive dysfunction likely present in old people affected by one or more ARD (including and also frailty), different among aged individuals owing also to the large heterogeneity of the number and location of senescent cells with their SASP contribution. Within such a complex scenario, recent advances in

systems biology, integrating clinical, immunologic, and omics data can help to identify stable and robust markers of vaccine response and move towards a better understanding of SARS-CoV-2 vaccine responses in the elderly (See [8, 16, 24] in this issue). In particular, motivated by the still unclear immunopathological mechanisms of SARS-CoV-2 infection, Ciabattini et al. stress that the design of vaccination strategies for older people is extremely challenging. Moreover, among the different SARS-CoV-2 vaccine platforms that have been developed, only a few are being tested in the older fraction of the population. Ciabattini et al. conclude that systems biology will help in addressing the complexity of this topic and in better understanding SARS-CoV-2 vaccine responses in the elderly ([24] in this issue).

5. Down syndrome and brain microglia as models to study the inflammaging and garbaging. Down syndrome is characterized by an intrinsic genetic defect (trisomy of chromosome 21 or part of it) and precocious aging on one hand, and a clear phenomenon of accelerated aging on the other hand. The immune dysregulation affects key cell types, both in myeloid and lymphoid compartments, and is associated with a chronic state of inflammation (see [25] in this issue). The latter also impacts at brain level. In this regard, microglia and glymphatic system become an excellent model to study mathematical models of how cell senescence, microbiota dysbiosis, sleep disturbance, and systemic/local inflammaging drive brain into aging (see [26] in this issue). The aging brain model illustrated in this paper focus on the accumulation and elimination of brain garbage during day and night, respectively, their change with aging, and the role played by senescent glial cells.

All these aspects have been elucidated in the current issue which suggest how complex is immunosenescence and inflammaging both locally and systemically and makes evident the still largely unexplored complexity of inflammaging and individual immunobiographies which in some older subjects may converge on a maladaptive function. However, the immune system is malleable and can be “forced” in the proper direction by a comprehensive, multitasking approach including not only vaccination but also nutrition, with particular attention to the gut microbiota, and physical exercise. On the whole, the heterogeneity of aging trajectories in humans suggests that an individually tailored approach is the future of immunosenescence and inflammaging, considering the increasingly appreciated importance of gender, ethnicity-geography, socioeconomic status, and multiple other differences.

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