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Immunology of Aging: the Birth of Inflammaging

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Abstract

The inflammaging concept was introduced in 2000 by Prof. Franceschi. This was an evolutionary or rather a revolutionary conceptualization of the immune changes in response to a lifelong stress. This conceptualization permitted to consider the lifelong proinflammatory process as an adaptation which could eventually lead to either beneficial or detrimental consequences. This dichotomy is influenced by both the genetics and the environment. Depending on which way prevails in an individual, the outcome may be healthy longevity or pathological aging burdened with aging-related diseases. The concept of inflammaging has also revealed the complex, systemic nature of aging. Thus, this conceptualization opens the way to consider age-related processes in their complexity, meaning that not only the process but also all counter-processes should be considered. It has also opened the way to add new concepts to the original one, leading to better understanding of the nature of inflammaging and of aging itself. Finally, it showed the way towards potential multimodal interventions involving a holistic approach to optimize the aging process towards a healthy longevity.

Keywords Immunosenescence · Inflammaging · Macrophages · Mitochondria · Free radicals · Cytokines · Signaling · Microbiome · SASP · Immunobiography · Trained immunity

Introduction

Aging is one of the most mysterious human experiences which always fascinated researchers, philosophers, and artists. Aging is a very complex process either from the biological or from the social/psychological point of view [1, 2]. There are many definitions of aging and none of them can capture its complexity, as many do not use the integration of complex systems [3, 4], but try to capture aging as a single reductionist phenomenon relying on unidirectional pathway. Nevertheless, a more complexified view of the aging process is emerging. Even the current definition of the hallmarks of aging seems to be a sort of catalogue of pathways without really defining the basic interactions between these hallmarks and how they interact, which would influence the whole complex process which is aging [5].

One of us (Prof. Claudio Franceschi) in his visionary article in 2000 entitled "Inflammaging: an evolutionary perspective on immunosenescence" attempted to use the network theory, to understand how stressors may influence their own feedback mechanisms and together what are their effects on aging [6]. He has chosen the immune system as an

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integrative model to try to explain more deeply how isolated phenomena may be integrated into a complex system which in turn would influence the fate of the whole organism. Since that time, the concept of inflammaging became one of the most important paradigms not only of immunosenescence, but also of the geroscience concept considering it as one of the main causes of the age-related diseases (ARD) [7–10]. However, there exist many uses and misuses of this original concept [11–16]. We will review how the experimental data on basic changes in the immune system occurring with aging ultimately led to the concept of inflammaging, what the original concept was, and how it evolved through the decades after 2000 considering its fundamental importance for the aging process.

Immune Changes with Aging

During the last century, there were considerable advances in the understanding of the immune changes during the process of aging [17–26]. Originally and even now for many immunogerontologists, the most important changes are occurring in the adaptive immune system [27–33]. Therefore, most of the studies were devoted to its study. However, some 40 years ago a paradigm change occurred also in the understanding of innate immune system aging, as it became evident that aging-associated changes are also occurring in this part of the immune response [34–39].

What Are the Changes in the Adaptive Immunity and Why They Were Considered as Determinant?

The adaptive immune response is evolutionarily the most sophisticated immune response. This is so because it is capable of specific memory (clonotypic immune system) [40, 41].

One of the most important causes of the aging-related changes in the adaptive immune system is the thymic involution [42–44]. This process starts early in life and results in the almost complete shrinkage of the T cell priming tissue in favor of a fibrotic and fat tissue. Thymic involution is considered the main reason for the most important changes observed phenotypically with aging, namely the decrease of naïve T cells (CD4 + and CD8 +) due to their output being reduced by about two orders of magnitude between the age of 20 and 70 [45, 46]. Concomitant increase of the proportion of memory T cells is in part a consequence of the reduced thymic output of naïve lymphocytes, and in part their "overproduction" in the periphery due to recurrent challenges by the cognate antigens including repeated virus reactivation [47, 48]. Over several decades, the paradigm was and still is that aging is related to the shrinkage of naïve T cells, which explains why certain diseases are increasing such as infection, cancer are increasing and why older subjects are not able to respond to the vaccination as efficiently as young subjects [49, 50]. This is most notably the case for the influenza vaccine [51–54], though recently this idea has been seriously challenged by the introduction of various adjuvanted new vaccines with greater efficacy in the elderly [55, 56]. The decrease in naive T cells, which never encountered their cognate antigens, results in a decrease of T cell repertoire (oligoclonality of the TCR) which are unable to recognize a fully new antigen such as those arising from cancer (neoantigens) [57]. This paradigm recently has been nevertheless questioned by a more evolutionary appraisal of this change by the more thorough evaluation of what is called the homeostatic proliferation, which could increase the naïve T cell pool independently of the thymus, as well as some type of stemness displayed by memory T cells [58]. Presently we are not sure whether it can be sufficient to supply sufficient numbers of functional effectors and whether the diversity of the TCR repertoire is enough to handle new antigens during lifespan [59, 60]. Moreover, the study of centenarians also raised the question of whether the repertoire really decreases with age, or only as a result of an individual's immune exposure history, called the "immunobiography" by Prof. Franceschi, which we think can be perfectly integrated in what we called the "envirobiography" [61]. These new approaches place the results of the studies of the aging immune system in a completely new perspective trying to escape from the only detrimental changes that occur in the immune system with aging [62].

Other changes in the T cell compartment should be mentioned if we want to relate these changes to what is called the inflammaging [48]. As mentioned above, the immune system reflects the lifetime exposures of an individual is subjected what we can call in a generic sense, stress [6, 63]. This stress can arise from a threatening situation with an adequate and measured immune response, but also from a chronic situation where the reaction becomes overvigorous and results in an uncontrolled and sustained inflammation [64, 65]. The T cell clones which encountered and responded to the challenge will shrink and leave behind them a few memory T cells. However, with aging these cells become more senescent or exhausted and produce a substantial amount of pro-inflammatory cytokines and mediators [66–68]. These pro-inflammatory factors in turn will also stimulate other cells to become metabolically active while immunologically non-functional. As a consequence, these phenotypic alterations result in changes of the T cell functions including proliferation, migration, cytokine production, and pathogens killing [69, 70].

Behind this dysfunction of T cells, many new processes could be unravelled such as changes in the cell membranes with aging. The membrane becomes more rigid which decreases the formation of the immune synapse, the primary

structure necessary to elicit a correct cellular response [71, 72]. The movement of various signaling molecules inside of the immune synapse is also compromised with aging [73, 74]. Therefore, the signaling elicited inside the T cells via the TCR and CD28 is compromised. In fact, almost all signaling pathways are compromised which precludes the initiation of a normal protective T cell function [75–77].

The complete loss of CD28 (and also its decreased expression observed in aging T cells) not only determines the fate of the T cells (from naive to TEMRA T cells) but also the decreased production of IL-2 and the changed immunometabolic capacities of the T cells [78]. When stimulated, T cell metabolism shifts from the oxidative phosphorylation (OXPHOS) to aerobic glycosylation which is much less productive in terms of ATP produced, but much more rapid [79–83]. Because of the alteration in the signal transduction pathway of mTOR, this switch cannot happen efficiently in aging T cells, and the required energy will not be provided [84, 85]. Therefore, all the phenotypic, functional, signaling pathway, and metabolic changes with aging together lead to an altered T cell function. Again, the question arises whether these changes are always detrimental or may have also some adaptive characteristics. We will elaborate on this idea later in this review.

In summary, all these changes in the adaptive immune response were considered as the basic mechanism behind the occurrence of so-called age-related diseases (ARD) which are the basic attributes to usual/pathological aging. However, in the meantime, some researchers started to question whether these changes in the adaptive immune system would explain *all* that we observe in aging from the pathological and clinical sides.

What Are the Changes in the Innate Immunity and Why They Were Considered as Dominant?

The role of phagocytic cells was well known since Metchnikoff description of the macrophage [86–88]. However, it was almost a heresy to conceive that the innate immune system being so unsophisticated (compared to the adaptive system) may change with aging. It can be conceptualized that these changes may be less dramatic, but the question nevertheless raised why the innate immune response should not be modulated by what we are now calling the immunobiography.

It should be noted that more diversity exists in the innate immune system than initially believed. The cells composing this immune arm are the neutrophils, monocytes, macrophages, NK cells, and some other cells not always well specified [89–93]. Their functions are also well diversified to answer to a multitude of challenges even if the response happens in a non-specific way and with a relatively limited number of effectors [94]. This situation resembles what has been called the bow tie or hourglass structure: numerous inputs pass through a limited number of effectors that coordinate a response based on the integrated information, with effects on a larger range of downstream targets [95].

There are also numerous phenotypic changes in all these cells of the innate immune system over time and exposures. With increased challenges, these cells exit their basic quiescent state and become more and more activated [96]. There are changes in the monocyte phenotypes which shift from the classical state to an intermediate and non-classical state [97–99]. There is no consensus whether these non-classical monocytes may be more reactive than the classical ones, but they are somehow more inflammatory and present some attributes of senescence/exhaustion [100, 101]. There is also a very clear shift considering the CD56 expression from the $CD56^{bright}$ to the $CD56^{dim}$ phenotype of NK cells with clear functional changes, the former being more inflammatory and the latter being more cytotoxic [102, 103].

The innate immune system has three main functions. The first is to avoid and mitigate the occurrence and progression of all types of internal and external damage caused by various challenges, by a sustained clearing function. In this sense, the innate system parallels the adaptive immune system for maintaining a functional homeostasis. The second is the priming of the adaptive immune system by the means of soluble mediators, such as IL-12. Last, but not least, the third function is the antigen presentation by all these phagocytic cells (but most importantly by the dendritic cells) which assure the transition of the defense to adaptive immune system when the innate response is not efficient enough or sufficient. Most studies concluded that these functions of the phagocytic cells (specifically the chemotactic, phagocytic, antigen presentation and killing functions) are altered with aging [16, 24, 26, 34, 64, 104].

The sensing of these challenges by innate immune cells is through various specific receptors, similarly to the adaptive immune system. The innate immune system also relies heavily on the adequate functioning of these so-called danger recognition receptors and pattern recognition receptors (PRRs). Among them the most important are the Toll-like receptors (TLR), the NOD-like receptors (NLRP), and RIG-like receptors (RLR) [105–108]. The specific signaling pathways of all of them assure an appropriate cellular response [109, 110]. With aging the number of these receptors as well as their signaling pathways may change [99, 111, 112]. These changes will result in decreased functions of these cells as described earlier [16, 24, 26, 34, 64, 104].

One of the most important findings in the case of the innate immune system is that the cells of older individuals are in a tonic activated state producing more proinflammatory mediators including free radicals and pro-inflammatory cytokines [37, 113, 114]. However, when stimulated, they cannot respond adequately by an increase in their protective

functions [26]. For the time being, there was no explanation for this phenomenon, but it has greatly contributed to the birth of the concept of inflammaging by Prof. Franceschi as will be described [6].

Recently, this mystery described earlier in aging started to be plausibly explained by invoking a process observed in the phagocytic cells. A few years ago, it was hypothesized that even the innate immune system possesses some sort of memory. This type of memory was named innate immune memory or trained innate memory [115–118]. This means that each time that the innate system meets a new challenge, through what was called immunobiography because of the metabolic and epigenetic changes occurring at the cellular levels, the involved cells became much more able to fight the aggression than if they would never encounter any challenge. However, this cascade cannot go for ever without causing any harm [119, 120]. In this concept, the other side of the coin is the final paralysis of the cells, meaning that when they are stimulated, they cannot react anymore and become paralyzed/non-functional. Interestingly, descriptions concerning the innate immune memory fit with the changes observed in the innate immunity during aging. This gave rise to the concept that aging results in a sort of trained innate immunity which may clearly benefit against repetitive infections or other challenges during life, but may become paralyzed after overstimulation [61, 96]. This fits with the concept of inflammaging even if the inflammaging is a much more global concept.

The Birth of Inflammaging or the Original Description of the Concept

Prof. Franceschi and co-workers published their new concept of aging/longevity by using the concept of inflammaging at 2000 [6]. This was a revolutionary concept which changed our entire thinking not only in relation to the aging of the immune system in immunology but to aging in general. It is interesting to note that the concept was born with a new century.

The concept indeed has its foundations in the observation that life is under continuous pressure of various stressors. For maintaining life, these stressors should be canalized either by minimizing their amplitude or by different anti-stress mechanisms which developed along with the different stresses [121, 122]. This was called by the authors as the anti-aging network. This should not be understood as the notion of anti-aging medicine is used nowadays [123]. During aging as the experimental data for both the innate and adaptive immune systems showed, there is a constant increase in the pro-inflammatory status underlying, what was later called by Prof. Franceschi as immunobiography and leading to the phenomenon of inflammaging [61]. Many different stresses/stressors arising from chemicals via cellular wasting to antigenic challenges are concomitantly resulting in increased sustained stimulation of the immune response. In the meantime, the organisms from the lower eukaryotes to the most evolved mammals including humans have developed very powerful and diversified means to combat these stresses. These include antioxidant, anti-inflammatory, and anti-cancer processes [124–127]. At this time, the whole immune system could be also considered as an anti-stress system and the macrophages may be at its center [128, 129]. They are those which receive the many stresses and simultaneously are able to orchestrate the body's responses including the priming of the adaptive immune response to various stresses. In this way, the macrophage is at the center stage of the inflammaging concept as they are the masters of the stress response [6].

From this point on, the whole inflammaging concept took its extraordinary role in the aging process which can be an adaptation or a maladaptation. This is based on the central network theory of adaptation and represents an evolutionarily important contribution to this concept of inflammaging. This could explain the whole evolution as if we consider the hormesis theory that all the continuous "good" minimal stress trains the system, while "bad," toxic stressors kill and paralyze the system [130, 131]. This is in line with the genial description of the stress phenomenon by Selye [132]. The next fundamental attribute of this thinking that, until a certain threshold is reached, the changes occurring with aging, including the immune changes may be considered as the result of an adaptive capacity integrating all reactions from the organismal level to the molecular level and including different system levels such as the neuro-endocrine-immune supersystem [6, 133]. Therefore, along this line of thinking, this whole process may be adaptative and leading to extreme longevity and an accurate and less damaging management of diseases. Alternatively, it may be maladaptive, crossing the threshold where there is no more possibility to contain it by any means and the result is in unsuccessful/pathological aging characterized by uncontrolled diseases and frailty which leads to early functional decline and death. This also puts the relative importance of time into the equation of the aging process, as in young subjects the rate of attaining the threshold is slowed down as is also in the case of centenarians, while in pathological aging the time is accelerated and for various reasons the threshold is reached very rapidly leading to loss of autonomy and death [134–137].

The concept of inflammaging led to announcement of the "two hits" theory and as already mentioned above to the perfect understanding the role of genetics and environment in the aging process [6]. Individuals are constrained in their rate of reaching the threshold of the proinflammatory point of non-return by their genetic make-up which is greatly modulated by the quality of the stressors and the reaction elicited by them [138, 139]. The part of each of them may

vary in all individuals which makes it very difficult to predict aging and its rate at an individual level [9]. This also underlines that with aging the age-related diseases may have two types of genetic components/backgrounds; the first is the genes responsible for the inflammatory background while the second is conferring either a robustness or frailty [6]. This explains why in the presence of similar envirobiographies the susceptibility to diseases of the individuals is very different [9, 140, 141].

This whole concept was underlined with the example of IL-6 demonstrating that with aging this pro-inflammatory cytokine is increased sometimes to extraordinarily high levels even in the case of centenarians, but its consequences are very different from one individual to the other [142, 143]. The centenarians are very resistant to this increase by a powerful anti-inflammatory network which protects them from this eventually harmful increase but also assures an adequate role in combating stress for the increased IL-6 levels.

In summary, inflammaging as originally conceptualized is neither harmful nor beneficial per se, but evolutionarily may be beneficial in an adaptive manner or harmful in a maladaptive manner depending on the genetic and environmental background depending on how the individual will age with pathological or successful/longevity aging [144].

The Evolution of the Original Concept of Inflammaging

Twenty years have now passed since the original introduction of the concept of inflammaging by Prof. Franceschi. There are more than 1000 publications devoted to this concept which greatly evolved from its original announcement. We will describe the major changes and highlight their importance.

How Did Inflammaging Evolve to a Generalized Multi-level Fueled Inflammatory Process from the Macrophage-Centered Concept?

During these last years, it was conceptualized that the inflammaging process is not arising exclusively from the leading cell of the innate system, the macrophages [6, 145], but also from many other aging-related processes that contribute to fueling inflammaging as an inflammatory process [9, 113]. First, senescence as a generalized aging phenomenon was considered as a powerful contributor to the process of inflammaging [146–152]. This originated from the Hayflick replicative senescence model where the cells became resistant to both proliferation and cell death after a certain number of divisions due to the consumption of the cell defense leading to telomere length decrease [153]. So, these senescent cells fill the space in organs. Originally, they were considered as metabolically inactive but lately it was shown that they may be extremely inflammatory and contribute to inflammaging [154–157]. This phenomenon is often referred as the senescence-associated secretory phenotype (SASP). There is yet no far-reaching consensus on what is the role of senescent cells in the aging process in humans in contrast to what was described in other organisms [158]. The process of transformation of functional cells into senescent ones is evolutionarily a very old and useful process. However, likely as in the case of inflammaging, it is the threshold of the number of cells involved or of their metabolic activity which will determine what could be their role either adaptive or maladaptive with regard to other aging processes.

Next, the role of the microbiome at any part of the organism by the development of dysbiosis or presence of pathobionts may contribute to inflammaging [159–161]. With aging there is a disbalance due to many circumstances between the commensal good microbes and the bad microbes in the various parts of the organism, especially in the gut. These bad microbes will induce the production of a huge quantity of proinflammatory mediators which may contribute to inflammaging. The microbiome is an independent metagenomic system but related very intimately to a well-functioning immune system during the whole life [162]. It is conceivable that what was originally described as inflammaging could potentially include the microbiome not only as a stressor but also as an integral part of the immune system [163, 164]. The evolution of the microbiota in the case of centenarians is also in perfect alignment with the original concept of inflammaging [165–168].

Next, we should mention (even if it is not a new process but the understanding of an old concept) the activation at the basic level of the immune system with aging, which could be perfectly conceptualized as a form of already mentioned innate immune memory of trained innate immunity [61, 96]. This states that because of epigenetic and metabolic changes all along the stimulation (lifelong) of the immune system there is a constant upgraded stepwise activation. The next response is being always more efficient than the previous one. This confers a strong powerful tool to the immune system [169]. The corollary, as the threshold theory introduced in the inflammaging, the trained immunity when crossing the threshold/point of non-return will turn against the organism and generate a paralyzed state. This mirrors what was originally described for inflammaging [6].

Finally, as not so often mentioned but the metabolic changes during aging orchestrated by the mitochondria may also contribute to inflammaging [169–172]. Mitochondria may contribute to inflammaging either directly by the direct production of free radicals or by the internal garbage production such as the mtDNA released into the cytosol and detected by the internal PRRs. Moreover, mitochondria are intimately participating in the immune process by protecting

against microbes resulting in vital cytokine production such as IFN-type I [173, 174]. Mitochondria are also producing various mitokines playing either pro- or anti-inflammatory roles [175] as such intimately participating in the immune response. The production of the energy inside of the immune cells will determine their functionality. In the future, mitochondria will become even a more important regulatory clock of the immune functions including inflammaging.

Inflammaging as the Primum Movens of the Detrimental Concept of Aging

During these last years and since the establishment of the nine hallmarks of aging, the inflammaging process (integrated in the intercellular communications hallmark) came to be viewed as an exclusively detrimental phenomenon to be combated if aging would be stopped, slowed down, or even cured [176, 177]. The nuanced original description of the inflammaging process almost disappeared to leave the place for an age-related unidimensional reductionist disease underlying process [14, 178–180]. Most of the time it is defined as an inflammatory process (low grade, clinically not perceptible, chronic, systemic) occurring in the absence of infection that is a fundamental attribute of aging [181]. Most of the time the anti-inflammaging process, a basic corollary of the inflammaging, was completely ignored, except by the follow-up publications of the Franceschi group [125].

Therefore, nowadays, the concept of inflammaging mostly became a detrimental age-related inflammatory process which underlies aging and the age-related diseases [182, 183]. This conceptualization of inflammaging is harming the nuanced appreciation of the aging phenomena as being also adaptive and as such must be optimized instead of combatted. One other perverse consequence of this unidirectional concept is the tentative assumption to consider the aging process as a disease in which the inflammaging is a risk factor which should be absolutely reversed for achieving a "healthy" aging [184, 185]. This is harming the evolution of the complex system approach of aging to conceptualize the many changes occurring with age as a physiological process in which, taking into account the many interrelated processes, a more fundamental multimodal intervention may be possible [186].

Moreover, this harmful conceptualization of inflammaging is detrimental to the holistic conceptualization of immunosenescence. Inflammaging and immunosenescence are the two sides of the same coin [187]. Both of them evolve fueled by the immunobiography integrated in the envirobiography, for a harmonized adequate and adapted response to internal and external challenges. This means that there is a mutual interaction between the inflammaging-producing factors provoking the immunosenescence and the immunosenescence-producing factors which contribute to the maintenance of the inflammaging.

In summary, the misunderstanding and the distortion of the original concept of inflammaging resulted in many deleterious conceptual applications of it. Most importantly it contributed to considering inflammaging in a unidirectional and reductionist way to explain what ever could happen in aging. This also precluded any attempt to holistically unite the immune changes with aging. Finally, it contributed to the erroneous concept of aging as a preventable disease as proposed by geroscience. This concept was also instrumental in the very recent misconception of the role of inflammaging in COVID-19.

Inflammaging and COVID-19

COVID-19, due to the SARS-CoV-2 virus, started in the world in late 2019 and became a pandemic in March 2020 [188]. This was a new not yet encountered virus. Early in the course of the pandemic, older subjects paid a great price as they were more seriously ill and died more often than their young fellows [189]. It is interesting to mention that the most plausible explanation for this fact was two well-known detrimental processes related to aging, namely immunosenescence and inflammaging. There have been many articles which tried to relate the clinical pathways and the mortality to the abovementioned two processes [190–193]. However, even if the explanation seemed very appealing, and the rationale was unattackable if we consider the nature of the original description of inflammaging, we would clearly understand that at most immunosenescence/inflammaging could be a contributing factor but in any case could not fully explain these early observations and statements. The recent development and shift of the disease towards the younger population is also supporting this latter contention.

Therefore, how can we conceptualize the relationship between immunosenescence/inflammaging and COVID-19 now? It is clear that not all older subjects suffering from COVID-19 were severely ill and died. We had many nonagenarians and centenarians who survived without any sequelae. This means that as the original concept of inflammaging stated the threshold of the intensity of the inflammaging as well the counteractive mechanisms will determine in the long run how the older organism will react to a very strong (out of hormesis) stress. It was conceptualized that the response in some cases may be adequate but the turn off was not while in other cases both the response and the turn off were inadequate. Thus, the evolutionary perspective of inflammaging may fully explain why in some cases it could contribute while in other cases not. This underlies the role of genetics and the environment but also, on some occasions, the hormetic role of some disease may play to either

aggravate or improve the response to the SARS-CoV-2 infection. We should also mention that the chronic inflammatory diseases of the older subjects may play a crucial role in their susceptibility to COVID-19 [194]. This misconception generated many theories and false treatment options, but most importantly a huge social, psychological, and physical harm to older subjects that will be present for years. There is also a question of how the long-term sequelae following recovery from this condition ("long COVID") would lead to an accelerated inflammaging resulting in increased and worsening age-related diseases even in younger individuals [195]. This new disease also raised the question of sex differences that could help in explaining the different aging trajectories and age-related disease propensity in the two sexes, particularly in very advanced age [196].

However, COVID-19 also catalyzed new studies in immunology which were almost unimaginable before the pandemic. This generated studies of multilayered omics as were predicted by Prof. Franceschi some years ago [197] showing that the immune response to SARS-CoV-2 could not be understood without an integrated multilayered analysis of the various components of the immune response at the single cell level [198, 199]. In this way, this new infection gave a new impetus for thinking differently and for understanding the process of immunosenescence/inflammaging by integrating it in a complex systems biology approach (Fig. 1).

What Inflammaging Taught Us About a Positive Conceptualization of Aging

The original concept of inflammaging was revolutionary considering how the immune aging and even the concept of aging were understood previously. However, we should stress that without the knowledge accumulated earlier this conceptualization could be hardly born. This puts into an evolutionary perspective a phenomenon which was considered as unidirectionally harmful. In turn, this new perspective opened the way to understand aging and the occurrence of age-related diseases in a more nuanced manner and may eventually open the way for a personalized understanding of the aging of each individual.

This also pointed to the fact that interventions may be possible as the various aging trajectories are not depending only on genetics but also on the environment which in turn will influence the epigenetics [200–206]. In the meantime, epigenetics was considered as one of the aging clocks being able to determine the biological age of the subjects [207].

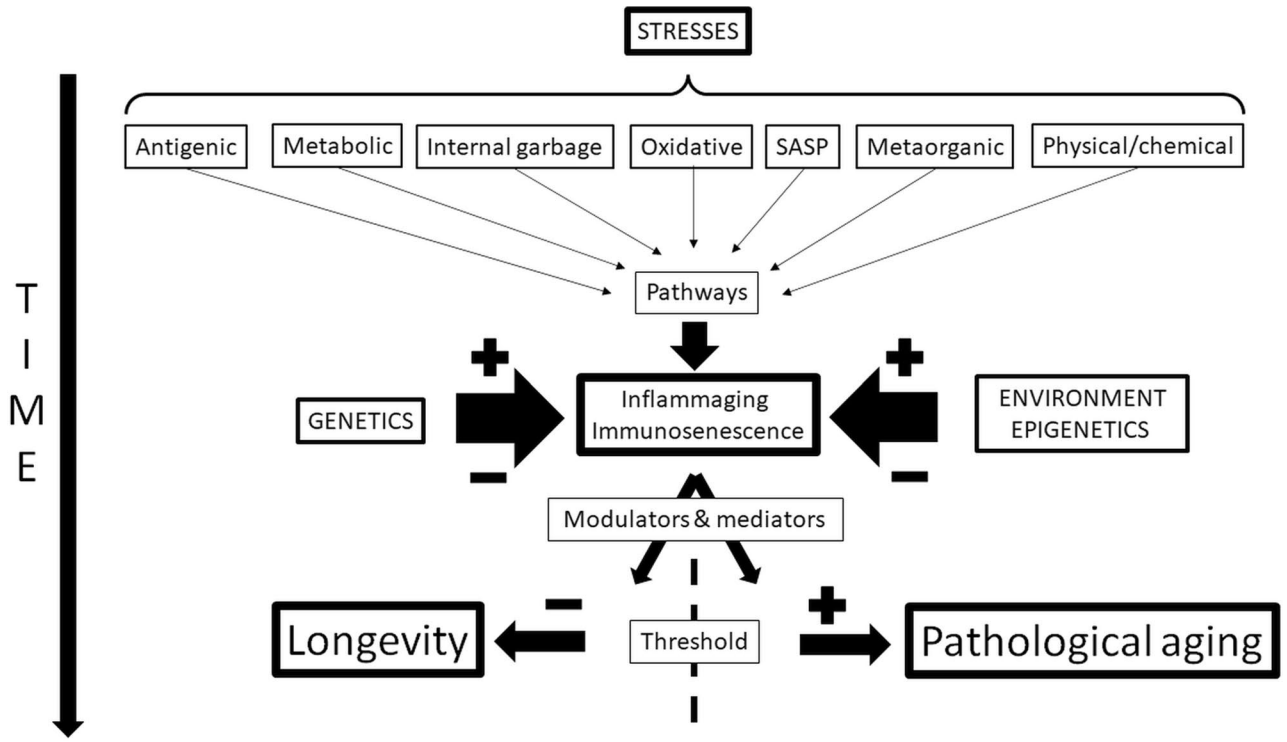

Fig. 1 The conceptualization of inflammaging by integrating the original concept to the latest scientific developments. There are numerous stresses which through various pathways contribute to the lifelong shaping of immunosenescence/inflammaging. The resulting mediators/modulators dependent on the physiological threshold will lead either to longevity or pathological aging. The concomitant role of genetics and environment/epigenetics is also illustrated. All these processes are time dependent and define the underlying concept of immunobiography

The inflammaging conceptualization helped to understand also that the aging process is a lifelong process starting early in life and becoming manifest late in life when the thresholds are crossed [9]. Unfortunately, on most occasions, only the tip of the aging iceberg is seen. Therefore, any treatment of the ARDS should embrace the whole concept in a holistic manner. The holistic multimodal approach by nutrition, exercise, "bad" stress management, and positive thinking may influence the threshold and initiate longevity/adaptAge instead of damnAge [130, 131, 200–204].

This revolutionary conceptualization showed us that we need to be more integrative, holistic, and less rigid in our biological aging appraisal. It is true that aging will end with death, but this inflammaging concept is showing us that a nuanced approach may delay and optimize the resources even without aiming to a rejuvenation. Rejuvenation in this concept may be more harmful than beneficial by improving the functioning at one body system without taking into account the functioning of the whole organism, which leads to disbalance and maladaptation. However, multimodal modulation is possible and necessary.

Conclusion and Perspectives

Prof. Franceschi's original concept of inflammaging was revolutionary and pioneering and remains as such. It would be highly desirable if the immunogerontological community would return to the original concept and would integrate the newly created knowledge in a way that aging became again a physiological, modulable, but however inevitable process. The concept behind how inflammaging is considered is valuable and far-reaching for many different processes in aging. Thus, it should create the basis of a systemic and integrative approach to aging leading to its personalized modulation to create an inside and outside environment of a healthy longevity.

Nowadays, several multimodal interventions aimed at inflammaging may exist to achieve the healthy longevity including nutrition, physical activity, stress management, and social activities, which perhaps in the future may be reinforced by pharmacological modulations.

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Declarations

Conflict of Interest The authors declare that they have no conflict of interest related to this article, except AAC who is founder and CEO at Oken.

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