Inflamm-ageing

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Purpose of review
Inflamm-ageing, defined as the chronic low-grade inflammation typical of ageing, seems to be the common biological factor responsible for the decline and the onset of disease in the elderly. The major age-related diseases share a common inflammatory pathogenesis, giving rise to the so-called 'diseasome of inflamm-ageing'. Main objective of this review is to provide a comprehensive view of the complex interactions responsible for inflamm-ageing, underlining its relationship with metaflammation and the role of senescent cells, gut microbiota and nutrition in determining when, where and how much this phenomenon impacts on the health status during human lifespan.

Recent findings
The ageing process and the health status of elderly people may be improved by facing and slowing down inflamm-ageing. Among the inflammation modulators, gut microbiota and nutrition should be exploited as potential powerful tools to promote healthy ageing and to extend the lifespan in humans.

Summary
The possibility to control inflamm-ageing represents a powerful tool to modulate and counteract the major age-related pathologies and it is urgent to clarify the shady areas of the complex mechanisms underpinning inflamm-ageing in order to carry out targeted therapeutic interventions towards an improvement of the health status in the elderly population.

Keywords
cellular senescence, gut microbiota, inflamm-ageing, metaflammation, nutrition

INTRODUCTION

With the term 'inflamm-ageing', we indicate the low-grade chronic inflammatory status characteristic of the ageing process. It was conceptualized for the first time in 2000 [1] as a consequence of the global reduction found in the elderly in the capability to cope with antigenic, chemical, physical and nutritional stressors, and of the concomitant progressive increase in proinflammatory markers. This phenomenon has become more evident with the recent dramatic increase in life expectancy, as the human immune system has to face antigen exposure several decades more than in our recent evolutionary past. Moreover, a plethora of evidence indicated that apparently different age-related pathologies, such as atherosclerosis, cardiovascular diseases, type 2 diabetes, metabolic syndrome, sarcopenia, osteoporosis, cognitive decline and frailty [2,3], share a common inflammatory pathogenesis. Therefore, inflamm-ageing could be seen in a global perspective as the common biological factor responsible for the decline and the onset of disease in the elderly, giving rise to the existence of the 'diseasome of inflamm-ageing' (Fig. 1).

Following this perspective, how can we reconcile the fact that inflamm-ageing (in term of increased plasma levels of inflammatory cytokines, acute phase proteins, and coagulation factors) is still present in centenarians, who largely escaped from major age-related diseases having a strong inflammatory pathogenetic component? Centenarians show a complex and peculiar balancing between proinflammatory and anti-inflammatory characteristics, either phenotypically or genetically [4], whose net result is a slower, more limited and balanced development of inflamm-ageing in

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KEY POINTS

- Inflamm-ageing is a multifactorial and systemic process, characterized by complex interactions of a plethora of molecular mediators, as exemplified by the nuclear factor (NF)-κB interactome.
- Concomitantly with the beneficial tumor suppression and tissue repair effects, senescent cells, accumulating with age, can determine the persistence of inflamm-ageing, thus contributing to cancer growth.
- Despite their fundamental differences, inflamm-ageing and metaflammation, which share stimuli and pathogenetic mechanisms, should be considered together within a systems medicine perspective.
- Facing and slowing down inflamm-ageing may improve the ageing process and the health status of elderly people.
- The manipulation of the gut microbiota and of the diet, owing to their immunomodulatory and anti-inflammatory properties, represents a powerful tool to extend healthy ageing and lifespan.

comparison to 'normal' people, who are characterized by either faster or inadequately counteracted anti-inflammatory responses [5].

A potentially important consequence of the age-related impairment of the balancing between inflammatory and anti-inflammatory agents is a profound, systemic modification of cellular microenvironment(s), which in turn can determine a different rate of ageing of organs and tissues, leading to the so-called 'mosaic of ageing' [6]. Furthermore, the age-related and inflammation-related change of cell microenvironment can also cause a remodelling in epigenetic and gene expression at different ages.

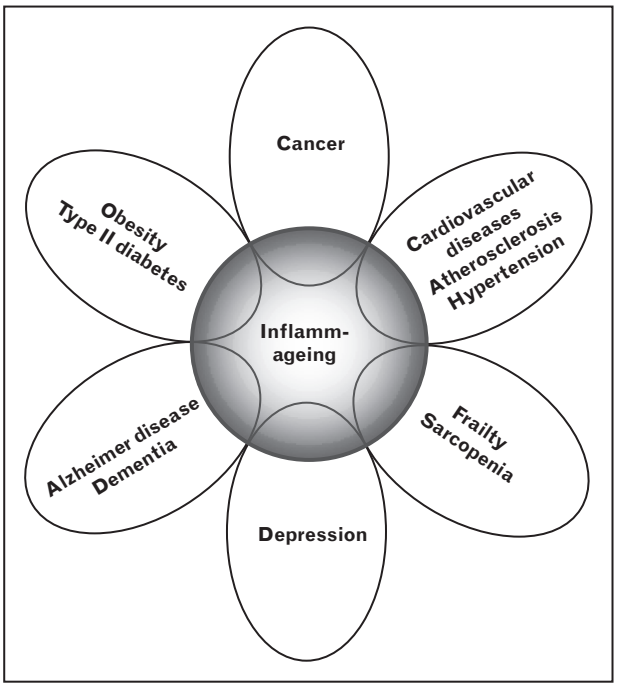

FIGURE 1. 'Diseasome of inflamm-ageing'. Inflamm-ageing, visualized by the central circle, is the shared mechanism of the pathogenesis of the major age-related diseases, visualized by the 'flower petals'.

At present, the phenomenon of inflamm-ageing has become more complicated than what was hypothesised because an increasing amount of experimental data on genetics, genomics, proteomics and other -omics are available, thanks to new high-throughput technologies. To analyze comprehensively these data, a systems biology approach has been proposed as the most powerful tool to characterize the systemic nature of inflamm-ageing, for example by developing predictive models of inflamm-ageing, needed to set up strategies for the modulation of inflammation [7]. A key point in such a complex framework is the dynamics of signalling pathways crucial to inflammation, such as the activation of Nuclear Factor (NF)-κB transcription factor, as well as the variety of different and unexpected sources of the inflammatory stimuli underpinning and sustaining inflamm-ageing, such as senescent cells, the so-called meta-inflammation, the gut microbiota and nutrition. The purpose of this review is to discuss recent developments in the field of inflamm-ageing and to consider the contribution of the main actors playing a role in determining when, where and how much this phenomenon impacts on the health status during human lifespan.

THE NF-κB INTERACTOME AND THE COMPLEXITY OF INFLAMMATION AND INFLAMM-AGEING

The five components of the NF-κB family are prominent mediators of inflammation, acting as key transcriptional regulators of hundreds of genes that in turn control cell proliferation, cell survival, as well as innate and adaptive immune response. NF-κB signalling seems to be the culprit of inflamm-ageing, as this signaling system integrates the intracellular regulation of immune responses in both ageing and age-related diseases [8].

Several signalling pathways activated by diverse stimuli converge on NF-κB activation, resulting in a regulatory system characterized by high complexity. The sheer complexity of such a crucial signaling system is intuitively evident from the intricate network of interactions among input and output signals, mediator proteins and feedback loops. Many proteins directly involved in such interactome are in turn products of genes that are controlled and

regulated in their expression by NF-κB. Framing structure and dynamics of the NF-κB interactome in a wider, systemic picture will be a significant step to definitively disentangle when, where and how it globally regulates diverse gene programs and phenotypes affecting inflamm-ageing [7]. In this perspective, we explored different sources (literature, functional enrichment web resources, protein–protein interaction and pathway databases) and constructed a comprehensive picture of NF-κB including 622 proteins and 6115 interactions [9▪▪].

Given that ageing and inflamm-ageing act at different levels of complexity, from molecule to cell, from organ to organ systems and finally to organism, a further important step will consist in reconstructing when, where and how much such a complex interactome will undergo specific changes with age in the different organs and cell types of the body. It can be predicted that new maps of cellular functions and new roles of NF-κB in physiology and in diseases will emerge.

CELLULAR SENESCENCE

During life, cells are continually exposed to a variety of damaging agents (e.g. ionizing radiations and oxygen free radicals, among others), as well as to proinflammatory cytokines, and their responses range from complete recovery to cell death. Proliferating cells can initiate an additional response by adopting a state of permanent cell cycle arrest, termed 'cellular senescence' and proposed to be a tumor suppression mechanism and a possible contribution to ageing.

The senescent phenotype is accompanied by upregulation of the DNA damage-response system, and by the robust secretion of numerous growth factors, proinflammatory cytokines (such as IL-6, IL-8), proteases, and other proteins, globally named Senescence Associated Secretory Phenotype (SASP) [10▪▪]. Senescent cells, over time, develop a phenotype that becomes increasingly complex, with both beneficial (tumor suppression and tissue repair) and deleterious (tumor promotion and ageing) effects on the health of the organism.

To understand how cellular senescence participates in these four complex processes having apparently opposing effects, it has been envisioned that the senescent phenotype progress through temporally regulated steps that orchestrate its activities. After exposure to senescence stimuli, *in vitro* experiments have demonstrated that the senescent growth arrest establishes rapidly [11–13], precluding the cell from developing into a cancer. Concomitantly, the senescent cell acquires a secretory phenotype, expressing proinflammatory cytokines such as IL-1α, that in turn activates NF-κB and CCAAT-enhancer-binding protein [14], which are required for the expression of many SASP proteins [15–17]. Some of these second-wave SASP proteins reinforce the growth arrest, whereas others facilitate tissue repair and drive cancer progression by acting on neighboring cells. As senescent cells increase with age, it can be envisaged that either the clearance is incomplete (and so senescent cells gradually accumulate) or aged individuals generate senescent cells faster than their immune system can handle, or both. Finally, in culture, senescent cells express two microRNAs, mir-146a and mir-146b [18,19▪], which comprise a negative feedback loop to dampen NF-κB activity [20,17] only in cells secreting very high levels of inflammatory cytokines. Thus, the above-mentioned microRNAs on the one hand prevent the SASP from generating persistent acute (robust) inflammation, whereas on the contrary, they allow the persistence of a low chronic inflammation (inflamm-ageing), that can drive the chronic pathologies associated with ageing [10▪▪].

Notably, cells that express senescent markers have been found to be relatively rare in the young organism, but their number increases with age. Estimates of how abundant senescent cells in aged organisms depend on the study, species and tissue ranging from less than 1 to 15% or more [21]. In particular, cells expressing senescent markers have been found *in vivo* at sites of chronic age-related pathologies such as osteoarthritis and atherosclerosis and they contribute to the ageing process [22,23], reinforcing the link between senescent cells, ageing and age-related diseases. However, the in-vivo role of senescent cells and why they accumulate with age is not completely known [10▪▪,24]. Recent findings suggest that the clearance of senescent cells is performed by host mechanisms, such as immune system, but nothing is known about whether these mechanisms change with age or in age-related diseases. Likewise, nothing is known whether the senescent cells found *in vivo* have escaped clearance or are in the process of being cleared [21].

Additionally, relevant epidemiologic data supports the notion that inflamm-ageing may promote cancer development by exerting positive selection on tumor-initiating cells, through different mechanisms. Inflamm-ageing can be considered as a breakdown in the multishell cytokine network, in which stem cells and stromal fibroblasts become proinflammatory cytokine over-expressing cells due to the accumulation of DNA damage, suggesting that cancer in the elderly is more dependent upon the microenvironment and that tumor cells in elderly people have a lower autonomous capability to grow and disseminate. Therefore cancer

treatment in the elderly may be improved by the inhibition of proinflammatory cytokines by exploiting currently available antibodies used in chronic inflammatory diseases [25,26]. The identification of small molecular compounds capable of inhibiting proinflammatory cytokines, such as IL-6, thus modifying the inflammatory microenvironment, will represent a new step in the cancer therapy of elderly patients [27▪].

METAFLAMMATION

Inflamm-ageing could be either the cause or the effect of the increased prevalence of a clustering of metabolic abnormalities with inflammatory pathogenesis including obesity, dyslipidemia, hypertension, insulin resistance, and type 2 diabetes [28]. These metabolic diseases have to be considered systemic diseases characterized by a pervasive and multisystemic state of inflammation. To this regard, the concept of 'metaflammation' (i.e. metabolic inflammation), defined as low-grade, chronic inflammation orchestrated by metabolic cells in response to excess nutrients and energy was recently proposed [29▪]. Excessive levels of nutrients, in particular of glucose and free fatty acids, induce a stress in the pancreatic islets and in adipose tissue, liver and muscle, which are insulin-sensitive tissues, and induce the local release of cytokines, chemokines and adipokines [30]. Moreover, adipose tissue that increases quantitatively with age above all in its visceral component is invaded by activated macrophages and T-cells, able to induce the activation of multiple signalling networks and the production of a variety of inflammatory compounds. The two concepts of metaflammation and inflamm-ageing have been developed and proposed separately in different fields and within different biomedical backgrounds (metabolic diseases and biogerontology, respectively). The classic idea is that metaflammation occurs in young or adult (obese) people whereas inflamm-ageing occurs later in life even in nonobese and lean people. However, the possibility of an overlapping of the two phenomena in the same individual cannot be excluded and it is an interesting perspective to pursue. Indeed, inflamm-ageing and metaflammation can share stimuli and pathogenetic mechanisms and they should be considered together, within a global (systems medicine) perspective. It is also likely that such a complex scenario represents the biological basis to better understand what has been conceptualized as 'metabolic plasticity' and 'metabolic memory', two key concepts to grasp the dynamics of metabolic alterations and the degree of their reversibility in old age [31].

GUT MICROBIOTA

Inflamm-ageing does not have a unique origin, as many factors and molecules produced by a different type of cells belonging to different tissues (adipose tissue, muscle), organs (brain, liver), immune system and ecosystem (gut microbiota) contribute to fuel and maintain inflamm-ageing both at local and systemic levels [32] (Fig. 2). To this regard, it is becoming more and more evident the role of gut microbiota, suggesting the urgent necessity to address this topic in future studies on ageing and longevity.

The complex bacterial community that populates the gut and that represents an evolutionary adapted ecosystem appears to limit the accumulation of potentially pathogenic bacteria and infections in all taxa, being able to affect the efficiency of the host immune system and exerting systemic metabolic effects. Given the symbiotic relationship between the host and the gut microbiota, humans can be considered as 'meta-organisms', in whom the gut microbiota and the gut-associated lymphoid tissue (GALT) coexist in a fine homeostasis [33]. This homeostasis has a profound impact on the human health status, and in ageing and longevity, as alterations in intestinal microbiota composition are associated with several chronic conditions, including obesity, frailty, sarcopenia and cognitive impairment among others [34▪].

The dynamics of cross-talk signals between gut microbiota and the GALT immune system allows the host to tolerate and to control the whole microbial complexity of gut microbiota by a 'constitutive low-grade physiological inflammation' state. This continuous level of a low physiological inflammatory tone, likely essential to preserve the symbiotic nature of the microbiota–host relationship, is also indispensable for the development, education, homeostasis and functionality of the human immune system [35]. However, under pathological circumstances, proinflammatory potentially pathogenic bacteria escape surveillance, compromise homeostasis, and consolidate the inflammatory state. We have proposed that the immunomodulatory and nutritional properties of the gut microbiota should be considered and exploited as powerful tools to promote healthy ageing and to extend the lifespan not only in humans but also in the classical animal models such as *Caenorhabditis elegans* and *Drosophila melanogaster*, owing to their potential capability to face and slow down inflamm-ageing [33]. Indeed, an aged gut microbiota, enriched in potentially pathogenic bacteria and anaerobes, positively correlated to an increase in proinflammatory

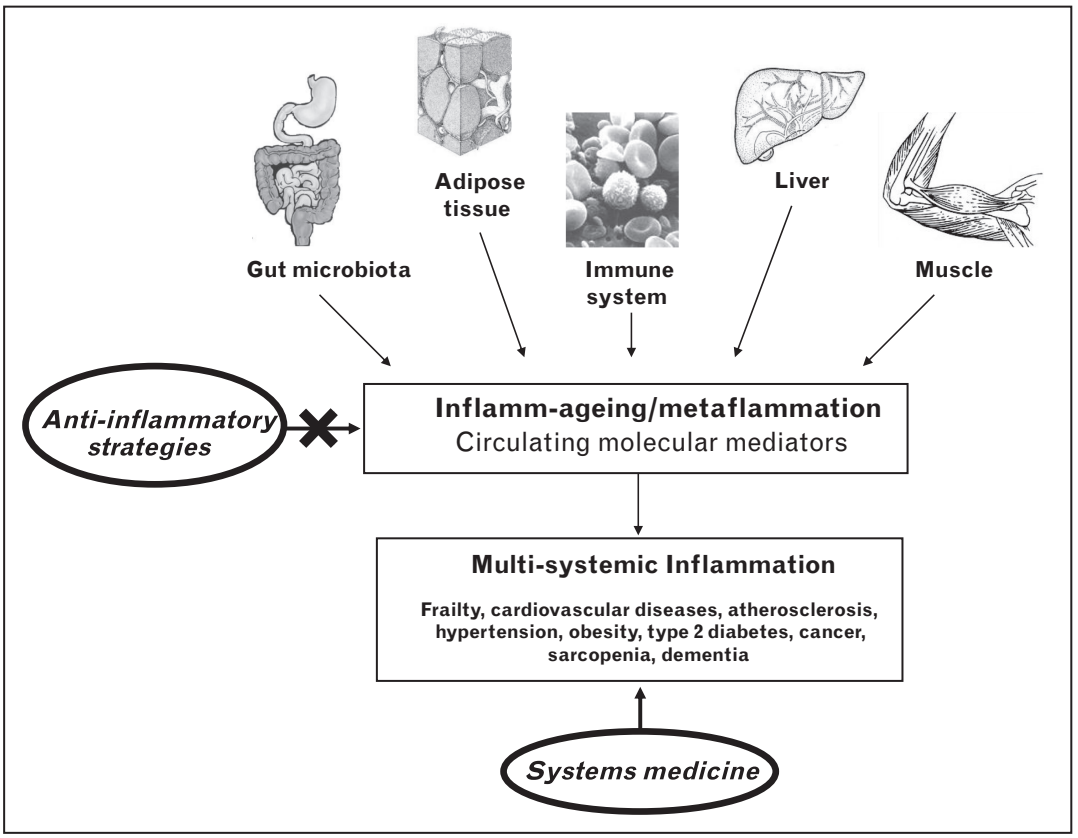

FIGURE 2. Inflamm-ageing and metaflammation. Contribution of some tissues (adipose tissue, muscle), organs (brain, liver), immune system and ecosystem (gut microbiota) to inflamm-ageing and metaflammation onset and progression, thus determining the multisystemic inflammation responsible for the major age-related diseases, that should be faced together in a systems medicine perspective. Anti-inflammatory strategies should be adopted to control both inflamm-ageing and metaflammation.

signals such as IL-6 and IL-8, and depleted in anti-inflammatory *Firmicutes*, such as *Clostridium* cluster XIVa and *Faecalibacterium prausnitzii* causes a dysbiosis that will contribute to the development of an overall proinflammatory profile [36,37▪▪]. Moreover, inflammatory disorders, such as inflammatory bowel diseases and irritable bowel syndrome, have been associated with proinflammatory imbalances of the intestinal microbiota analogous to the ones that characterized an aged gut microbiota [38]. It is thus reasonable to predict that the ageing of the gut microbiota has a strong impact on the health status in the elderly [36,37▪▪,32,39]. Indeed, while a healthy profile of the intestinal microbial community supports human longevity, its transition to an aged type contributes to unsuccessful ageing. At present it is not feasible to define exactly the 'age threshold' for the starting of the ageing of gut microbiota, but the still scanty data suggest that more than 70–80 years could represent a limit beyond which an aged gut microbiota is present [37▪▪]. In any case, it is of primary importance to understand the genetic and environmental factors that impact on the ageing of the human gut microbiota. In particular, it is an urgent priority to investigate how environmental or behavioural variables, such as the lifestyle, nutritional habits and ethnicity interact to define the individual 'age threshold' at which the gut microbiota is affected by the ageing process, with the aim to preserve as long as possible its integrity. Thus, it appears possible to extend healthy ageing and lifespan by targeting the host as a metaorganism by manipulating the complex symbiotic ecosystem of gut microbiota. To this purpose, it is possible to act on controllable environmental factors, such as deterioration in dentition, salivary function, digestion, intestinal transit time [40] and diet, which have been shown to influence microbiota composition.

However, at present, the sources of the inflammatory stimuli underpinning and sustaining inflamm-ageing are not completely clarified as little is known about how the composition (i.e. the precise types of species present and the relative abundance of each) of other microbiota (such as lung and

vaginal) changes during ageing and potentially affects the health status in humans.

NUTRITION AND THE NU-AGE EU PROJECT

Among the different factors that can modulate ageing and inflamm-ageing, nutrition plays a pivotal and fascinating role. Indeed, nutrition, impinging upon immune system and inflammation, can be a trigger for both pathogenic and protective processes during the entire lifespan. Accordingly, nutrition is probably the most powerful and pliable tool that we have to attain a chronic and systemic modulation of ageing process, towards an enhancement of health status of the elderly population. Within this scenario, the 'New dietary strategies addressing the specific needs of elderly population for an healthy ageing in Europe' (NU-AGE) Project (http://www.nu-age.eu/) represents a possible tool to shed light into the possibility to improve health and quality of life in the elderly. The main assumption and rationale of NU-AGE is the possibility to counteract inflamm-ageing through a whole diet approach (an *ad hoc* modified/fortified Mediterranean diet) newly designed according to the nutritional needs of people over 65 years of age. Previous studies evaluated how single nutrients can impact on inflammatory parameters, while the NU-AGE approach considers the whole diet. This allows targeting not only a higher number of vulnerable processes involved in inflammation and ageing, but also studying the synergy of multiple subtle effects. In order to identify cellular and molecular targets and mechanisms responsible for the effects of the whole diet intervention, a large number of volunteers (1250 elderly 65–79 years old) will be recruited in five European countries (Italy, France, Poland, the Netherlands and UK) and fully characterized before and after dietary intervention by evaluating their health and nutritional status, physical and cognitive functions, immunological, biochemical and metabolic parameters, as well as by a variety of -omics (high throughput techniques) regarding genetics, epigenetics, transcriptomics, metagenomics, and metabolomics. All these parameters will be analyzed adopting a Systems Biology approach, highly innovative and timely in the field of human elderly nutrition. The results of dietary intervention will be used to develop elderly tailored prototypes of functional foods and to improve traditional foods, in order to improve the health status of elderly European citizens.

CONCLUSION

Ideally, inflammation should clear out the infection and then subside to allow normal tissue to be rebuilt, according to a physiological beneficial process. However, inflammation, becoming chronic, can cause in the majority of older people a low-grade inflammation, recognized as one of the key risk factors for age-related diseases. Paradoxically, centenarians, despite the high levels of proinflammatory markers, have escaped or postponed disease onset, making it difficult to understand whether inflamm-ageing is beneficial or detrimental. We offer the opinion that both benefits and adverse effects of the inflammatory reaction largely depend on the extremely complex network of mediators involved, on the context in which such mediators operate and on their temporal, spatial and quantitative relationships. For these intricate interactions and for the multifaced nature of inflamm-ageing, at present it is difficult to determine when, where and how much inflamm-ageing exhibits its salutary or detrimental effects.

In this framework, one of the most fascinating anti-ageing strategies seems to be the possibility to decrease inflamm-ageing without compromising the physiological role of inflammation, fundamental for survival [41]. To this aim, it is urgent to clarify the shady areas of the complex mechanisms underpinning inflamm-ageing in order to carry out targeted therapeutic interventions. At present, one possible intervention could be represented by a whole diet approach, such as that envisaged by the above-mentioned NU-AGE project, and/or by a nutriceutical functional food approach that, acting on digestive processes and immune systems, is able to modulate the inflammatory and degenerative processes of the body. Indeed, *ad hoc* dietary adjustments, such as reducing or eliminating saturated and *trans* fat, increasing the intake of omega-3 fat, vitamins, micronutrients and antioxidants, can help minimize inflammation. Similarly, prebiotics and probiotics, when adequately administered, as well as potential manipulation of the gut microbiota, such as intestinal microbiota transfer [42▪], could confer beneficial effects to the host by influencing the gut microbiota composition and directly affecting the inflammatory state and metabolic disturbances related to inappropriate nutrition and diet in humans [43].

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Conflicts of interest

There are no conflicts of interest.

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