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REVIEW

Inflammaging and Anti-Inflammaging: The Role of Cytokines in Extreme Longevity

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Abstract Longevity and aging are two sides of the same coin, as they both derive from the interaction between genetic and environmental factors. Aging is a complex, dynamic biological process characterized by continuous remodeling. One of the most recent theories on aging focuses on immune response, and takes into consideration the activation of subclinical, chronic low-grade inflammation which occurs with aging, named "inflammaging". Long-lived people, especially centenarians, seem to cope with chronic subclinical inflammation through an anti-inflammatory response, called therefore "anti-inflammaging". In the present review, we have focused our attention on the contrast between inflammaging and anti-inflammaging systems, by evaluating the role of cytokines and their impact on extreme longevity. Cytokines are the expression of a network involving genes, polymorphisms and environment, and are involved both in inflammation and anti-inflammation. We have described the role of IL-1, IL-2, IL-6, IL-12, IL-15, IL-18, IL-22, IL-23, TNF-α, IFN-γ as pro-inflammatory cytokines, of IL-1Ra, IL-4, IL-10, TGF-β1 as anti-inflammatory cytokines, and of lipoxin A4 and heat shock proteins as mediators of cytokines. We believe that if inflammaging is a key to understand aging, anti-inflammaging may be one of the secrets of longevity.

Keywords Inflammaging · Anti-inflammaging · Cytokine · Aging · Longevity

Abbreviations

IL	Interleukin
NK	Natural killer cells
TNF	Tumor necrosis factor
IFN	Interferon
IL-18BP	IL-18 binding protein
SNPs	Single nucleotide polymorphisms
IL-1Ra	IL-1 receptor antagonist
Hsp	Heat shock proteins
LX	Lipoxin
TGF	Transforming growth factor

Introduction

Aging is an unavoidable, universal, complex process characterized by progressive loss of functional reserves and reduction of the capability to adapt to the environment. This biological phenomenon derives from an interaction between genetic and environmental factors. Healthy lifestyle and favorable environment allow genetically predisposed subjects to reach extreme longevity and maintain acceptable health status and autosufficiency (Nicita-Mauro et al. 2008). As an expression of this, it is known that centenarians belong to families of long-lived people (Motta et al. 2007).

The aging process is dynamic and characterized by a continuous remodeling. The main actors in this remodeling

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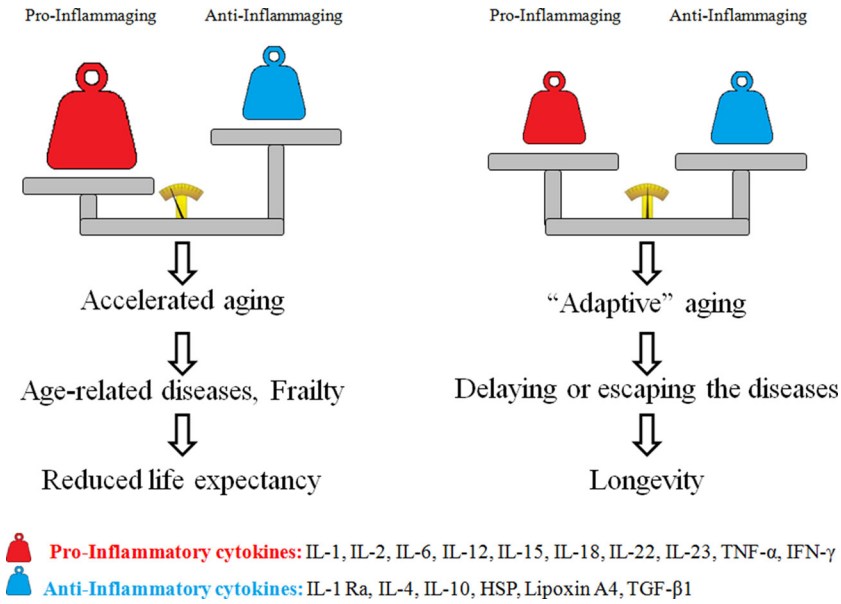

Fig. 1 The "weight" of pro- and anti-inflammatory cytokines in aging and longevity. Increase in pro-inflammatory cytokines promotes frailty and age-related diseases, and reduces life expectancy. The balance between pro-inflammaging and anti-inflammaging favors adaptation to the conditions of life, allows avoidance of diseases or delays onset, and leads to longevity

theory are DNA repair, apoptosis, immune response, oxidative stress and inflammation. To reach extreme longevity, it is necessary for all these mechanisms to interact in an efficient way. Robustness and frailty may occur concomitantly in aged bodies, and the phenotype of aged subjects is the result of their capability to repair molecular damage and/or adapt to the accumulation of such damage. Many theories on aging have been developed. One of the most recent focuses on the activation of a subclinical, chronic low-grade inflammation that occurs with aging, named "inflammaging" (Franceschi et al. 2000a). It is a manifestation of immunosenescence, which is the sum of changes affecting the functionality of the immune system in older people.

A major contributor of inflammaging is the antigenic load of persistent infection which starts from intrauterine life and continues for an entire lifespan. The pro-inflammatory phenotype of senescent cells protects against infectious diseases but, at the same time, contributes to inflammaging, as large quantities of pro-inflammatory cytokines are produced/released to repair damage at tissue level (Larbi et al. 2008). Like other aging mechanisms, these responses are positive for early survival and reproduction, but may become detrimental in the post-reproductive period of life. Many age-related diseases, such as obesity, metabolic syndrome, diabetes, cardiovascular diseases, cancer, depression, and Alzheimer's disease, share an inflammatory pathogenesis; moreover, the activation of inflammatory pathways appears to be involved in the pathophysiology of sarcopenia and frailty. Long-lived people, especially centenarians, seem to cope with chronic subclinical inflammation through an anti-inflammatory response, called therefore "anti-inflammaging" (Franceschi et al. 2007). We believe that if inflammaging is a key to understand aging, anti-inflammaging may be one of the secrets of longevity (Fig. 1). Circulating cytokines are involved both in inflammation and anti-inflammation, and are the expression of a system that involves genes, polymorphisms and environment.

We have focused our attention on the contrast between inflammaging and anti-inflammaging systems, by evaluating the role of cytokines and their impact on extreme longevity. The aim of this review is to summarize what, to date, we know about this balance, tracing an overview of the studies that have investigated the roles of serum cytokines in humans during aging (Table 1).

Proinflammatory Cytokines

Interleukin 1

Interleukin (IL)-1 is a potent proinflammatory cytokine that acts as an endogenous pyrogen. It is produced by tissue macrophages, monocytes, fibroblasts, and dendritic cells (DCs), but is also expressed by B lymphocytes, natural killer (NK) cells and epithelial cells. The cytokine has diverse potentiating effects on cell proliferation, differentiation, and the function of many innate and specific immunocompetent cells. It mediates many inflammatory diseases by initiating and potentiating immune and inflammatory responses (Akdis et al. 2011). High levels of IL-1, together with IL-6, tumor necrosis factor (TNF) and interferon (IFN)-γ are associated with increased risk of morbidity and mortality in the older subject. In particular, cohort studies have indicated that IL-1 is involved in the alteration of nutritional status, in cognitive decline, and

Table 1 Studies of the effects of cytokines on elderly population

Cytokine	Population age	Population nationality	Effects	References
Pro-inflammatory cytokines				
IL-1	85 years	Dutch	Increased levels correlate with depression	van den Biggelaar et al. (2007)
	81 years	Danish	Decreased levels compared to young controls	Bruunsgaard et al. (1999a)
	<35–>85 years	Italian	No association between cytokine levels and age	Di Iorio et al. (2003)
	Nonagenarians	Finnish	No association of IL-1 polymorphisms with longevity	Wang et al. (2001)
	20–102 years	Italian	No association of IL-1 gene cluster polymorphism with longevity	Cavallone et al. (2003)
	83 ± 7 years	Swedish	Men with the high-producing IL-1β −511T allele had shorter survival	Cederholm et al. (2007)
IL-2	Octogenarians and nonagenarians	Irish	Decreased levels compared to young controls	Rea et al. (1996)
	60–70 years	Polish	No altered levels compared to young controls	Myśliwska et al. (1998)
	25–101 years	Italian	Age-dependent increase in $CD8^+$ T cells	Zanni et al. (2003)
	Nonagenarians	Italian	No alteration compared to young controls	Palmeri et al. (2012)
	Centenarians	Italian	Increased −330TT genotype frequency	Scola et al. (2005)
	80–97 years	Irish	No age association for IL-2 polymorphisms	Ross et al. (2003a)
IL-6	Nonagenarians	Italian	Increased levels compared to young controls	Palmeri et al. (2012)
	20–102 years	Italian	Increased levels compared to young controls	Ferrucci et al. (2005)
	>80 years	Italian	Increased levels correlate with mortality	Giovannini et al. (2011)
	70–79 years	North American	Increased levels correlate with the risk of community-acquired pneumonia requiring hospitalization	Yende et al. (2005)
	65–98 years	Italian	IL-6 −174 G>C polymorphism is a predictor of cardiovascular death	Antonicelli et al. (2005)
	75 ± 10 years	Italian	IL-6 $-174C^-$ genotype correlates with severe atherosclerosis	Giacconi et al. (2004)
	>60 years	Brasilian	IL-6 −174G allele is implicated in a greater cardiovascular risk in women	Tonet et al. (2008)
	76 ± 8 years	Italian	IL-6 −174GG genotype is a risk factor for multi-infarct dementia	Pola et al. (2002)
	>80 years (including centenarians)	Italian	No association between the IL-6 polymorphism and very old age	Di Bona et al. (2009)
		Irish Danish Finnish	IL-6 −174GG genotype is negatively associated with longevity only in Italian centenarians	Meta-analysis
	18–95 years	Turkish	IL-6 $-174C^+$ genotype correlates with longevity	Kayaaltı et al. (2011)
	83 ± 7 years	Swedish	IL-6 −174GG genotype correlates with prolonged survival in women	Cederholm et al. (2007)

Table 1 continued

Cytokine	Population age	Population nationality	Effects	References
IL-12	Nonagenarians	Italian	Increased levels compared to young controls	Palmeri et al. (2012)
	23–93 years	Belgian	Decreased levels correlate with poor nutritional status and frailty	Compté et al. (2013)
	80–97 years	Irish	No age association for IL-12 polymorphisms	Ross et al. (2003a)
IL-15	95–>100 years	Italian	Increased levels compared to young controls	Gangemi et al. (2005a)
IL-18	83 ± 5 years	Spanish	Increased levels correlate with mortality for heart failure	Sanchez et al. (2014)
	68 ± 16 years	Italian	Increased levels with age	Ferrucci et al. (2005)
	Centenarians	Italian	Increased levels compared to young controls Increased IL-18BP levels compared to healthy controls and patients with chronic ischemic syndromes	Gangemi et al. (2003)
IL-22	Centenarians	Italian	Increased levels compared to young controls	Basile et al. (2012)
IL-23	23–93 years	Belgian	Decreased levels correlate with poor nutritional status and frailty	Compté et al. (2013)
TNF	25–101 years	Italian	Age-dependent increase in $CD8^+$ T cells	Zanni et al. (2003)
	85 years	Dutch	Increased production correlates with mortality from a cardiovascular event	van den Biggelaar et al. (2004)
	89 years	North American	Increased levels correlate with early mortality	Mooradian et al. (1991)
	72–92 years	North American	Increased levels correlate with mortality	Roubenoff et al. (2003)
	>80 years	Italian	Levels do not correlate with mortality	Giovannini et al. (2011)
	70–79 years	North American	Increased levels correlate with the risk of community-acquired pneumonia requiring hospitalization	Yende et al. (2005).
	Centenarians	Danish	Increased levels correlate with mortality	Bruunsgaard et al. (2003)
	37–91 years	Danish	Increased levels at 1 week post pneumococcal pneumonia compared to young controls	Bruunsgaard et al. (1999b)
	Centenarians	Danish	TNF –308GA genotype correlates with decreased prevalence of dementia AA genotype correlate with higher mortality	Bruunsgaard et al. (2004)
	83 ± 7 years	Swedish	TNF −308AG genotype correlates with prolonged survival in women	Cederholm et al. (2007)
	80–97 years	Irish	TNF polymorphisms do not correlate with longevity	Ross et al. (2003b)
	Nonagenarians	Finnish	No association of TNF polymorphisms with longevity	Wang et al. (2001)
IFN-γ	25–101 years	Italian	Age-dependent increase in $CD8^+$ T cells	Zanni et al. (2003)
	21–99 years	Italian	IFN-γ^+ cells decreased in virgin $CD4^+$ subset in old people and nonagenarians	Alberti et al. (2006)
	Nonagenarians	Italian	No alteration compared to young controls	Palmeri et al. (2012)
	Centenarians	Italian	IFN-γ +874A allele correlates with longevity	Lio et al. (2002a)
	80–97 years	Irish	No age association for IFN-γ polymorphisms	Ross et al. (2003a)
	Centenarians	Italian	No age association for IFN-γ polymorphisms	Pes et al. (2004)

Table 1 continued

Cytokine	Population age	Population nationality	Effects	References
Anti-inflammatory cytokines				
IL-1Ra	Nonagenarians	Finnish	Increased levels correlate with mortality	Jylhä et al. (2007)
	20–102 years	Italian	Age-related increased levels	Cavallone et al. (2003)
IL-4	Nonagenarians	Italian	Reduced levels compared to young controls	Palmeri et al. (2012)
	25–101 years	Italian	Age-dependent increase in $CD8^+$ T cells	Zanni et al. (2003)
	21–99 years	Italian	IL-4^+ cells increased in activated/memory T cells from nonagenarians	Alberti et al. (2006)
IL-10	85 years	Dutch	Increased production correlates with a reduced risk of mortality from a cardiovascular event	van den Biggelaar et al. (2004)
	Centenarians	Italian	IL-10 −1082GG genotype correlates with longevity	Lio et al. (2002b)
	90.2 years (mean)	Jordanian	IL-10 polymorphisms correlate with longevity only in men	Khabour and Barnawi (2010)
	83 ± 7 years	Swedish	IL-10 −1082GG genotype correlates with survival	Cederholm et al. (2007)
	55–>100 years	Italian	IL-10 −1082GG genotype correlates with longevity IL-10 −1082AA genotype correlates with AMI	Lio et al. (2004)
	Nonagenarians	Finnish	No association of IL-10 polymorphisms with longevity	Wang et al. (2001)
	80–97 years	Irish	No age association for IL-10 polymorphisms	Ross et al. (2003a)
	Centenarians	Italian	No association of IL-10 polymorphisms with longevity	Pes et al. (2004)
	65–90 years	Bulgarian	IL-10 genotype −1082G/A, −819C/C, −592C/C correlates with longevity	Naumova et al. (2004)
	85 years	Dutch	IL-10 −2849AA genotype correlates with cardiovascular mortality risk	Van Den Biggelaar et al. (2004)
TGF-β	40–79 years	Japanese	Serum levels inversely correlate with age	Lin et al. (2009)
	86–90 years	Swedish	Increased levels correlate with age	Forsey et al. (2003)
	Centenarians	Italian	Increased levels correlate with age	Carrieri et al. (2004)
	Centenarians	Italian	The haplotype combination G −800/C −509/C 869/C 915 inversely correlates with longevity	Carrieri et al. (2004)
	65–92 years	Austrian	Serum and mRNA levels did not correlate with age	Halper et al. (2015)
Hsp	75 years (mean)	North American	Reduced induction of Hsp90 in lymphocytes with age	Faassen et al. (1989)
	≥90 years	Irish	Decreased levels of Hsp70 correlate with age	Rea et al. (2001)
	Centenarians	North American	Decreased Hsp70 levels correlate with longevity	Terry et al. (2006)
LX	Centenarians	Italian	Decreased LXA4 levels with age	Gangemi et al. (2005b)

Table 1 continued

Cytokine	Population age	Population nationality	Effects	References
sTNFR	65–102 years	North American	sTNFR1 correlates with mortality	Varadhan et al. (2014)
		Italian		
	68–91 years	Danish	Increased levels in patients with pneumococcal infections compared to young controls	Bruunsgaard et al. (1999b)
	61–69 years	Danish	Increased sTNFR1 levels following endotoxin administration	Krabbe et al. (2001)
	59 ± 8 years	Polish	Increased sTNFRl levels correlate with severe coronary artery disease symptoms, past myocardial infarction	Safranow et al. (2009)
			Increased sTNFR2 levels correlate with lower HDL cholesterol, higher uric acid, and metabolic syndrome	
	≥70 years	Swedish	Increased sTNFR1 and sTNFR2 levels correlate with the most relevant clinical markers defining disease stage and progression risk in chronic kidney disease	Carlsson et al. (2014a)
	≥70 years	Swedish	Increased sTNFR1 levels correlate with the risk for mortality (especially for cardiovascular diseases and cancer)	Carlsson et al. (2014a)

BP binding protein, *AMI* acute myocardial infarction

development of Alzheimer's disease (Michaud et al. 2013) in aged people. Another study on a population aged 85–90 years found that a higher production of IL-1β, by ex vivo whole blood stimulations, was a risk factor for depressive symptoms but no relation was found with cognitive decline (van den Biggelaar et al. 2007). However, other studies showed different results. In a study involving a cohort of octogenarians from Denmark, elderly men and women had decreased levels of IL-1β and TNF in whole blood supernatants after in vitro lipopolysaccharide stimulation, compared to young men but not compared to young women (Bruunsgaard et al. 1999a). Moreover, IL-1β production was significantly lower in octogenarians with chronic diseases. In another study, IL-1β serum concentrations did not appear to be associated with aging (Di Iorio et al. 2003).

Two studies have investigated the role of genetic variability of IL-1 gene cluster and a possible association with longevity (Cavallone et al. 2003; Wang et al. 2001). In the Finnish study on nonagenarians and younger controls, no statistically significant differences emerged by comparing different IL-1 gene cluster haplotypes, with no evidence of association of IL-1 complex gene polymorphism with longevity (Wang et al. 2001). Neither did the Italian study report any significant difference in IL-1α, IL-1β and IL-1 receptor antagonist (IL-1Ra) allelic, genotypic and haplotypic frequencies among the age groups considered (young, elderly and centenarian subjects), nor between males or females (Cavallone et al. 2003). The Italian and Finnish studies investigated a large number of nonagenarians and centenarians (a total of 1780 subjects) of different genetic backgrounds and life styles, and no evidence of change in IL-1 gene cluster frequencies in the different age groups was observed, suggesting that IL-1 genetic variability does not affect longevity (Franceschi et al. 2005). However, later, a Swedish study found clear differences in survival of elderly people with regard to gender in IL-1β −511C/T polymorphism, showing that men with the high-producing IL-1β −511T allele had shorter survival times than those without this allele. No differences were found in females (Cederholm et al. 2007).

IL-2

IL-2 is mainly produced by $CD4^+$ and $CD8^+$ T cells. Target cells of IL-2 include $CD4^+CD8^+$ T cells, NK cells, and B cells. IL-2 plays a central role in T cell-dependent immune responses (Akdis et al. 2011). The data on IL-2 in longeval people are controversial. An age-related decrease in IL-2 production by stimulated peripheral blood mononuclear cells (PBMC) or lymphocytes and IL-2 serum levels has been reported (Candore et al. 1992; Caruso et al. 1996, 2005; Gillis et al. 1981; Pawelec et al. 2002; Rea et al. 1996; Rink et al. 1998). However, in another study, the serum levels of IL-2 were not altered in healthy aged people (Myśliwska et al. 1998). Other authors found that intracellular production of IL-2 showed a progressive age-dependent increase in $CD8^+$ T cells (Zanni et al. 2003). In a group of Sicilian centenarians, IL-2 levels were unmodified (Palmeri et al. 2012).

Studies on a T → G polymorphism at −330 nucleotide of the IL-2 gene promoter region have demonstrated that T lymphocytes from 330GG homozygous subjects are able to produce, in vitro, higher amounts of IL-2 than −330TG heterozygous or −330TT homozygous subjects (Hoffmann

et al. 2001). An Italian study found a marginally significant trend for an increased −330TT genotype frequency in centenarians compared to controls (Scola et al. 2005). The authors concluded that a genetic background favoring increased IL-2 production might be detrimental for longevity and that reduction of −330G allele frequency might be protective for healthy aging, limiting cell mediated inflammation in age-associated diseases (Scola et al. 2005). However, no association was observed for IL-2 −330 polymorphism and a healthy aged Irish population (nor with respect to gender) (Ross et al. 2003a).

IL-6

IL-6 is a multifunctional, pleiotropic cytokine involved in regulation of immune responses, acute phase responses, hematopoiesis, and inflammation. It possesses context-dependent pro- and anti-inflammatory properties with different signaling pathways. IL-6 is produced by endothelial cells, fibroblasts, monocytes, and macrophages in response to different stimuli (IL-1, IL-17, and TNF-α) during systemic inflammation (Akdis et al. 2011; Wolf et al. 2014). IL-6 expression is normally low, and serum levels are usually non-detectable in the absence of inflammation. However, with advancing age, serum levels become detectable, and this may reflect an age-associated loss in the normal regulation of gene expression for this molecule. IL-6 has been called the "cytokine for gerontologists" for nearly 20 years (Ershler 1993). Increased serum levels of IL-6 is a characteristic of aging (Palmeri et al. 2012), which may reflect age-associated pathological processes that develop over decades, even in apparently healthy subjects (Ferrucci et al. 2005; Sansoni et al. 2008). IL-6 has damaging effects on aging and has been proposed as a reliable marker for functional decline, as a predictor of morbidity and mortality in old age (Giovannini et al. 2011). IL-6 serum levels influence the onset of frailty, poor physical performance, loss of muscle strength, cognitive decline, and cardiological, neurological, and vascular events. They are also closely linked to the genesis of cancers, with cardiac remodeling in heart failure (Di Bona et al. 2009; Michaud et al. 2013), and with the risk of community-acquired pneumonia requiring hospitalization (Yende et al. 2005).

IL-6 cytokine polymorphisms have been linked to longevity. Several data suggest that IL-6 −174C/G locus variability is capable of modulating individual susceptibility to common causes of morbidity and mortality amongst the oldest old, such as type 2 diabetes, cardiovascular diseases, and dementia among others, thus impinging upon the individual capacity to reach the extreme limits of human life span (Antonicelli et al. 2005; Franceschi et al. 2005; Giacconi et al. 2004; Pola et al. 2002; Tonet et al. 2008). Persons who are genetically predisposed to produce high levels of IL-6 have a reduced capacity to reach the extreme limits of human life (Nigam 2011). A meta-analysis that analyzed individual data on long-living subjects and controls from eight case–control studies conducted in Europeans, showed no association between the IL-6 polymorphism and the probability of achieving a very old age, when the oldest old subjects (>80 years) were compared to controls (<80 years). However, when Italian centenarians (>100 years) were compared to controls (<80 years), the IL-6 −174GG genotype appeared to be negatively associated with longevity and reduced the chance for male GG carriers of achieving centenarian status, by twofold (Di Bona et al. 2009). Later, a Turkish study found an association between IL-6 −174G/C promoter region polymorphism and longevity (Kayaaltı et al. 2011), and a Swedish study found that, in the female elderly only, 3-year survival was doubled in those with the high-producing genotypes of IL-6 −174GG compared with those with low producing alleles (Cederholm et al. 2007).

IL-12

IL-12 is a pleiotropic cytokine able to activate both innate and adaptive immunity. It induces Th1-cell differentiation and cytotoxicity and has been shown to have potent immunomodulatory, antitumor, and anti-infection activities (Akdis et al. 2011). Nonagenarians show to have significant increased IL-12 serum levels compared to young controls that might be related to the increase of NK cell functions characterizing aging processes (Palmeri et al. 2012). In particular, in a study on octo/nonagenarians, subjects with a specific haplotype of killer immunoglobulin-like receptors, receptors of NK cells, produced high serum levels of IL-12 which could serve to heighten and prime the immune response (Rea et al. 2013). Different data were shown by Compté et al. (2013) who found that age was not correlated with Toll-like receptor (TLR)-mediated IL-12 production by stimulated whole blood cells. In contrast, poor nutritional status and frailty in aged people were associated with decreased IL-12 production (Compté et al. 2013). No age association was observed for the polymorphic IL-12 markers in a healthy aged Irish population when examined as a whole or when separated with respect to gender (Ross et al. 2003a).

IL-15

IL-15 is a cytokine produced after exposure to environmental stimuli and infectious agents. Stimulation and maintenance of cellular immune response are included among its biological functions, promoting the proliferation

of human memory T cells. IL-15 is similar to IL-2 in biological functions and is characterized by pleiotropic activity that results in an immunoregulatory role between natural and specific immunity (Fehniger and Caligiuri 2001). In a previous study, we assessed IL-15 serum levels in a population of ultralongeval subjects. They showed significantly higher IL-15 levels compared to both young and old controls (Gangemi et al. 2005a). These findings may explain, at least in part, the characteristic increase of memory cells in elderly subjects and may help lead to a better understanding of the capacity of adaptation to the environment of centenarians, defending themselves from infections through immune-inflammatory responses.

IL-18

IL-18 is a potent proinflammatory cytokine able to activate killing by lymphocytes, and essential to host defenses against severe infections. IL-18 can induce both Th1 and Th2 responses depending on surrounding cytokine conditions. Indeed, with IL-12, IL-18 induces IFN-γ production, whereas without IL-12, IL-18 induces IL-4 and IL-13 production (Nakanishi et al. 2001). IL-18 is highly expressed in macrophages from human atherosclerotic plaques (Mallat et al. 2001), suggesting its involvement in ischemic syndromes. A recent study showed that IL-18 is a predictor of mortality for heart failure in a group of octogenarians. After a mean follow-up of 2.4 years, subjects who died for heart failure had higher serum values of IL-18 compared with those who were alive (Sanchez et al. 2014). IL-18 serum levels increase with aging (Ferrucci et al. 2005), but at the same time longevity is characterized by a reduced incidence of ischemic events. Our group evaluated serum levels of IL-18 and IL-18 binding protein (IL-18BP) in healthy centenarians, younger healthy controls and patients with chronic ischemic syndrome. Centenarians have shown significantly higher levels of IL-18 and IL-18BP compared to each control group. Elevated IL-18 levels were present also in patients with chronic ischemic syndrome; centenarians exhibited a lower level of free IL-18 than chronic ischemic patients. These results indicate that inactivation of IL-18 by IL-18BP may explain the apparent paradox of high serum levels of IL-18 in centenarians, without signs of vascular diseases (Gangemi et al. 2003). Another study identified multiple single nucleotide polymorphisms (SNPs) associated with IL-18 and, in particular, a novel region on chromosome 2 associated with IL-18 serum levels. The newly identified IL-18 association signal spans five genes, one of which seems to be related to inflammation given that it codes for a platform protein that assembles the inflammasome, a cluster of proteins reflecting very early responders to inflammatory stimuli (Matteini et al. 2014).

IL-22

IL-22 is a proinflammatory cytokine belonging to the IL-10 family and represents an important effector molecule of activated Th22, Th1, Th17 cells (Sanjabi et al. 2009; Wolk et al. 2010). IL-22 stimulates the production of acute phase reactants and promotes antimicrobial defense and, therefore, is involved in inflammatory and immune responses in several organs (Kotenko 2002). Increased IL-22 serum levels in healthy centenarians have been demonstrated in a previous study by our group. It is likely that this pro-inflammatory condition is protective against infection, promoting the longevity of these subjects (Basile et al. 2012). It might be speculated that under certain circumstances the activity of this cytokine against infection may be more relevant to survival than its potential negative impact on inflammation.

IL-23

IL-23 is a pro-inflammatory cytokine composed of two subunits, p19 and p40. The p40 subunit is shared with IL-12. IL-23 and IL-12 have different receptors and different effects. While IL-12 induces development of Th1 cells, which produce IFN-γ, IL-23 is involved in differentiation of Th17 cells in a pro-inflammatory context and especially in the presence of transforming growth factor (TGF)-β and IL-6 (Duvallet et al. 2011). Compte et al. (2013) indicated that frailty and not age by itself affected IL-23 (as IL-12) production by whole blood cells upon TLR stimulation. A decreased IL-23 production in frail, elderly patients could account for their susceptibility to many pathogens.

TNF

Tumor necrosis factor was originally described as a circulating factor that can cause necrosis of tumors, but has since been identified as a key regulator of the inflammatory response. TNF interacts with two different receptors, which are differentially expressed on cells and tissues and initiate both distinct and overlapping signal transduction pathways. These diverse signaling cascades lead to a range of cellular responses, which include cell death, survival, differentiation, proliferation and migration (Bradley 2008). In the inflammatory process, TNF, together with other molecules such as IL-1β and IL-6, shows an age-related upregulation (Zanni et al. 2003). Vascular endothelial cells respond to TNF by undergoing a number of pro-inflammatory changes, which increase leukocyte adhesion, transendothelial migration and vascular leak and promote thrombosis (Bradley 2008). A high TNF production in supernatants of whole blood samples was found to be associated with a greatly elevated risk of death from a cardiovascular event in longeval people (Van Den Biggelaar et al. 2004).

An early study showed that detectable TNF serum levels in elderly nursing home patients may be a predictor of early mortality (Mooradian et al. 1991). Some time later, another study demonstrated that greater levels or production of TNF and IL-6 by PBMC were associated with increased mortality in community-dwelling elderly adults (Roubenoff et al. 2003). Moreover, elevated plasma levels of TNF were associated with mortality in centenarians, suggesting that it has specific biological effects and is a marker of frailty in the very elderly (Bruunsgaard et al. 2003). However, on the contrary, other authors did not find a significant association between TNF plasma levels and mortality in people of 80 years and older (Giovannini et al. 2011).

Elevated levels of TNF were also associated with frailty, to significant decrease in muscle strength, to risk of cerebrovascular and cardiovascular events and to a more rapid cognitive decline in the elderly population (Michaud et al. 2013).

In well-functioning elderly subjects, pre-infection systemic levels of TNF (and IL-6) were associated with higher risk of community-acquired pneumonia requiring hospitalization in smokers and those with coexisting medical conditions (Yende et al. 2005). Moreover, elderly (68–91 years) patients with confirmed pneumococcal pneumonia at 1-week post-admission showed significantly higher levels of TNF, soluble TNF receptor and the anti-inflammatory cytokine IL-10 compared to younger patients. Resolution of infections in the elderly has been shown to be prolonged and associated with worsened outcomes (Bruunsgaard et al. 1999b).

In a study on TNF polymorphisms in centenarians, octogenarians and younger controls, there was no difference in distribution of TNF −308 genotypes across the three different age groups, but GA genotype was associated with decreased prevalence of dementia in centenarians. The few centenarians with AA carrier status had higher mortality risk and tended to show higher plasma levels of TNF-α (Bruunsgaard et al. 2004). Another study observed prolonged survival in women with high-producing genotype in TNF-α −308AG compared with women with the low producing genotype GG (Cederholm et al. 2007). In other studies, no differences emerged between octogenarians and nonagenarians and younger controls by comparing TNF polymorphisms with longevity (Ross et al. 2003b; Wang et al. 2001).

IFN-γ

IFN-γ is secreted by a number of cell populations from both the innate and adaptive immune system. Production is controlled by antigen-presenting cells (APC)-secreted cytokines, mainly IL-12 and IL-18. The Th2-inducing cytokine IL-4, as well as IL-10 and TGF-β, negatively regulate the production of IFN-γ. IFN-γ plays a pivotal role in defense against viruses and intracellular pathogens and in the induction of immune-mediated inflammatory responses. It promotes cytotoxic activity, regulates MHC class I and II protein expression and antigen presentation, inhibits cell growth and apoptosis and controls the extension of the immune response by inducing activation-induced cell death of $CD4^+$ T cells (Akdis et al. 2011; Billiau et al. 1998). An increase of intracellular IFN-γ, together with other type 1 cytokines, within three $CD8^+$ T subsets (naïve, effector/cytotoxic and memory) was observed in aged subjects. In particular, within either memory or effector/cytotoxic cells, the percentage of both IFN-γ positive cells rose from 20–40 % in young subjects to more than 60–70 % in old subjects (Zanni et al. 2003). Conversely, the percentage of IFN-γ positive cells significantly decreased in a virgin $CD4^+$ subset both in old and nonagenarian subjects, as well as in activated/memory T cells from old, in comparison with young, subjects (Alberti et al. 2006). However, in a study on nonagenarians, IFN-γ (and IL-2) plasma levels are unmodified compared to young controls, suggesting a substantial maintenance of relevant T-cell functions (Palmeri et al. 2012).

A study evaluated the distribution of +874T → A IFN-γ polymorphisms in 174 Italian centenarians to investigate if the two alleles might be differently represented in people selected for longevity. The +874T allele was found less frequently in centenarian women than in centenarian men or in control women, whereas no significant differences were observed in the distribution of the two alleles between male or female controls. Possession of the +874A allele, known to be associated with low IFN-γ production, significantly increases the possibility to achieve extended longevity, suggesting that the pro-inflammatory status, characteristic of aging, may be detrimental for successful aging. Moreover, these data seem to strengthen the idea that gender may be a major variable in the biology of the aging process (Lio et al. 2002a). However, in an Irish study on octogenarians and nonagenarians (Ross et al. 2003a) and another Italian study on centenarians (Pes et al. 2004), no association was observed for IFN-γ polymorphisms when examined as a whole or when separated with respect to gender.

Anti-Inflammatory Cytokines

IL1-Ra

IL-lRa is synthesized and released in response to the same stimuli that drive IL-1 release. IL-lRa neutralizes the effects of IL-1 (Eisenberg et al. 1990).

A prospective population-based study, including 285 both community-dwelling and institutionalized

nonagenarians, demonstrated that plasma levels of IL-1Ra were higher in subjects who died during a 4-year follow-up than in those who survived. Therefore, IL1-Ra can be considered a significant predictor of mortality in nonagenarians (Jylhä et al. 2007).

However, another study on 1131 elderly Italians, including 134 centenarians, evaluated IL-1 gene cluster in longevity. No significant differences in genotype and allele distributions were found, but a significant age-related increase of IL-1Ra plasma levels was observed. In long-lived individuals, this seems to be a safeguard mechanism to cope with the age-associated increased inflammatory state (Cavallone et al. 2003).

IL-4

IL-4 is a pleiotropic cytokine mainly produced by Th2 cells and also by basophils, mast cells and eosinophils. It is the major stimulus of Th2-cell development and suppresses Thl development; it also induces IgE class switching in B cells, increases the expression of class II MHC molecules in B cells and upregulates B-cell receptors. IL-4 plays a central role in the regulation of allergic conditions, and the protective immune response against helminths and other extracellular parasites (Akdis et al. 2011).

Contrasting data emerge from studies on aged and ultra-longeval people. Palmeri et al. (2012) found a reduction of IL-4 serum levels and an increase of IL-13 in a group of nonagenarians, mirroring the maintenance of some effector mechanisms of the immune response in advanced ages. On the contrary, Zanni et al. (2003), found that type 2 intracellular cytokines, including IL-4, increased within virgin, memory and effector/cytotoxic $CD8^+$ T cells in aged people. The percentage of type 2 cytokine-positive cells was much lower when compared to type 1 cytokine-positive $CD8^+$ T-cell subsets. However, a trend towards an age-dependent increase was observed, particularly among memory $CD8^+$ T cells (Zanni et al. 2003).

Another study determined IL-4 production in three $CD4^+$ T subsets—virgin, activated/memory, and effector/memory—at different ages. IL-4 positive cells appeared to increase with age. In particular, IL-4 positive cells significantly increased in activated/memory T cells from nonagenarian subjects. The authors also found a statistically significant decreased ratio of IFN-γ/IL-4 within activated/memory T cells both in old and nonagenarians in comparison with young people. The authors concluded that these data suggest a dynamic shift towards an increased role of type 2 cytokines and a diminished role of type 1 cytokines in human aging. However, it is important to remember that this phenomenon, which could be interpreted as a compensatory mechanism to counteract the increased pro-inflammatory status characteristic of the aging process, occurs within a background where type 1 cytokines are quantitatively dominant (Alberti et al. 2006).

IL-10

IL-10 is arguably the most potent anti-inflammatory cytokine. It is produced by almost all innate and adaptive immune cells. As a potent immunosuppressive cytokine, IL-10 blocks immune responses at different levels by acting directly and indirectly on both the innate and adaptive arms of the immune system. Consequently, IL-10 can inhibit production of proinflammatory cytokines, antigen presentation, and cell proliferation (Saxena et al. 2015).

A high IL-10 production capacity in whole blood samples was found to be associated with successful aging and, particularly, with a markedly reduced risk of death from a cardiovascular event in people aged 85 years (Van Den Biggelaar et al. 2004) but diminished resistance to infectious diseases (McElhaney et al. 2012). High levels of IL-10 have been found in centenarians; this condition may result in protection from cancer (Salvioli et al. 2009).

IL-10 production is tightly regulated and several SNPs controlling production have been described. IL-10 low-producer genotypes seem to play a particular role in susceptibility to inflammatory diseases, together with age-related ones, where IL-10 high producer genotypes are involved in the attainment of longevity (Caruso et al. 2007). A positive significant association between –1082 polymorphism and longevity was found in Italian centenarian men but not in women (Lio et al. 2002b), and similar results were reported in a study on Jordanian oldest old (Khabour and Barnawi 2010). This allele is associated to significantly increased IL-10 production. Moreover, another study reported that possession of the high-producing IL-10 −1082GG genotype favored 3-year survival only in aged men (Cederholm et al. 2007). Conversely, the frequency of the allele associated to low IL-10 production was significantly higher in myocardial infarction patients (Lio et al. 2004). Thus, high IL-10 production seems to be protective against myocardial infarction and a possible biomarker for longevity. These findings suggest that gender is a major variable in the genetics of longevity and that men and women probably follow different strategies to reach longevity. However, discordant results have been obtained in other populations. The frequency of high producer IL-10 polymorphism was not increased in separate studies in some other Caucasian elderly, nor for male subjects analyzed separately (Pes et al. 2004; Ross et al. 2003a; Wang et al. 2001), except for a study on elderly Bulgarians that showed that a IL-10 genotype, related to low level of production, was negatively associated with longevity (Naumova et al. 2004). Therefore, cytokine/-longevity associations have a population-specific

component, being affected by the population-specific gene pool as well as by gene-environment interactions, behaving as survival rather than longevity genes (Pes et al. 2004). Other authors studied genetic variations of the IL-10 gene promoter, in association with cardiovascular mortality in 85 years old subjects, and found that the −2849AA carriers, which is the genetic variant associated with the lowest IL-10 production, had an almost threefold higher cardiovascular mortality risk (Van Den Biggelaar et al. 2004).

TGF-β

TGF-β is a potent regulatory cytokine with diverse effects on haemopoietic cells. This cytokine has been shown to play an essential role in inflammation, in maintenance of immune response homeostasis and in prevention of undesirable self-targeted responses (Gorelik and Flavell 2002; Letterio and Roberts 1998). Contrasting data are reported on correlation between TGF-β levels and age. A Japanese study reported serum TGF-β1 levels inversely associated with age in both men and women, with decreasing serum levels as age advanced, even if these levels were higher in males than in females (Lin et al. 2009). However, high levels of TGF-β have been found in a group of octogenarians and nonagenarians (Forsey et al. 2003) and in two different groups of centenarians (Carrieri et al. 2004; Salvioli et al. 2009). This condition suggests that TGF-β could both counteract and counterbalance the harmful effects of inflammaging and may result in protection from cancer. Moreover, a significant difference was demonstrated between centenarians and younger control subjects for the genotype and allele frequency distributions at the TGF-β1 +915 site in the signal peptide. This finding suggests that polymorphism is associated with long life expectancy (Carrieri et al. 2004). A significantly decreased frequency of a particular haplotype combination, among the less frequent, was observed in centenarians compared with the controls, and there was a survival advantage for subjects who did not have this haplotype combination to become centenarians compared with subjects with this combination (Carrieri et al. 2004). A recent study did not detect any differences in serum levels of TGF-β and TGF-β mRNA levels from PBMCs between young and old women (Halper et al. 2015).

Mediators of Cytokines

Heat Shock Proteins

Heat shock proteins (Hsp) are considered highly conserved proteins, considered to be a danger signal, that chaperone, fold and transport proteins when cells are exposed to several stresses. Increased synthesis of extracellular Hsp stimulates the release of proinflammatory cytokines by monocytes and macrophages, which induce up-regulated expression of antigen-presenting and co-stimulatory molecules on the immature DCs as the maturation process of these APCs and influences the capacity of these cells to take part in the immune response (Temajo and Howard 2014). Moreover, Hsp constitute the internal endogenous signals that activate the DCs as they translocate internalized antigen to the cytosol in DCs (Udono 2012). These functions can be either protective, in the context of a cellular insult, or detrimental as they could lead to excessive inflammation (Terry et al. 2006). Since oxidation and inflammation are interlinked processes, and Hsp70 has been shown to confer protection against the harmful effects of oxidative stress as well as modulating the inflammatory status, it could play a role as a regulator of the rate of aging (de Toda and De la Fuente 2015). In fact, the capacity of cells to respond to stress and synthesize Hsps is reduced with age (Faassen et al. 1989). A study by Rea et al. (2001) showed significantly lower Hsp70 levels in a ≥90 age group compared to a younger group, and declining levels were significantly associated with increasing age. Another study involving centenarians and their offspring showed that low serum Hsp70 level is associated with longevity; however, no genetic associations were found with two SNPs within two Hsp70 genes (Terry et al. 2006).

Lipoxin

Products derived from the lipoxygenase pathway of arachidonic acid metabolism are key mediators of the inflammatory response and its resolution. In particular, cysteinyl leukotrienes (cysLTs) exert pro-inflammatory functions (Kanaoka and Boyce 2004), whereas lipoxin (LXs) carry potent anti-inflammatory signals (McMahon and Godson 2004). LX and especially LXA4, antagonize a number of pro-inflammatory mediators, resulting in inhibition of leukocyte-dependent inflammation (Takano et al. 1997). LXs exert several biological actions, such as inhibiting chemotaxis, adhesion to/transmigration across endothelial and epithelial cells and, specifically, inhibiting IL-8 gene expression in human leukocytes (József et al. 2002), and regulating airway epithelial release of IL-6 and IL-8 (Bonnans et al. 2006). Moreover, LXs block TNF-α secretion from human T cells (Ariel et al. 2003). In a previous study, we documented a significant decrease with aging in urinary levels of LXA4, with very low levels in centenarians. Moreover, the LXA4/cysLTs ratio, which may be considered an index of the endogenous anti-inflammatory potential was significantly lower in centenarians compared to younger people. Therefore, aging seems to be associated with a switch in arachidonic acid that prevents formation of key "stop signals" of the

inflammatory reaction, promoting the development of age-related disease. Nevertheless, centenarians displayed the lowest urinary LXA4 levels and LXA4/cysLT ratio. This observation suggests that additional factors may compensate for the fall in anti-inflammatory mediators to prevent the development of disease in extreme longevity (Gangemi et al. 2005b).

TNF Receptors

TNF receptors (TNFRs) are homotrimers which exist either as membrane-bound or as truncated soluble forms (Baker and Reddy 1996). Two distinct surface receptors mediate the effect of TNF, TNFR1 and TNFR2. Despite the conserved extracellular domains, the cytoplasmic domains of the two receptors lack homology, suggesting activation of different downstream transduction pathways (Safranow et al. 2009). The soluble form of TNFR1 (sTNFR1) has been demonstrated to have a powerful predictive value for adverse outcomes in population-based studies of older adults with acute and chronic disease states (Varadhan et al. 2014). For example, in a study of 22 hospitalized patients with confirmed pneumococcal pneumonia, at 1 week post-admission, plasma levels of sTNFR1 were significantly higher in the elderly (68–91 years) compared to younger patients (37–55 years) and were positively correlated with age (Bruunsgaard et al. 1999b). In a model of endotoxemia, elderly volunteers presented longer circulating levels of sTNFR1 showing a prolonged inflammatory response (Krabbe et al. 2001). In another study, plasma concentrations of sTNFR1 and sTNFR2 were measured in 167 older patients with coronary artery disease. Common factors significantly associated with higher sTNFR1 and sTNFR2 were lower glomerular filtration rate, older age, higher BNP (a plasma marker of heart failure), lower blood hemoglobin, and the presence of asthma or chronic obstructive pulmonary disease. Higher sTNFR1 was associated with more severe coronary artery disease symptoms, past myocardial infarction, lower left ventricle ejection fraction, and higher waist circumference, while higher sTNFR2 was associated with lower HDL cholesterol, higher uric acid, and the presence of metabolic syndrome (Safranow et al. 2009). High serum sTNFR1 (but not sTNFR2) levels are also associated with a higher risk of progression from mild cognitive impairment to Alzheimer's disease (Diniz et al. 2010). In a study on elderly individuals from two independent community-based cohorts of participants, both circulating sTNFR1 and sTNFR2 were closely associated with the most relevant clinical markers defining disease stage and progression risk in chronic kidney disease, even in the absence of diabetes (Carlsson et al. 2014a).

Recently, two studies have explored the association between sTNFR1 and mortality; one demonstrated that a simple index that combined sTNFR1 and IL-6 was the most robust cytokine predictor of 10-year mortality in two large populations of older adults among 15 biomarkers measured (Varadhan et al. 2014), the other found and validated an association between circulating sTNFR1 and an increased risk for mortality (especially for cardiovascular diseases and cancer) in two independent community-based cohorts (Carlsson et al. 2014b).

Discussion and Future Perspectives

Longevity is characterized by a balance between pro-inflammatory and anti-inflammatory agents, which act as key players. A pro-inflammatory tendency can confer high resistance against infectious diseases but, on the other hand, may increase susceptibility to inflammation-based diseases throughout life. An anti-inflammatory trend, instead, may cause an increased susceptibility to infections in pre-reproducing life and might not allow attainment of old age. The currently available knowledge is of great importance but not sufficient to explain the secret of longevity. The data reviewed in this work on both serum levels of cytokines and polymorphism are sometimes conflicting. The reason for the discrepancy of these data is unknown, however, several factors may be involved. Ethnic differences, as well as lifestyle and cultural and genetic differences among the population analyzed in the diverse studies, could play a role. The populations studied are very heterogenic; the cohorts of patients present discrepancies and are not comparable. Some works were performed on healthy aged people, other works enrolled people only considering age, without considering health status and without selecting people for pathologies. Furthermore, it is known that low-grade inflammation is also associated with conditions such as obesity, diet, smoking, and physical inactivity. Therefore, the balance between life style and physiological changes during aging on the one hand and risk factors for age-associated diseases on the other should be taken into consideration. Another factor that should be taken into account to explain the variance among the findings reported is the type of sample each study used: some studies analyzed the values of cytokines present in serum or plasma, others those secreted by PBMC. Moreover, a further reason for the dichotomy in results on cytokines might include differences in measurement methods, such as the time between collection and cytokine measurement, different time release curves for cytokines or ambient temperature. Other studies may have had insufficient statistical power due to the small sample size, may have used different ELISA methods, threshold values or

different methods of collection, storage or assay of blood which could theoretically have allowed cytokines to be released from activated cells (Rea et al. 2003). Finally, it should be noted that some cytokines, such as IL-6, can simultaneously generate functionally distinct or sometimes contradictory signals through their receptor complex. The final physiological output can be thought of as a consequence of the orchestration of the diverse signaling pathways generated by a given ligand. This concept, the signal orchestration model, may explain how some cytokines can elicit pro-inflammatory or anti-inflammatory effects, depending on the in vivo environmental circumstances (Kamimura et al. 2003).

However, despite all these controversial data regarding the clinical relevance of different cytokines, several studies have assigned a pivotal role in inflammatory or anti-inflammatory processes to some mediators.

The high prevalence of women among centenarians suggests that men and women follow different trajectories to reach extreme longevity. In particular, females benefited from healthier lifestyles and favorable environmental conditions in the past century (Franceschi et al. 2000b). Moreover, the differences in longevity between genders are related to free radical production; mitochondrial oxidative stress is higher in males than females; higher levels of estrogens in females give them better protection against aging, through an up-regulated expression of antioxidant longevity-related genes (Vina et al. 2011).

A phenotype which is potentially capable of achieving longevity is identified by a high $CD34^+$ cell count, a cluster of circulating progenitor cells; $CD34^+$ cells may act as spare cells for several cell types and systems, and are negatively affected by acute and chronic inflammation (both low and high grade) and oxidoreductive imbalance, but positively by changes in lifestyle (Di Stefano et al. 2013). Very old people with a high $CD34^+$ cell count may be capable of counteracting inflammatory and oxidative stressors and of living longer (Mandraffino et al. 2012). Continuous and sustained endothelial progenitor cell mobilization in centenarians might represent a particular mechanism for improving tissue reparation (Coppolino et al. 2007). We speculate that progenitor cells are another important piece in the mosaic of longevity.

According to a perspective suggested in recent years, the best candidates to become centenarians are not the strongest and most robust subjects among their age cohort, but subjects that better adapt to the environment, showing more biological plasticity. Some characteristics emerged among this group of exceptional individuals: better control of oxidative stress, and remodeling of the immune system with intense anti-inflammatory activity. For example, the preservation of normal values of vitamin A and vitamin E, and the correlation between their concentrations, protect centenarians against oxidative stress and contribute to their extreme longevity (Basile et al. 2003).

Low-grade chronic inflammation is characteristic of aged people and centenarians, but long-lived are able to avoid the main age-related diseases and reach exceptional ages thanks to the contrasting action of anti-inflammatory agents (Salvioli et al. 2013).

Longitudinal studies on oldest old are awaited to evaluate the role of inflammaging and anti-inflammaging in achieving extreme longevity. Even mathematical and bioinformatic models inspired by a biological approach have been proposed to shed light on this topic (Salvioli et al. 2006). An extremely interesting field to further explore is represented by the possible interactions between changes of the immune system with age and exercise, diet and gut microbiota (Biagi et al. 2010; de Araújo et al. 2013; Ostan et al. 2015). Future research should verify if the impact of lifestyle on longevity is mediated by the balancing between pro- and anti-inflammatory agents.

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