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SI: FRAILTY, AGEING AND INFLAMMATION

Aging, frailty and age-related diseases

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Abstract The concept of frailty as a medically distinct syndrome has evolved based on the clinical experience of geriatricians and is clinically well recognizable. Frailty is a nonspecific state of vulnerability, which reflects multisystem physiological change. These changes underlying frailty do not always achieve disease status, so some people, usually very elderly, are frail without a specific life threatening illness. Current thinking is that not only physical but also psychological, cognitive and social factors contribute to this syndrome and need to be taken into account in its definition and treatment. Together, these signs and symptoms seem to reflect a reduced functional reserve and consequent decrease in adaptation (resilience) to any sort of stressor and perhaps even in the absence of extrinsic stressors. The overall consequence is that frail elderly are at higher risk for accelerated physical and cognitive decline, disability and death. All these characteristics associated with frailty can easily be applied to the definition and

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characterization of the aging process per se and there is little consensus in the literature concerning the physiological/biological pathways associated with or determining frailty. It is probably true to say that a consensus view would implicate heightened chronic systemic inflammation as a major contributor to frailty. This review will focus on the relationship between aging, frailty and age-related diseases, and will highlight possible interventions to reduce the occurrence and effects of frailty in elderly people.

Keywords Frailty · Aging · Immunosenescence · Chronic diseases · Inflamm-aging · IRP

Introduction

The concept of frailty began to emerge as a medically distinct, clinically recognizable syndrome some years ago based on the clinical experience of geriatricians (Rockwood et al. 1994, 1999, 2000; Fried et al. 2001; Fried and Walston 2003; Bandeen-Roche et al. 2006; Bergman et al. 2007; Rockwood and Mitnitski 2007a, b). This has become a fascinating concept despite difficulties in providing an exact definition of the term. The causes of frailty are complex and must be accepted as multidimensional based on the interplay of genetic, biological, physical, psychological, social and environmental factors (Walston et al. 2006; Rockwood and Mitnitski 2007a, b). The term "frailty" is commonly used in different ways under different circumstances but mainly to describe a physical and functional decline which may occur as a consequence of certain diseases, but most intriguingly also in the absence of identifiable specific disease (Kanapuru and Ershler 2009). Thus, frailty is viewed as a physiologic loss of reserves and resilience (Rockwood and Mitnitski 2007a, b; Fried et al. 2009; Rockwood et al. 2010).

How best to evaluate frailty clinically is debated (Martin and Brighton 2008). One clinical syndromic definition of frailty according to Fried includes self-reported exhaustion, reduced physical activity, slow walking speed, reduced grip strength and unintentional weight loss (Fried et al. 2001). Frailty was considered to be present when at least three of these five characteristics can be seen, but, as mentioned above, psychological, cognitive and social factors most likely also contribute to this syndrome (Pel-Littel et al. 2009; De Lepeleire et al. 2009; Rothman et al. 2008). Frailty is associated with reduced functional reserves and consequently decreased adaptation (resilience) to any sort of external or possibly even internal stressors (Fried et al. 2009). All these parameters represent a lack of homeostatic reserve ("homeostenosis") (Zoppini et al. 2008). This definition is merely an operational syndromic description of frailty because true comprehension of the underlying pathophysiological pathway(s) is lacking. If this definition of frailty (clinical and physiological) is accepted, a relatively high proportion of very elderly people must be classed as frail (Woods et al. 2005; Chin et al. 2003). An alternative method for evaluating frailty employs a frailty index, which is calculated by considering a number (usually 40 or more) of potential deficits. These deficits can be symptoms, signs, diseases, disabilities or abnormal laboratory values (Mitnitski et al. 2001, 2005; Goggins et al. 2005; Gu et al. 2009; Yang and Lee 2010). The overall consequences are that frail elderly are at higher risk of accelerated physical and cognitive decline, disability and finally death (Rockwood and Mitnitski 2007a, b; Kulminski et al. 2008c; Fried et al. 2009; Gill et al. 2009). Clearly, all the defining characteristics of frailty can be easily applied to the definition and characterization of the aging process itself (Mitnitski et al. 2001; Bergman et al. 2007). Thus, from the practical point of view, an early identification of a propensity to frailty would be useful to prevent or delay its more severe clinical consequences (Bortz 2002). Once overt clinical symptoms have appeared, it may be too late for effective intervention, except for palliation. In this line of thinking the most promising parameters for investigation could be biological variables (Reiner et al. 2009; Blaum et al. 2009; Bandeen-Roche et al. 2009). It is tempting to think that precisely quantifiable parameters could assist with the definition of this otherwise vague syndrome, which although well-characterized from the clinical and physiological point of view is entirely operationally-defined. However, there is currently little consensus in the literature concerning the biological parameters associated with or determining frailty (Walston et al. 2006). This review will discuss the relationship between aging and frailty and how frailty and age-related diseases intertwine.

Aging and frailty: what is their relationship?

Aging

Aging is a complex phenomenon, also difficult to define at its different levels, i.e., molecular, cellular, physiological and psycho-social. Aging can be conceptualized as a process of accumulation of deficits, taking place in different individuals in different ways, with a variety of rates for different organ systems, depending on the interplay of intrinsic and extrinsic factors (Mitnitski et al. 2001; Kirkwood 2005). To compare aging and frailty we would need a physiological definition of aging (Bergman et al. 2007; Izaks and Westendorp 2003; Rockwood 2005). The most widely accepted functional definition is that a decrease in physiological reserves, while still supporting acceptable functioning in the steady state, cannot adapt to any additional, even physiological, stress. Thus, aging itself is associated with progressive homeostatic/homeodynamic dysregulation that makes the organism less and eventually, non-, resilient (Yates 2002; Lipsitz 2004). Thus, aging is a dynamic process which manifests as "mosaic" progression. Aging presents itself to a greater or lesser degree from "successful" aging to "pathological" aging depending on the reserve functions of the different physiological systems, their resilience and the consequent appearance of disease. Frailty may be considered to reflect an intermediate, but distinct state between these two extremes, where a certain reversibility of pathological processes may still exist (Bortz 2002). This would imply that although aging predisposes to frailty, not all elderly are frail (Schuurmans et al. 2004; Bergman et al. 2007) and suggests common, but not identical, pathways between aging and frailty. This opens up the possibility that frailty can be amenable at least to some extent to interventions (De Lepeleire et al. 2009). Nevertheless, the question is raised whether frailty is simply a "semi-pathological" result of the usual aging process and not a real distinct clinical entity. Thus, we need to examine what constitutes frailty in more detail.

Frailty

Most geriatricians can describe frailty, but as discussed above, quantifiable variables are not established for a distinct definition. Although frailty is associated with increased comorbid disease (Rockwood et al. 2004; Klein et al. 2005) and functional limitations, it may also occur in the absence of known comorbidity. Even some patients who meet the frailty criteria can still function relatively well. Thus, frailty can be operationalized in several ways, e.g., accumulation of deficits, clinical syndrome, clinical phenotype (Rockwood et al. 2006; Rockwood and Mitnitski 2007a, b; Fried et al. 2001). Most important for the concept of frailty is the ability to predict it, so it can be modulated or even prevented. This necessitates better knowledge of its signs and symptoms, causes and characteristics, as well as instruments to identify and predict frailty (Mitnitski et al. 2001; Fried et al. 2001; Jones et al. 2005; Searle et al. 2008). The best-known aspect of frailty is its consequences including morbidity, institutionalization and ultimately mortality. The signs and symptoms of frailty have been extensively investigated and some appear essential for describing this state. The most important may be self-reported functional deterioration which is almost always present according to the ADL and IADL assessments (Cook 2009). These functional changes almost invariably signal the presence of frailty even if no evident underlying disease is diagnosed. Impaired nutritional status is also one of the key characteristics in frailty, mostly related to poor nutrient intake. Most frail patients experience fatigue, disturbances of balance, decreased endurance and difficulties in adapting to changing circumstances (Pel-Littel et al. 2009; De Lepeleire et al. 2009). There is still controversy as to whether cognitive impairment is a symptom of frailty or whether Mild Cognitive Impairment is a separate syndrome, or indeed, a sign of early dementia (Buchman et al. 2008; Boyle et al. 2010). Not all frail elderly will experience all the symptoms mentioned, and this seems to be strongly associated with their remaining reserve capacity and hence resilience. Therefore, it is proposed that only when this reserve capacity of interconnected physiological systems is reduced to a crucial level, most of the signs and symptoms of frailty become clinically manifest. This is the moment when the aging process may cause a clinically apparent disease entity, namely frailty. The reserve capacity is decreased and the adaptation mechanisms to stressors cannot be mobilized any longer, leading to a breakdown of homeostasis and crossing the threshold to clinically manifested frailty syndrome.

Biological parameters associating with clinical frailty have also been energetically sought. The results of several large studies clearly demonstrate that in addition to inflammatory status, some lipid parameters could also be convincingly associated with the frailty syndrome (Hazzard 2001; Schalk et al. 2004; Landi et al. 2008; Morley 2009). Most specifically, increased plasma IL-6 levels were found to be the most strongly associated with frailty (Ferrucci et al. 1999; Ershler and Keller 2000; Leng et al. 2002; Cesari et al. 2003; Reiner et al. 2009). Among the lipid parameters, decreased total cholesterol and HDL-C were the most strongly associated (Schalk et al. 2004; Landi et al. 2008). It is of note, however, that some studies could not confirm these associations (although they are in the minority). All other biological parameters assessed so far showed either moderate, weak or no associations with frailty (Table 1). The moderate to weak associations were found for nutritional and coagulation parameters. No real associations were found with hormones and immunological parameters or with telomere length (Woo et al. 2008). Thus, what effectively triggers this homeostatic failure, whether one versus multiple physiological parameters, chronic versus acute diseases, is still not clearly established, despite extensive investigation (Fried et al. 2009; Kanapuru and Ershler 2009).

Table 1 Differential association of different biological parameters with frailty

Parameters	Association			
	Strongly	Moderately	Variable	No association
Inflammatory				
IL-6	+			
TNFα				−
Lipids				
TC	+			
HDL-C	+			
Hormonal				
DHEAS			+	
IGF-1			+	
GH			+	
Nutritional				
Vitamins			+	
Coagulation		+		
Immunological			+	
Hyperglycemia	+			
IR	+			
Anemia		+		
Telomere length				−

TC total cholesterol; *GH* growth hormone; *IR* insulin resistance; *IGF-1* insulin like growth factor 1; *DHEAS* dehydroepiandrosterone sulfate; *IL-6* interleukin-6; *TNFalpha* tumour necrosis factor

It is therefore not surprising that there is currently no exact universally accepted consensus concerning the causes of frailty, probably reflecting the complexity of the multiple interconnected physiological processes which become dysregulated with age. These physiological processes/pathways include immune/inflammatory processes, neuroendocrine deregulation, coagulation disorders and metabolic alterations (Walston et al. 2006). These interrelated physiological pathways are modulated in a complex manner by the underlying aging process manifesting through such events as increased free radical production, telomere shortening and mitochondrial dysfunction as well as genetic predispositions and different diseases (comorbidities) that may have extrinsic cause (e.g., infections). These modulators impact on subclinical alterations of the physiological pathways leading ultimately to the appearance of clinical manifestations of frailty after crossing the frailty threshold. Although the earlier stages of frailty may not be clinically apparent, later stages manifest when a critical mass of deficits accumulates and a threshold of vulnerability is passed from molecular to cellular and finally to the organismic level. The important question remains: is there a more dominant physiological pathway which can underlie frailty?

Role of inflammation in frailty

The finding that systemic low-level inflammation is strongly associated with frailty is consistent with the consensus that inflammation is associated with aging and chronic age-related diseases too (Franceschi et al. 2000). This may be due to chronic antigenic stimulation throughout life, whereby an important stressor appears to be infection with the persistent reactivating herpesvirus CMV (Derhovanessian et al. 2009). Age-associated altered immunological profiles and dysregulated immune responses, loosely termed "immunosenescence," may themselves contribute to

Table 2 Putative alterations of major biological parameters differentiating between aging and frailty

Aging	Frailty
Low grade inflammation	High grade inflammation
No lipid alterations	Lipid alterations
Immune response: ↓	Immune response: ↓↓
Hormones: low	Hormones: very low
No anemia	Anemia
No nutritional alterations	Nutritional alterations

Frailty = Aging + syndrome

pathology in addition to amplifying inflammatory processes. Moreover, Alzheimer disease, atherosclerosis, and autoimmune diseases, increased with advancing age, may contribute additional antigenic stressors and enhance chronic inflammatory processes (Fulop et al. 2005). Again, it is not clear how frailty could be distinguished from these events. It may reflect additive effects, as an "aging *plus*" syndrome associated with inflammation (Table 2). The physiological characteristics of frailty such as low muscle strength, exhaustion, reduced physical activity and unintentional weight loss can all be at least partially explained by increased levels of inflammatory mediators, especially by the increase of IL-6. This cytokine, together with its surrogate, CRP, is one of the most studied inflammatory parameters which is strongly, possibly causally, related to the frailty syndrome. Thus, the inflammatory process could be a unifying biological process leading to the frailty syndrome. This idea also has consequences for the prevention and the eventual reversibility of frailty. The relationship of frailty with some lipoproteins could also be indirectly explained by invoking inflammation; they may be secondarily perturbed in an inflammatory state. Thus, HDL is a powerful anti-inflammatory agent, a decrease of which is related to increased inflammatory status. Furthermore, lipids have important roles in cellular metabolism and the cell membrane, and their dysregulation would cause generally altered cellular function in all organs (Fulop et al. 2006a). Thus, a decrease in non-HDL-C is also related to disability, mortality and decreased longevity and as such is a determinant of the frailty syndrome. This chronic systemic inflammatory process can lead to one of the most important symptoms of the frailty syndrome, namely sarcopenia (Pel-Littel et al. 2009), which is defined as a loss of muscle mass and strength leading to functional alterations (Roubenoff and Harris 1997). The causes of sarcopenia, prevalent in the elderly, healthy or not, are most probably also multifactorial, including endocrine changes, nutritional alterations, physical inactivity, and perhaps most importantly, inflammatory processes (Cesari et al. 2004). IL-6 is a major factor modulating muscle mass and ultimately causing sarcopenia as well as reduction in bone density.

What are the consequences of this sarcopenia? Mostly, these are indeed related to frailty. One of the most important is the loss of muscle strength and function, as included in Fried's clinical syndrome definition (Fried et al. 2001). Together, this determines the increased risk for falls and fractures. Ultimately, sarcopenia results in greater dependency and disability. Other consequences of sarcopenia could be changes with aging in body composition leading to concomitant increase in fat, accumulating mostly at the abdominal site. Here, it is associated with a low grade systemic inflammation which is a major step toward the development of metabolic syndrome (Fulop et al. 2006a, b). The latter is also associated with increased insulin resistance (IR). Using homeostasis model assessment (HOMA), it was recently shown that IR predisposes elderly persons to frailty (Barzilay et al. 2007). However, whether frailty via its physiological derangements increases IR compared to healthy aging remains unknown. Furthermore, the co-morbidities associated with IR may potentially contribute to the development and maintenance of the frailty syndrome (Abbatecola and Paolisso 2008). In this manner, abdominal adiposity, whether or not accompanied by obesity, is important in frailty pathogenesis. Moreover, the inflammatory process is one the most powerful free radical generators in the body, which can further contribute to frailty via skeletal muscle damage (Abbatecola and Paolisso 2008). This results in a vicious circle further increasing the inflammatory process. Furthermore, the IR accompanying sarcopenia and increased abdominal fat in aging induces even more pronounced IR in frailty. Therefore, it may be hypothesized that chronic inflammation represents a triggering factor in the origin of the link between IR and frailty syndrome in the elderly. In fact, resistance to the anti-inflammatory actions of insulin would result in enhanced circulating levels of pro-inflammatory cytokines such as IL-6 which in turn would result in

persistent low-grade inflammation as seen in aging (Barzilay et al. 2007). However, which of these effects is the primary alteration for inducing frailty remains to be determined. Recently, hyperglycemia was shown to contribute to frailty in addition to or as part of its role in IR (Blaum et al. 2009). Ultimately, these alterations can increase the risk for diabetes mellitus and cardiovascular diseases.

In line with the role of abdominal obesity, Hubbard et al. (2010) recently published data on the association between BMI and frailty which showed a U curve relationship. Frailty was more prevalent, measured by a Frailty index and the Fried frailty definition in those with BMI 25-29. In this group, those having a greater waist circumference, a surrogate for abdominal fat, were more frail. We also conducted a study (Goulet et al. 2009) where the goals were to determine (1) whether frail elderly are more insulin resistant than their healthy counterparts, and (2) the influence of abdominal fat mass, muscle mass index, inflammation, hormonal and lipid status, oxidative stress, antioxidant capacity, and physical activity on insulin sensitivity (IS) in frail elderly subjects. To be able to dissect out the effect of obesity on IS in frail elders, we compared a group of healthy, non-obese (HN) elderly subjects to a group of frail lean (FL) and a group of frail obese (FO). Because of the key role played by abdominal fat mass in the development of the aging-related decrease in IS (Beaufrère and Morio 2000), and its interrelationships with many of the variables listed above (Després et al. 2008), it was hypothesized that this depot would be the best predictor of IS. Thereby, FO subjects would have a lower IS compared with FL and HN subjects, but that FL and HN would have a similar IS. Our results demonstrated that central obesity is the key factor responsible for IR in frail elderly individuals. Furthermore, frailty without obesity is not associated with a greater IR than is healthy aging. Thus, central obesity is a key factor of frailty through several different pathways including generating inflammation (Després et al. 2008) and oxidative stress (Pou et al. 2007) as well as releasing free fatty acids into the circulation (Fulop et al. 2006a, b).

Frailty and age-related diseases

Frailty is linked to the development and progression of many age-related diseases and could also be the final pathway directly to some important age-related diseases such as osteoporosis and the consequent fractures, malnutrition favouring infections and sarcopenia leading to falls and functional dependence. Interestingly, frailty is likely the underlying process that leads to the clinical manifestations that occur as geriatric syndromes (Bergman et al. 2007; Fried et al. 2009; Cook 2009). A positive feedback relationship may exist between shared risk factors for geriatric syndromes and frailty, which increases the propensity to progress to even poorer outcomes. Studies show that comorbidities like congestive heart failure, myocardial infarction, rheumatoid arthritis, peripheral vascular diseases, diabetes and hypertension increase the risk for frailty (Klein et al. 2005; Newman et al. 2001). However, it should be stressed that not all older people with these comorbidities become frail and not all who meet the criteria for frailty have a recognizable underlying medical condition (Fried et al. 2001; Kanapuru and Ershler 2009). The terms "primary" and "secondary" frailty have been used to refer to frailty in the absence or presence of chronic illnesses, respectively (Fried et al. 2003). This may mean that the relationship between frailty and comorbidities is not directly causal but may become so if other factors are also present (such as an acute stress or due to the accumulation of too many deficits (Rockwood and Mitnitski 2007a, b) (Fig. 1). The approach to define frailty through deficit accumulation (indicated system damage/burden) is gaining in popularity (Mitnitski et al. 2001, 2005; Rockwood and Mitnitski 2007a, b; Kulminski et al. 2008a, b, c, d; Yashin et al. 2008; Gu et al. 2009; Yang and Lee 2010). Deficits are indicators of physiological deregulation and therefore by counting them one can quantify the level of such deregulation. Moreover, it can also be hypothesized that frailty precedes these diseases in a subclinical manner, such that when resilience is overwhelmed it becomes manifest concomitantly with the appearance of chronic medical illness. From this perspective frailty can be a susceptibility factor for the appearance of chronic diseases.

What could be the contribution of immunosenescence to frailty and to longevity?

A systematic review of the literature reveals that only a few altered physiological pathways can be

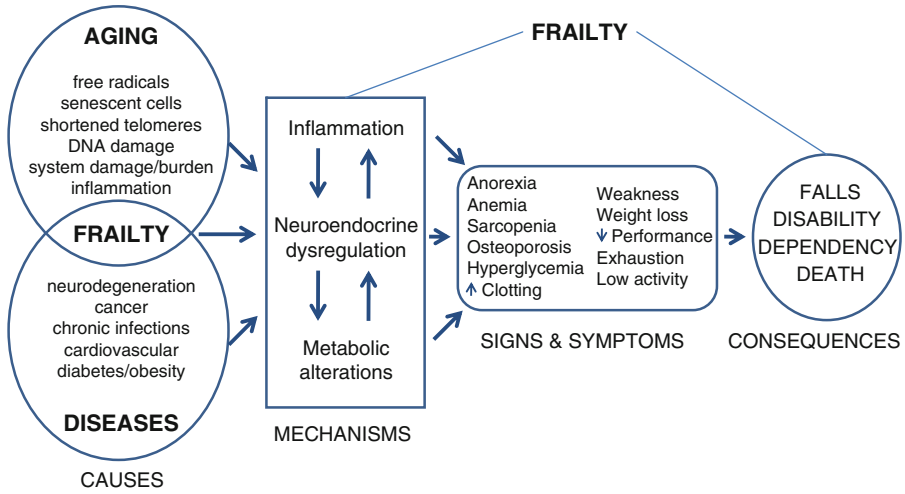

Fig. 1 Interrelation between aging and diseases leading to the development of frailty. There is a strong interrelation between the biological aging changes and the development of age-related diseases. The interface could be the development of the frailty syndrome. Besides this intersection, either the biological aging or the age-related diseases can lead to the frailty syndrome characterized by the clinically apparent changes leading to catastrophic consequences

definitively related to frailty, of which one of the most important seems to be the altered inflammatory response, and elevated levels of IL-6, related to frailty and to its components such as sarcopenia, disability and weight loss (Walston et al. 2005). Interestingly, the presence of an inflammatory milieu is also linked to most of the age-associated diseases which could be related to some extent to frailty, including Alzheimer's disease (AD), cardiovascular diseases (via atherosclerosis), type 2 diabetes, anemia of chronic disease and cancer. Low grade inflammation is intimately linked to more general alterations of the immune response in the elderly, together termed immunosenescence.

What is the relationship between immunosenescence and the chronic inflammatory processes leading to age-associated diseases and frailty? Is this a one-way process or a mutually interacting phenomenon? Alterations of certain pro-inflammatory (IL-6, TNF, IL-1) as well as anti-inflammatory cytokines (IL-10, IL-4) are observed at greater frequencies in age-associated diseases than in healthy aging. For example, a specific association was demonstrated between elevated TNF and dementia (Angelopoulos et al. 2008). Similar associations could be shown for endothelial dysfunction as a first step in the development of atherosclerosis (Katagiri et al. 2008). The persistence of chronic inflammatory foci such as in periodontitis, also leads to the development of age-associated diseases including atherosclerosis. Thus, age-related immune dysregulation associated with chronic inflammation and suppression of the adaptive response, together with retained relatively intact functioning of innate immunity, exacerbates these chronic inflammatory processes. The presence of this inflammation over decades eventually leads to the development of clinically significant pathological conditions such as cardiovascular disease, dementia, diabetes mellitus, osteoporosis and arthritis. The occurrence of these diseases together with immunosenescence and/or frailty makes the elderly more vulnerable to infections. Thus, the age-related low grade inflammatory process seems to accelerate the progression of chronic diseases, such as cardiovascular and neurodegenerative diseases, induce metabolic changes manifesting by the appearance of IR and muscle wasting, as well as having an immunosuppressive effect on cellular immune responses and finally, overregulation of the anti-inflammatory cytokine response (e.g., IL-10) (Fig. 2). To date, specific patterns of multimorbid chronic inflammatory diseases or conditions that commonly co-occur with frailty have not been elucidated well, but would be a fertile area of investigation. It is not known whether the proinflammatory state associated with a specific disease activates the etiologic cascade that has been

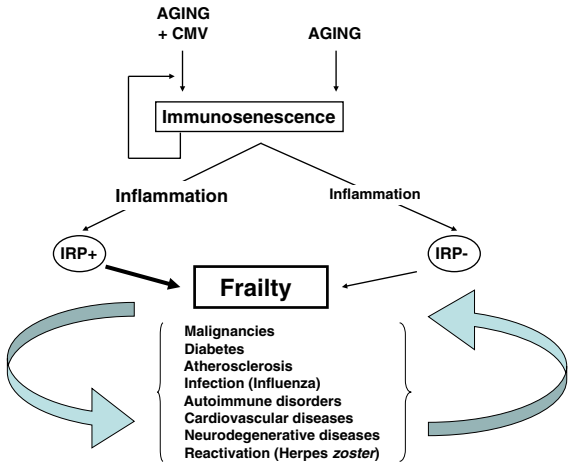

Fig. 2 Clinical importance of CMV infection, immunosenescence and the IRP on the development and interaction between frailty and age-related diseases. In aged individuals CMV exacerbates immunosenescence, which in turn reduces the control of CMV itself and its associated effects. Although immunosenescence also occurs in CMV seronegative individuals, the IRP associated with increased mortality rates consists a cluster of parameters including CMV seropositivity. Together with an increased pro-inflammatory environment, individuals in the IRP category (IRP+) may face more age- and/or immune-associated diseases than individuals not in the IRP category (IRP−) who may also have a more balanced inflammatory environment. All these alterations may lead to frailty and/or pro-inflammatory age-dependent diseases. Frailty may induce pro-inflammatory age-dependent diseases or, vice versa, frailty can be the consequence of these age-dependent diseases

postulated to result in frailty or whether this occurs through non-disease-mediated specific pathways (Fried et al. 2009). Even so, the relationship between inflammatory markers and frailty appears to be robust across different definitions of frailty (Hubbard et al. 2009). Identification of a combination of inflammatory diseases that act synergistically to heighten the risk of frailty would provide information about mechanistic pathways that induce a pro-inflammatory frail state. The contrary could be also envisaged, as the development of frailty must be occurring well before the frailty threshold is attained and manifested in a clinically apparent manner Alterations of multiple physiological pathways including hormonal, inflammation, IR, that cause frailty are the same underlying susceptibility factors for age-related pro-inflammatory diseases. Independently of the relationship, these alterations alone or in combination render the elderly more susceptible to new diseases, whether subclinical or clinical, and ultimately at greater risk of becoming frail. A recent study by Chang et al. (2009) has shown that synergistic interactions between specific inflammatory diseases may further heighten the risk of frailty.

While inflammatory status has been extensively studied, immune responses related to inflammation leading to frailty have scarcely been explored (Leng et al. 2009). As already well-known, the immune response is altered with age and most probably even more in frailty mainly when this is related to chronic age-associated diseases via the immunosuppressive effects of increased pro- and anti-inflammatory cytokines. The question arises as to whether this pro-inflammatory activity is the *primum movens* or just a reaction to the decreased primary anti-inflammatory response. The link between these two arms of the immune response, i.e., the anti- and pro-inflammatory, could be represented by a special subset of T cells, the T regulatory cells (Treg; with the phenotype CD4+CD25+Foxp3+). These cells have been shown to mediate self-tolerance and their deletion leads to auto-immune diseases. Moreover, Treg may influence the immune response to infections (Lages et al. 2008). Whether Treg numbers and functions are altered with age is controversial. Some investigators have concluded that the proportion and activity of T reg is increased with aging, also contributing to the reduced proliferative capacity of T cells from elderly individuals. Treg may originate from the thymus or from anergized peripheral CD4 T cells. As this is an important issue with still rather few data available, Treg activity and effects on other T cell activities in the elderly, especially in frailty and chronic diseases, would be worth addressing.

Whether and which factors relevant to immunosenescence can be related to longevity remains poorly documented, despite numerous theories and proposals being put forward. Recently, on the basis of longitudinal studies unusually taking immune responses into account, some evidence has emerged that immunosenescence can be a factor influencing individual longevity. What could the mechanism for this be? Longitudinal studies in representative as well as very healthy people 85 years of age at baseline have allowed the definition of an ''immune risk profile'' (IRP) as a predictor of 2, 4 and 6-year mortality. The IRP is based on several parameters of adaptive immunity, the most important of these being an inverted CD4:8 ratio, most likely due to the accumulation of clonally expanded

CD8+ T cells, many of which are specific for CMV (Pawelec et al. 2009). The IRP appears to have no predictive ability for 55 year-olds, but may begin to be informative from 65 years of age (Wikby et al. 2008). Changes in innate immunity observed in frail elderly may be related to these alterations in adaptive immunity defined as the IRP, but this has not yet been systematically investigated. Thus, immunosenescence via alteration of both innate and adaptive immune response is likely to make a strong contribution to longevity and frailty (Larbi et al. 2008).

The IRP and the cumulative illness rating scale (CIRS)

Longitudinal studies are crucial for defining individual parameters associated with healthy aging or morbidity and mortality. As alluded to above, pioneering longitudinal studies in Sweden were aimed at identifying factors predicting 2, 4, and 6 years mortality and have resulted in the emerging concept of an IRP. This consisted of a cluster of parameters including high CD8 counts, low CD4:8 ratio and poor T-cell proliferative response predicting higher mortality at follow-up. Intriguingly, CMV seropositivity and large increases in the number of CD8+CD28−CD57+ T-cells, known to be associated with CMV carrier status, were significantly associated with the IRP (Pawelec et al. 2009). It is significant that the IRP defined in this manner in the OCTO study was equally applicable to the NONA study. This is important because OCTO subjects were selected for excellent health, whereas the NONA subjects were a representative non-institutionalized population, only one-third of which were really healthy. The remaining two-thirds included many who were frail, but the IRP applied to this population equally well. It is therefore unlikely to be unduly influenced by frailty. However, independently of the IRP, IL-6 levels were also predictive of mortality, most likely matching better with frailty in these longitudinal studies in which the concept of increasing allostatic load was invoked, i.e., belonging to the IRP group was a bad prognostic indicator; ditto belonging to the high IL 6 group, but both together were even worse. Thus, additive diagnostic factors exist, and the question arises as to whether each influences morbidity and mortality in a different way, which merely accumulate and exhaust reserves more rapidly.

The most frequent diseases observed in the elderly are infections, malignancies, cardiovascular diseases derived from atherosclerosis, and neurodegenerative diseases including Alzheimer's and Parkinson's diseases. One major difficulty here is to dissect the role of aging in the decreased immune response compared to the role of chronic disease, itself causing immune alterations exacerbating other chronic diseases (Castle et al. 2005, 2007). The question is whether a high chronic disease burden leads to impaired immunity or the impaired immunity leads to high chronic disease burden or perhaps more likely, interactions in both directions. Recent studies at UCLA (Castle et al. 2007; Rafi et al. 2005) on the burden of chronic diseases used the CIRS for quantifying this parameter via the determination of health status. CIRS measures disease burden in individuals who have different chronic diseases but no evidence of acute deterioration or infection. There is strong evidence that the effects of chronic diseases rather than those of age itself are at least in part responsible for immune dysregulation and consequently for low grade inflammation in elderly patients. It is clear that age-associated alterations and the accumulation of more and more debilitating chronic diseases will worsen and accentuate the already existing alterations, as well frailty. Thus, at this stage it is difficult to make a definitive separation between aging, frailty and chronic diseases. The finding that substantial T cell alterations (phenotypes and functions) are still present in SENIEUR-compatible elderly subjects (Larbi et al. 2006) may reflect the inadequacy of the selection protocol in screening out all subclinical disease, especially the effects of chronic infections on immunity, and is consistent with the findings of the OCTO/NONA longitudinal studies mentioned above. These data therefore suggest that it is possible to extract a set of altered immune parameters predictive of mortality apparently independently of the health status of the subjects at baseline. Further studies will certainly contribute to our understanding concerning the interrelation between immune response alterations, frailty and the morbidity of elderly subjects.

Infections

Infectious diseases are increased in incidence and severity in the elderly, resulting in a large number of deaths (Castle et al. 2005). The most important causes

of these are respiratory pathogens including influenza and *Streptococcus pneumoniae* and urinary infections due to gram-negative bacteria. Elderly subjects are much more susceptible to Gram-negative bacterial colonization and sepsis than young adults. The reactivation of some latent infections is also more common in the elderly, such as *Mycobacterium tuberculosis* and *Herpes zoster*. One of the most significant public health problems is influenza, which causes 10,000–40,000 excess deaths in the USA alone, of which 90% are in persons over 65 years (Castle et al. 2007).

The relationship between immunosenescence and the increased incidence of infections with aging might well be primary. It is likely that thymic involution together with chronic antigenic stimulation and other age-associated changes, decreases the number and repertoire of naïve T cells which leads to an inability to respond appropriately to a new antigen (Fulop et al. 2005). As part of innate immunity, the proinflammatory response to infection is not diminished in the elderly, and may contribute to the increased proinflammatory state commonly observed and already discussed. However, it should be mentioned that in SENIEUR elderly subjects, selected for exceptionally good health, this low grade inflammation is practically non-existent. This state of "Inflamm-aging" seems to manifest by an increase in the IL-6 level which may be a reliable marker for functional disability and a predictor of frailty with subsequent disability and mortality in the elderly (Maggio et al. 2006). The Swedish OCTO/NONA studies also found a significant association of baseline IL-6 levels with mortality at follow-up. Together, these data reinforce the notion of an important contribution of altered innate immune responses to the increased incidence of infections with aging.

Susceptibility is also influenced by concomitant illnesses, medication, psychological status, nutritional status and altered homeostasis all being attributes of frailty. It is well-recognized that chronic inflammatory diseases contribute to the further deterioration of defense mechanisms and thus patients suffering from chronic diseases are more susceptible to infections such as influenza or pneumonia. Hence the severity of infectious diseases is greater in patients with chronic underlying disorders compared to healthy elderly subjects. Hospital mortality is also related to severity of the underlying chronic diseases, including cardiovascular insufficiency, chronic obstructive pulmonary disease and kidney failure. This is even more striking in nursing home settings (Fulop et al. 2009). Thus, frailty as a common final pathway in many chronic diseases contributes to the increased incidence of infections.

Neurodegenerative diseases

Dementia is highly prevalent among the elderly, increasing with age. The question naturally arising in this context is whether low grade inflammation related to immunosenescence contributes to the development of AD by altering the adaptive immune response and favouring an inflammatory status, or whether these changes are only epiphenomena. The production of inflammatory cytokines originating from the innate immune response is stimulated by the increased production of aggregating beta amyloid (Aβ) (Richartz et al. 2005). These cytokines could have a dual role, since they can be protective by increasing the elimination of Aβ or they can cooperate as costimuli during chronic Aβ stimulation, thereby enhancing a pro-apoptotic effect. Moreover, Aβ primes T-cells, eliciting the appearance of autoreactive T-cells which can participate either directly or by the production of IFNγ in the destruction of neurons and formation of plaques. Recent studies raised the possibility that AD pathology may contribute to frailty or that frailty and AD pathology share a common pathogenesis (Buchman et al. 2007, 2008). One of these underlying pathogenetic factors may be inflammation. We have recently shown dramatic alterations in naïve and memory subsets of CD4+ cells in patients with mild AD, with greatly decreased percentages of naïve cells, elevated memory cells and increased proportions of CD4+ as well as CD8+ cells lacking the important costimulatory receptor CD28. CD4+CD25^{high} potentially T regulatory cells with a naïve phenotype are also reduced in AD patients. These data provide evidence for more highly differentiated CD4+ as well as CD8+ T cells in AD patients, consistent with an adaptive immune system undergoing persistent antigenic challenge and possibly manifesting dysregulation as a result, and as such contributing to the pathogenesis of AD (Larbi et al. 2009). Thus, alterations of the immune system contributing to low grade inflammation with aging might contribute to the development of AD but the exact role played is still under intense scrutiny.

Diabetes type 2

Diabetes is one of the most common diseases of the elderly, with almost 10% suffering overtly and probably another 10% unrecognized. Diabetes type 2 (T2DM) alone or associated with metabolic syndrome is related to chronic inflammation (Fulop et al. 2006a, b), which in turn is related to the pro-inflammatory activity of the adipose tissue leading to some degree of IR and decreased insulin production by pancreatic Langerhans islet cells. It has also been shown that some inflammatory markers such as F2 isoprostane in urine, IL-6, TNF and CRP are increased in T2DM. It has been suggested that the increase of these parameters is associated with increased oxidative stress (Mori et al. 2003). T2DM is often associated with complications at the levels of arteries, eyes and kidneys. These complications are further associated with an inflammatory process exaggerated by the presence of advanced glycation end (AGE) products. Thus, diabetes is itself an inflammatory disease, and combined with other alterations and with immunosenescence further alters the immune response. It was in fact shown by Muszkat et al. (2003) that diabetes type 2 was associated with a lower seroconversion rate following influenza vaccination in nursing home residents. This further supports the role of chronic inflammatory diseases associated with age-related immune dysregulation in the altered response to vaccination. The participation of frailty in the development of T2DM could be multiple as the pro-inflammatory state and the high free radical production are linked to sarcopenia, to IR, to micro- and macrovascular changes. It is also well established that T2DM patients are more prone to frailty. T2DM could be an excellent model to investigate the various interactions between frailty and chronic diseases.

Atherosclerosis

Atherosclerosis is a typical inflammatory disease and is the pathological basis of cardiovascular diseases, which are extremely frequent in the elderly (Libby 2002) and even more in frail elderly. This inflammatory disease may be initiated by certain auto-antigens, such as possibly HSP65, modified low density lipoproteins, or by infectious agents such as *Chlamydia pneumoniae* (Wick et al. 2001). These agents stimulate cellular immune infiltration of the intima of the arterial wall. The most abundant infiltrating cells are CD4+ T-cells which bear activation markers (Libby 2002). This leads to the secretion of IFNγ which in turn stimulates innate immune responses and creates a vicious circle leading to clinical events such as acute coronary syndrome with rupture of the plaque. Moreover, a link between the IRP-related CD8+CD28− T-cell population and coronary artery disease was demonstrated independently of any CMV infection. This latter finding further suggests that T cell subset changes during immunosenescence may contribute to the development and progress of atherosclerosis. It is of note that atherosclerosis develops as a life-long process which starts at a young age and only manifests itself clinically at more advanced age. Together, it seems clear that alterations of the immune system with aging contribute to the development of clinically manifested atherosclerosis such as coronary heart disease which are intimately linked to frailty.

Chronic heart failure (CHF)

CHF is a very frequent multisystem disorder encountered in frail elderly, mainly those in nursing homes. It affects not only the cardiovascular system, but also neuroendocrine, renal and immune systems. CHF is associated with a state of chronic inflammation (Anker and von Haehling 2004). TNF, IL-6, and IL-1β in the myocardium and peripheral tissues have been shown to play an important role in the pathogenesis and progression of myocardial dysfunction. Indeed, plasma levels of these pro-inflammatory cytokines predict short- and long term survival in patients with CHF. Furthermore, in hearts of patients with CHF, the accumulation of these TLR4 regulated pro-inflammatory cytokines and expression of TLR4 receptor itself have been reported to be increased (Birks et al. 2004). Recently, the expression of TLR4 and TLR2 was measured on monocytes from CHF patients. Monocyte TLR4 expression was found to be increased in patients with CHF and fluvastatin was able to inhibit the excessive innate immune response via inhibition of monocyte Toll-like receptor signaling (Földes et al. 2008). Such increased TLR4 expression could be a link with the increased pro-inflammatory cytokines found in CHF. Similar alterations were observed in the TLR system of

leukocytes with aging. Thus, the interplay between frailty and CHF may occur via several altered physiological parameters such as inflammation, neuroendocrine, metabolic status; however, this requires further investigation.

Can frailty be predicted, measured and modulated?

As is clear from the above, to predict frailty we need to know more about its nature and causes. There are clear indications that changes in certain functional and biological parameters would be good candidates to predict and measure frailty. Among these candidates, changes in functionality can be very strong predictors as well as measures of frailty. As sarcopenia is an important cause of frailty, instruments measuring it directly (MRI) or indirectly (anthropometric measurements, BMI) could also contribute to predicting frailty. Many biological parameters can also potentially be used either for predicting or for measuring frailty. These include inflammatory parameters, among which the most well-characterized is IL-6, representing a pro-inflammatory status. CRP can be used as a surrogate if hepatic function is normal. The exact role of TNF remains to be elucidated in the context of frailty. Lipid, neuroendocrine and nutritional parameters also need to be included. It is clear that the best way to predict and measure frailty is a multidimensional evaluation as it is not a syndrome with a single cause.

All the interventions being tested today target only one aspect of frailty such as nutrition, physical activity or hormone deficiency. Multiple simultaneous interventions will probably need to be devised to overcome this problem. Modulation of the inflammatory process, for example by decreasing the antigenic burden throughout life, could be valuable. Good lifestyle habits started in young or in middle age could be also helpful.

Could the clinical relevance of frailty be translated into any potential intervention strategy?

Targeted vaccination

Vaccines developed not only for pathogens causing acute infections, but also chronic infections may help decrease chronic inflammation and reduce frailty. One of the major targets in the latter case would be CMV. This could have important consequences on immunosenescence and related low-grade inflammation. A prophylactic vaccine against CMV has recently been developed (Pass et al. 2009) but eradicating this virus would be a major long-term public health undertaking, unlikely ever to be accomplished. The newly-developed vaccine against herpes zoster which is already standard in the USA is of interest in this context. This is not an immunomodulator but can reinforce the cell-mediated immune response by decreasing the burst of herpes zoster overwhelming the immune system of the elderly (Oxman 2007).

Other vaccination approaches in the elderly could also be very important, such as those in cancer therapy and recently for treatment of AD. An adequate response to immunotherapy in cancer heavily relies on an intact immune system which is lacking in the elderly. Thus, because of the decreased DC, NK cell and adaptive immune responses the expectation of cancer vaccination successes in the elderly should be tempered (Derhovanessian et al. 2008). Improving immunity in the elderly is a condition *sine qua non* for the success of active immunotherapy. In AD, the immune system may also be effective for eliminating Aβ via antibody generation following vaccination, according to data from animal models. These events have beneficial effects in clearing Aβ. This was the leading principle of the vaccination trials which were effective in mice, and possibly also in humans, before serious side effects prevented full exploration of benefit. Thus, the first generation amyloid vaccine, AN-1792, demonstrated a trend toward efficacy in that patients who developed an antibody response showed significantly improved memory tests over a 1-year period. However, owing to the development of aseptic meningoencephalitis in 6% of the patients, the AN-1792 program was discontinued. This underlines the potential role of immunosenescence and the need for better understanding of the immune and inflammatory response alterations in AD (Larbi et al. 2009) to efficiently intervene in the developing AD and possibly frailty.

Immune rejuvenation for decreasing frailty burden

Other means could be used to rejuvenate the immune response in the elderly. Some of them are relatively

simple, public health education exercises, such as a healthy lifestyle including healthy nutrition and exercise, but other more invasive interventions have mainly been tested in animal models so far. However, they could become everyday medicine in the future. We mention some of them very briefly as eventual potential clinical interventions. One of the most important research areas is the potential rejuvenation of the thymus. This could be achievable by several means such as cytokines, growth hormones, signaling manipulations or by transplantation. Hormonal modulation is also possible including use of Vitamin D, sex hormones, IGF-1 or growth hormone. The use of anti-inflammatory agents such as statins, aspirin, antioxidants or lipids could be also promising. The in vitro expansion of immunocompetent cells which could be reinjected when needed is also under consideration by some investigators. Many other interventions might become apparent as our knowledge increases on the causes of frailty.

Metabolic, nutritional and hormonal interventions

As many systems are involved in the development of frailty it is judicious to think that multiple and concerted interventions will be necessary. Metabolic interventions reducing the burden of hyperglycemia, IR, sarcopenia, nutritional interventions reducing sarcopenia, obesity, abdominal fat as well as hormonal interventions modulating sarcopenia, the immune response, the overwhelming adrenergic and stress hormone axis may be used concomitantly to obtain a clinically perceptible modulation of frailty (Daniels et al. 2008; Hackstaff 2009; de Souto Barreto 2010; Kim et al. 2010).

Conclusions and perspectives

No doubt frailty exists as a clinical geriatric syndrome, but much work needs to be done on a better and more widely-accepted frailty definition and studies designed to lead to the elucidation of the interrelated physiological pathways to frailty. Alterations of many interacting physiological systems may contribute to the decrease in resilience to adverse stressors and will need systems biological approaches to analysis. Inflammation is part of these alterations determined by and feeding back to alterations in the immune system with aging. However, in humans, unlike in spf mice, pathogen loading cannot be put to the test in this context, because everyone has encountered multiple pathogens over their life time, leaving indelible effects on the composition and function of the immune system. This effect is further complicated by the higher occurrence of chronic diseases associated with or driven by chronic inflammation. There is likely to be a final common pathway for interactions of these many factors altering the immune response to infections and leading to the increased prevalence and incidence of chronic inflammatory diseases. The clinical burden most likely resulting from such immune dysregulation is overwhelming. Thus, understanding the pathophysiological basis of frailty would be of great importance as a handle for manipulation and eventually prevention.

What are the future directions for research in this area? Currently, it seems that in addition to parameters of inflammation, no other biological parameters can be directly and reliably linked to frailty. Worse, no biological parameter at all can be causally linked to frailty. Thus, we need well-designed longitudinal studies of elderly and ideally not-so-elderly populations to identify individuals who will develop frailty. In the meantime, different biological parameters should be studied in parallel (Table 3). It would be very important to test dynamically the functional reserves and not only study static parameters. It seems emergent that frailty is on the continuum of aging having characteristics much more marked than the "normal" aging process per se. Thus, although it is currently very difficult to assign a definitive, unique biological pathway to frailty, inflammation could eventually take this role. This means that inflammation should already be considered an important target for prevention and intervention to investigate whether this would decrease the incidence of frailty in the elderly population. Despite these reservations, it is still worthwhile to try to intervene. In the meantime our research efforts should continue to elucidate the pathophysiological basis of frailty in order to design better interventions to improve the quality of life of the elderly in the rapidly increasing aging populations of the developed, and increasingly also developing, countries.

Table 3 Areas of biological markers for more extended future studies in frailty

Specific immune parameters: e.g., T cell phenotypes, T cell functions
Oxidation markers/antioxidants: e.g., oxLDL
Telomere length/telomerase activity
Mitochondria
Cytokines and inflammatory markers: IL-10, sFASL, sVCAM, sICAM
Dynamic physiological and biological tests for reserves: e.g., vaccination
Hormones: vitamin D, adrenalin, noradrenalin

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