

## Frailty and sarcopenia

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DOI:

[10.1016/j.arr.2017.01.006](https://doi.org/10.1016/j.arr.2017.01.006)

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*Document Version*

Publisher's PDF, also known as Version of record

*Citation for published version (Harvard):*

Wilson, D, Jackson, T, Sapey, E & Lord, JM 2017, 'Frailty and sarcopenia: The potential role of an aged immune system', *Ageing Research Reviews*, vol. 36, pp. 1-10. <https://doi.org/10.1016/j.arr.2017.01.006>

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## Review

## Frailty and sarcopenia: The potential role of an aged immune system



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## ARTICLE INFO

## Article history:

Received 22 November 2016  
 Received in revised form 26 January 2017  
 Accepted 31 January 2017  
 Available online 20 February 2017

## Keywords:

Immunesenescence  
 Inflammaging  
 Frailty  
 Sarcopenia  
 Neutrophil  
 Inactivity

## ABSTRACT

Frailty is a common negative consequence of ageing. Sarcopenia, the syndrome of loss of muscle mass, quality and strength, is more common in older adults and has been considered a precursor syndrome or the physical manifestation of frailty. The pathophysiology of both syndromes is incompletely described with multiple causes, inter-relationships and complex pathways proposed. Age-associated changes to the immune system (both immunesenescence, the decline in immune function with ageing, and inflammaging, a state of chronic inflammation) have been suggested as contributors to sarcopenia and frailty but a direct causative role remains to be established. Frailty, sarcopenia and immunesenescence are commonly described in older adults but are not ubiquitous to ageing. There is evidence that all three conditions are reversible and all three appear to share common inflammatory drivers. It is unclear whether frailty, sarcopenia and immunesenescence are separate entities that co-occur due to coincidental or potentially confounding factors, or whether they are more intimately linked by the same underlying cellular mechanisms. This review explores these possibilities focusing on innate immunity, and in particular associations with neutrophil dysfunction, inflammation and known mechanisms described to date. Furthermore, we consider whether the age-related decline in immune cell function (such as neutrophil migration), increased inflammation and the dysregulation of the phosphoinositide 3-kinase (PI3K)-Akt pathway in neutrophils could contribute pathogenically to sarcopenia and frailty.

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## 1. Introduction

## 1.1. Frailty

The concept of frailty is probably recognised by most biogerontologists but its emerging importance as a hallmark of ageing has led to a more rigorous medical definition of physical frailty.

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'A medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death' (Morley et al., 2013).

This definition describes the syndrome but does not attempt to interpret the condition or its underlying biological mechanisms. Two intrinsically different models of frailty have been proposed in an attempt to operationalise the syndrome. The first model, the frailty phenotype model, was proposed by Fried and colleagues (Fried et al., 2001). This suggests that a step-wise increase in self-reported disability is analogous with an increasing frailty state and correlates with adverse health outcomes such as death, hospitalisation and falls. Fried demonstrates that the presence of 3 components, out of a total of 5 (unintentional weight loss, self-reported exhaustion, weakness, slow walking speed and low physical activity), has predictive power in identifying mortality risk. Fried extrapolates this to suggest that the presence of 3 components in a person identifies them as frail and the presence of 1 or 2 components as pre-frail (Fried et al., 2001). The model has been validated by Fried and independent groups with concurrent or predictive validity assessed in 17 different samples or cohorts (Bouillon et al., 2013), but no attempt has been made to assess the reliability of the phenotype.

Conversely Rockwood et al. suggested that frailty was not a categorical phenomenon but best described as a dynamic, continuous process of deficit accumulation and as a result they proposed the Frailty Index (Mitnitski et al., 2001). The most striking difference with the Fried definition of frailty was that any variable could be considered a deficit as long as it was associated with adverse health outcomes, increased in prevalence with age into the tenth decade and had a prevalence of at least 1% which did not saturate in older age. Using this model Rockwood showed there was a greater correlation of time to death with frailty index rather than age (Mitnitski et al., 2001). The Frailty Index has also been widely tested for validity with concurrent or predictive validity assessed in 13 different samples or cohorts (Bouillon et al., 2013), but not reliability.

One of the difficulties in deciding upon the most elegant and clinically applicable model is that each model describes a slightly different population. The Frailty Index has better discriminatory ability for adults with moderate and severe frailty (Rockwood et al., 2007). This is probably due to its broader approach to the diagnosis of frailty and the inclusion of cognitive and psychosocial markers rather than solely relying on physical markers. There are also higher rates of frailty reported with the Frailty Index, likely due to the continuous nature of the model (Song et al., 2010). This may make it a better objective marker of the assessment of the efficacy of an intervention. The frailty phenotype may have utility in identifying older adults at risk of disability. It has been suggested that these assessment instruments should not be considered as alternatives, but rather as complementary.

Both the Frailty Index and the Frailty Phenotype are utilised in research but the more global concept of frailty as described by the Frailty Index is probably better accepted in the gerontology community. This is reflected in recent diagnostic and screening tools, Edmonton Frail Scale and PRISMA 7, including the assessment of several domains of health (Rolfson et al., 2006; Raiche et al., 2008). However, the relative ease of utilising the Frailty Phenotype means it is still used in research as a method of identification of frailty.

## 1.2. Sarcopenia

Sarcopenia can be considered as one of the main physical drivers of frailty or perhaps even a precursor state if it is present without a medical classification of frailty as described above. As with frailty, definitions of sarcopenia have evolved over time reflecting greater

understanding of the condition. The current broadly accepted definition includes the effects on function as well as including muscle mass and strength:

'A syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death.' (Cruz-Jentoft et al., 2010a).

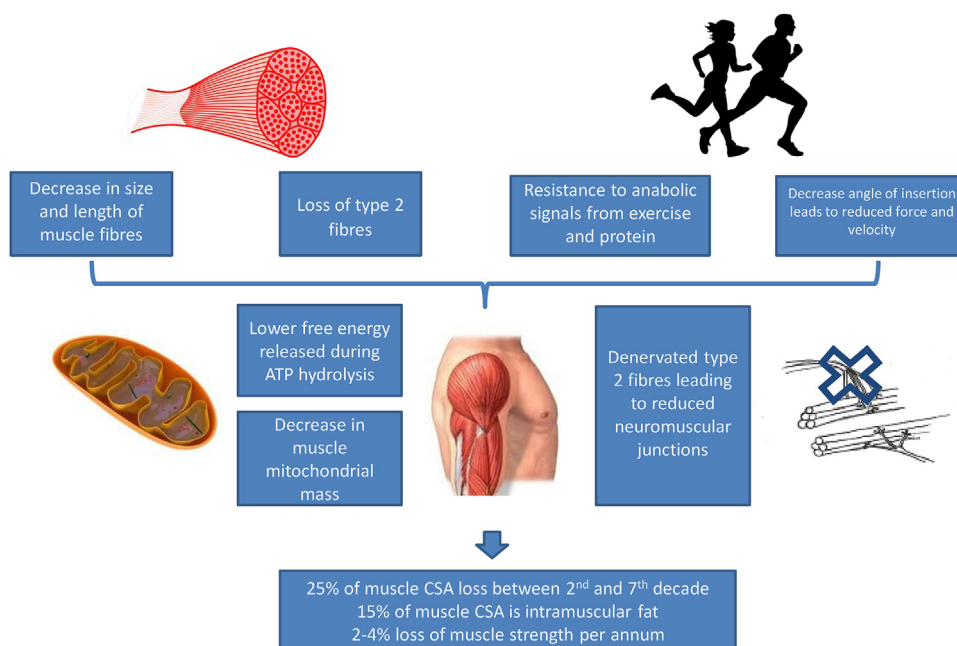
Similar to the frailty phenotype the European Working Group on Sarcopenia in Older People (EWGSOP) recommend categorising sarcopenia into pre-sarcopenia, sarcopenia, and severe sarcopenia depending on the presence of certain criteria. They suggest that the pre-sarcopenia stage is characterised by low muscle mass with no impact on muscle strength or physical performance, whereas the sarcopenia stage is low muscle mass with either low muscle strength or low physical performance and severe sarcopenia is the presence of all three criteria (Cruz-Jentoft et al., 2010a).

The cut off point for each criterion is not currently standardised and is dependent on both the method of measurement and the researcher. It is generally accepted that low physical performance is defined as a gait speed of less than 0.8m/sec. Low muscle strength is usually defined by handgrip strength of less than 30 kg for men and less than 20 kg for women (Cruz-Jentoft et al., 2010a; Cruz-Jentoft et al., 2010b). Low muscle mass is usually measured by a skeletal muscle mass index with a variety of cut offs quoted in the literature ranging from 7.23 kg/m<sup>2</sup> to 8.87 kg/m<sup>2</sup> in men and 5.45 kg/m<sup>2</sup> to 6.42 kg/m<sup>2</sup> in women (Baumgartner et al., 1998; Newman et al., 2003; Chien et al., 2008; Cruz-Jentoft et al., 2010a). The diversity in the cut offs, particularly in defining low muscle mass, utilised in research has led to huge disparity in the prevalence of reported low muscle mass with prevalence reported as between 3.3 to 41.5% in community populations over 65 (von Haehling et al., 2010). This has been recognised by the EWGSOP who have recommended that more research is urgently needed in order to obtain good reference values for populations around the world.

The inclusion of both muscle mass and strength within the definition of sarcopenia has partially occurred in response to extensive research which has shown that whilst loss of muscle mass is associated with loss of muscle strength, the relationship is not linear; the decline in strength is more rapid than the concomitant loss of muscle mass. Goodpaster et al. demonstrated in a community dwelling population aged between 70 and 79 that muscle mass declines at 0.5-2% per annum compared to 2-4% loss of muscle strength (Goodpaster et al., 2006). Thus age-related changes in the quality of the muscle may be as important as the reduced mass and reduced muscle quality, notably loss of type II fibres, reduced mitochondrial mass and increased fat infiltration, may contribute to loss of muscle strength and power (Narici and Maffulli, 2010). Potentially a more inclusive definition of sarcopenia may incorporate the loss of muscle mass, reduced muscle quality and a loss of functional strength, as shown in Fig. 1, which depicts age-related changes occurring within the muscle from the whole muscle level through to a cellular level and how these contribute to the loss of muscle mass, quality, strength and power.

## 1.3. Relationships between frailty and sarcopenia

The relationship between frailty and sarcopenia is not yet fully characterised but these conditions share many of the same clinical outcomes, associations and suggested pathophysiology. Despite this, sarcopenia is considered a component of frailty but frailty is not considered a component of sarcopenia. However, there is considerable overlap between the defining criteria of the Frailty Phenotype and sarcopenia. Severe sarcopenia as defined by EWGSOP is pre-frailty by the Fried phenotype. Sarcopenia is often considered a pre-cursor syndrome or the physical component to frailty.



**Fig. 1.** Age related changes occurring within the muscle. Figure depicting the age related changes occurring within the muscle from a whole muscle level through to a cellular level and their impact on muscle mass, quality, strength and power. CSA – cross sectional area.

Sarcopenia is reported to be twice as common as frailty in the general population (von Haehling et al., 2010). The prevalence of both conditions is dependent on population and definition. Using the EWGSOP definition and criteria of sarcopenia the prevalence ranges from 4.6%, community dwelling men in the UK aged 68–76 (Patel et al., 2014), to 68%, male Italian nursing home residents over 70 (Landi et al., 2012). A recent systematic review of frailty prevalence in a community population (Collard et al., 2012) reported the range to be 4.0%, independently mobile men over 65 (Cawthon et al., 2007), to 59.1%, community dwelling Dutch older than 70 (Metzelthin et al., 2010). The calculated weighted average of frailty as defined using the Frailty Phenotype is 9.9% (Collard et al., 2012).

Research has shown that in frail community dwelling adults the most common positive Fried criteria was slow gait speed (43%) and weakness (54%), the functional defining criteria of sarcopenia (Rothman et al., 2008). It has also been reported that the relative risk of developing weakness and low activity was higher than developing any other frailty defining criteria over 7.5 years of follow up in initially non-frail women (Xue et al., 2008). This suggests that theoretically while it is possible to have frailty without sarcopenia clinically it is unlikely. However, a recent isolated report investigating the concordance of frailty and sarcopenia demonstrated that frailty was more common than sarcopenia and the concordance between frailty and sarcopenia was poor (Reijnierse et al., 2016). This is the only literature investigating the concordance of frailty and sarcopenia but is contrary to previous understanding and an isolated report.

Importantly both frailty and sarcopenia are considered partly reversible conditions. Several epidemiological studies have shown that whilst transition between lesser and greater frailty is always the most frequent outcome, a number of participants will transition from greater to lesser frailty (Gill et al., 2006; Fallah et al., 2011; Espinoza et al., 2012; Lee et al., 2014). Health status and baseline function is important, as those with poor mobility at baseline in a longitudinal study experienced faster acceleration of their frailty than those with good mobility (Fallah et al., 2011). The reversal of frailty has also been demonstrated in intervention studies. A multifactorial intervention in community dwelling frail adults resulted in a significant difference in frailty prevalence between the two

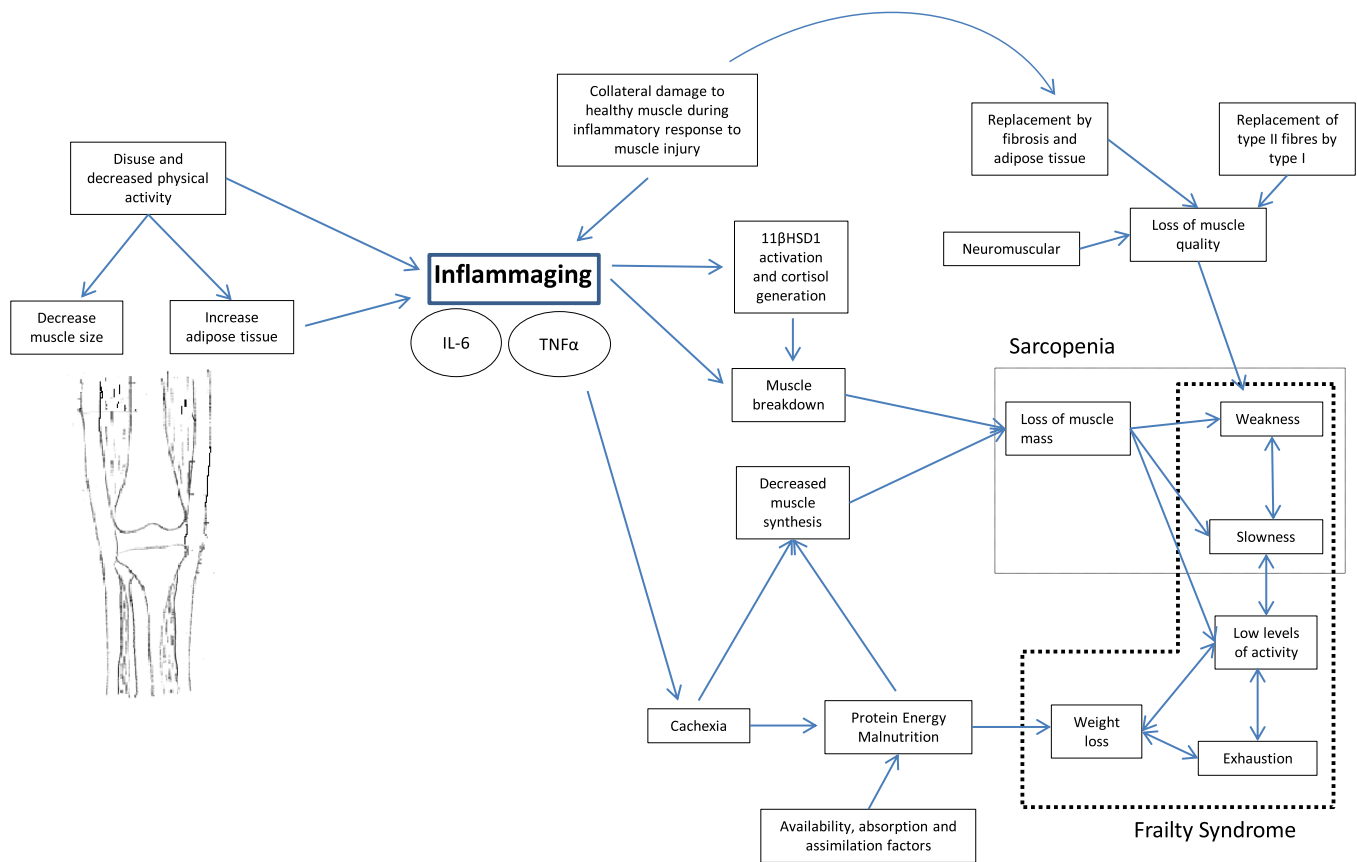
groups who were identical at baseline. Of note, the intervention was specific to the individual depending on their positive frailty criteria at baseline assessment, for example those scoring for weight loss would be assessed and managed by a dietician, consistent with a personalised medicine approach. Importantly, this study reported an actual reduction in diagnosis of frailty in the intervention group not just a slowing of progression (Cameron et al., 2013). It is also possible to improve components of frailty and sarcopenia. Several resistance exercise programmes have documented improvements in gait speed and strength in groups of frail older adults, with programmes of 8–12 weeks able to reverse loss of muscle strength equivalent to that lost over 20 years (Fiatarone et al., 1994; Liu-Ambrose et al., 2004). Improved understanding of the processes underlying sarcopenia may allow the development of even more efficacious and targeted interventions.

## 2. Pathophysiology of sarcopenia and frailty

The pathophysiology of both sarcopenia and frailty is complex. Proposed models for both syndromes incorporate multiple causes, inter-relationships and elaborate pathways (Fried et al., 2009; Cruz-Jentoft et al., 2010a). However, both syndromes are incompletely characterised and there is insufficient understanding of the underlying cellular mechanisms driving the development and maintenance of states of frailty and sarcopenia. Sarcopenia is better understood than frailty largely due to its effects being concentrated on a single system, the neuromuscular system, and for this reason it has been suggested as a physical model of frailty.

### 2.1. Regulation of muscle mass

Our current understanding of the regulation of muscle mass is predominately based on data from animal studies, with much less known of the key regulatory processes in human muscle. Studies in rodents suggest that muscle synthesis is intrinsically linked with muscle atrophy via the PI3k-Akt pathway which is central to both processes (Schiaffino and Mammucari, 2011). Muscle synthesis is activated by insulin-like growth factor 1 (IGF-1) binding to



**Fig. 2.** Relationships between inflammaging, sarcopenia and frailty. Figure depicting a proposed model of inflammaging, frailty and sarcopenia. The model describes a central role for inflammaging within the creation and maintenance of frailty and sarcopenia states.

IGF-1 receptor which triggers the activation of a signalling pathway including PI3k, Akt, and the mammalian target of rapamycin (mTOR), which in turn phosphorylates S6 kinase and other factors which promote protein synthesis (Schiaffino and Mammucari, 2011). There are multiple modulators of the pathway, both intrinsic and extrinsic. Intrinsic regulators include S6 kinase 1 inhibition of insulin receptor substrate (IRS) (Harrington et al., 2004) and mTORC2 upregulation of Akt (Sarbasov et al., 2005). Extrinsic regulators include: amino acids which can directly activate mTORC1 (Kim et al., 2008; Sancak et al., 2008) and beta adrenergic agents (Kline et al., 2007) and Wnt7a which both upregulate the PI3k-Akt pathway (von Maltzahn et al., 2012).

Muscle atrophy via both the ubiquitin proteasome pathway and autophagy lysosomes is centrally regulated by forkhead box proteins (FoxO). FoxO when present in the nucleus induces the ubiquitin E3 ligases atrogen-1 and muscle RING finger protein-1 (MuRF-1) (Williamson et al., 2010) which cause myofibril degradation. FoxO also regulates ATG genes which promote mitochondrial degradation via autophagy (Polager et al., 2008). As expected there are multiple modulators of these pathways and arguably the most important is the effect of Akt on FoxO: Akt phosphorylates FoxO and transports it from the nucleus to the cytoplasm preventing it from inducing either E3 ligases or ATG genes (Stitt et al., 2004; Huang and Tindall, 2007; Jang et al., 2007). Myostatin, via the action of Smad 2 and 3, upregulates FoxO (McFarlane et al., 2006) and muscle disuse produces neuronal nitric oxide synthase (nNOS) which enhances FoxO3 mediated transcription of E3 ligases (Suzuki et al., 2007).

The majority of studies investigating sarcopenia in humans have suggested that loss of muscle mass is primarily driven by a blunted synthetic response to both feeding and exercise, termed anabolic resistance (Murton and Greenhaff, 2009; Markofski et al.,

2015; Wall et al., 2015). Moreover, there is little data to suggest that atrogenes or ubiquitin proteasomal degradative pathways are enhanced in older adults, indeed in the fasted state (when protein breakdown is at its highest) there is no difference in protein turnover or signalling through synthetic pathways such as Akt between young and old adults (Francaux et al., 2016).

Anabolic and catabolic pathways may be relevant in periods of extreme inactivity, such as bed rest, and in chronic inflammatory states, such as chronic obstructive pulmonary disease (COPD). In a recent 5 day bed rest study in well characterised healthy young and old subjects, leg lean mass and strength were reduced only in the old subjects. Both subject groups had blunted mTORC1 signalling and increased MURF1 expression in skeletal muscle after bed rest, but only the older group had reduced amino acid induced protein synthetic rates and increased atrogenes expression (Tanner et al., 2015). A study investigating the effect of resistance training in participants with COPD, a chronic inflammatory condition, demonstrated higher levels of MAFbx and MURF1 protein expression (atrogenes) and increased phosphorylation of p70s kinases (Constantin et al., 2013). These studies suggest a decrease in muscle synthesis and an increase in muscle degradation (dysregulated muscle homeostasis) is seen with inactivity and chronic inflammatory conditions.

Patients with sepsis are subject to both periods of extreme inactivity and a pro-inflammatory state and could therefore be considered a model of accelerated ageing (Singer et al., 2016). Following sepsis and admission to critical care 70–100% of patients reported prolonged weakness (Callahan and Supinski, 2009) which is due both to muscle loss and changes in muscle cell functionality. This group deserves further study for a link between inflammation and sarcopenia.



### 3. Ageing of the immune system

The decline in immune function with age, termed immunosenescence, is well documented and includes increased susceptibility to infections, reduced vaccination responses in older adults and increased risk of chronic inflammatory diseases such as Rheumatoid Arthritis (Weng, 2006; Shaw et al., 2010; Goronzy and Weyand, 2013). The many changes that occur in the components of the immune system with age have been reviewed previously (Gruver et al., 2007; Ongradi and Kovesdi, 2010; Shaw et al., 2010) and we will thus consider only those elements of innate immunity that could contribute to frailty and sarcopenia, primarily through their role in inflammation.

Immunosenescence includes *inflammaging*, the increased presence of a low-grade chronic systemic pro-inflammatory state with age (Franceschi et al., 2000; Baylis et al., 2013b). Inflammaging is characterised by increased levels (typically 2–4 fold those seen in healthy young subjects), of pro-inflammatory cytokines such as interleukin 1 $\beta$  (IL-1 $\beta$ ), interleukin 6 (IL-6) and tissue necrosis factor alpha (TNF $\alpha$ ) as well as c-reactive protein (CRP), and a reduced serum level of anti-inflammatory cytokines including interleukin 10 (IL-10) (Baylis et al., 2013b) and IL-1ra. The factors driving inflammaging are multiple (Fig. 2) and can include increased output of pro-inflammatory cytokines by resting monocytes (Doyle et al., 2010; Jackaman et al., 2013; Pinke et al., 2013), reduced IL-10 production by regulatory lymphocytes (Duggal et al., 2013), increased adiposity leading to production of pro-inflammatory adipokines such as leptin and reduced anti-inflammatory adipokines such as adiponectin (Lutz and Quinn, 2012), reduced physical activity with age (Woods et al., 2012), and senescent cells which build up with age and secrete pro-inflammatory cytokines (Coppe et al., 2010).

Neutrophils have a fundamental role in the defence against bacterial infections and in older adults many aspects of their function such as phagocytosis, superoxide production, and NET generation are impaired with age (reviewed in Hazeldine and Lord, 2015). In this review we focus on reduced chemotactic ability (Sapey et al., 2014). Neutrophils migrate from the blood to a site of infection or tissue damage in response to chemoattractants, moving through tissue by releasing proteases such as neutrophil elastase at their leading edge and damaging healthy tissue in the process resulting in inflammation (Cepinskas et al., 1999). Our previous work has shown that chemotaxis is reduced in older adults making migration inefficient, leading to greater tissue damage and secondary systemic inflammation (Niwa et al., 1989; Wenisch et al., 2000; Butcher et al., 2001; Hazeldine et al., 2014; Sapey et al., 2014).

Whilst investigation of the role of the immune system in frailty and sarcopenia lags behind similar research into ageing and age-related conditions, there is evidence that the immune system, and its dysregulation, may play a role in both processes.

#### 3.1. Role of increased systemic inflammation

Multiple associations have been demonstrated between frailty and sarcopenia and the individual cytokine components of inflammaging, though evidence of a causal relationship remains to be proven.

##### 3.1.1. Inflammatory cytokines, IL-6 and TNF $\alpha$

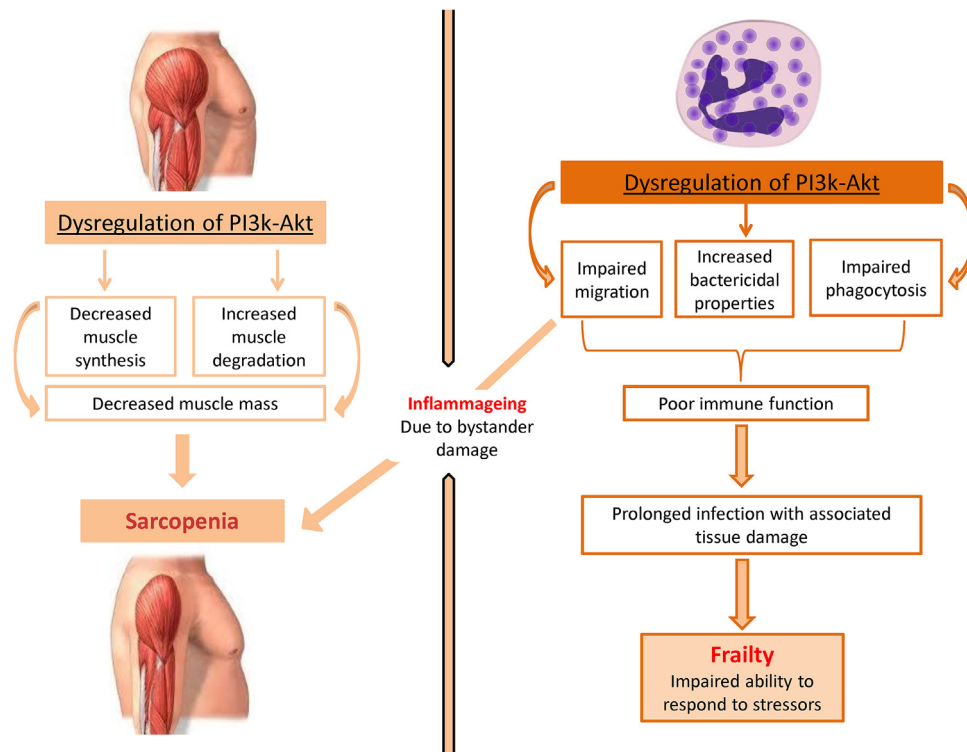
The potential role of IL-6 in sarcopenia is complex. This cytokine, initially thought to be only produced by immune cells, was eventually identified as being produced by muscle and in this context was termed a 'myokine' (Pedersen and Febbraio, 2008). In uninfected individuals muscle is in fact a major source of circulating IL-6. IL-6 expression increases acutely in contracting skeletal muscle and is released following exercise (Steensberg et al., 2000), enhancing muscle metabolism, fatty acid oxidation, and glucose uptake

(Kelly et al., 2009). However, there is increasing evidence that IL-6 can act via the ubiquitin proteasome muscle degradation pathway, with raised systemic IL-6 associated with increased ubiquitin protein and mRNA (DeJong et al., 2005), E3 ligase protein and mRNA (White et al., 2012) and proteasome activity (Ebisui et al., 1995). In addition IL-6 can induce insulin resistance which suppresses Akt-mTOR activity and inhibits muscle synthesis (Febbraio et al., 2004; Franckhauser et al., 2008). Another pro-sarcopenic effect of inflammation is on the generation of cortisol within tissues. Cortisol is profoundly catabolic and can be synthesised from inactive cortisone in tissues including muscle and bone, by the actions of the enzyme 11 $\beta$ HSD1 (Morgan et al., 2009). 11 $\beta$ HSD1 activity increases with age and is induced by cytokines including TNF $\alpha$  and IL-6 (Tomlinson et al., 2004). The systemic increase in inflammation with age may indirectly impact on muscle turnover via induction of 11 $\beta$ HSD1.

A positive association between chronically raised serum IL-6 and TNF $\alpha$  and frailty has been demonstrated in several epidemiological studies (Leng et al., 2002; Walston et al., 2002; Leng et al., 2004). Higher serum levels of IL-6 predict development of sarcopenia (Payette et al., 2003; Schaap et al., 2006) and increased IL-6 also predicts disability and mortality, recognised outcomes of frailty and sarcopenia (Cesari et al., 2012). In addition, high serum IL-6 and CRP at baseline assessment have been associated with a two to threefold greater risk of losing more than 40% of grip strength over three years (Schaap et al., 2006). Using centenarians as a model for 'healthy ageing' has also given some support for a link between IL-6, with frailty and sarcopenia in humans. Specifically, the IL-6 174GG genotype, which is associated with higher plasma levels of IL-6, is under-represented in centenarians (Franceschi and Bonafe, 2003).

However, a major limitation in understanding the role of inflammation in sarcopenia is the limited number of studies that have measured inflammatory cytokines, whether at the mRNA or protein level, in human skeletal muscle with age. Two studies comparing healthy young and old males reported 3.3 and 2.8 fold increases in mRNA for IL-1 $\beta$  (Przybyla et al., 2006) and TNF $\alpha$  (Leger et al., 2008) for older men. A study comparing frail older adults, defined by physical function testing, with young subjects reported raised TNF $\alpha$  mRNA and protein in myocytes from the frail subjects. Moreover, an exercise intervention in these frail adults reduced TNF $\alpha$  mRNA and protein levels and improved muscle strength (Greiwe et al., 2001). In contrast, three studies have found no differences in skeletal muscle IL-6 mRNA with age (Hamada et al., 2005; Przybyla et al., 2006; Trenerry et al., 2008) and two found no age-related increase in TNF $\alpha$  mRNA in males (Hamada et al., 2005) or females (Raue et al., 2007).

The apparent discrepancies between studies of systemic inflammation and sarcopenia may indicate that it is the degree and chronicity of inflammation that dictates the effect on muscle mass, strength and quality. Thus relatively mild levels of inflammation such as those seen with normal ageing or with obesity may not be sufficient to effect loss of muscle mass or strength, but could contribute to sarcopenia by affecting metabolic quality (Murton et al., 2017). When systemic inflammation is more severe and accompanied by inflammation in skeletal muscle itself, as may be seen in frailty (Greiwe et al., 2001), then inflammation may also contribute to loss of muscle mass and strength. In support of this proposal exogenous administration of TNF $\alpha$  to mice causes: (1) anorexia and muscle loss, achieved via several mechanisms including reduced amino acid availability via upregulation of leptin (Grunfeld et al., 1996; Sarraf et al., 1997); (2) activation of the transcription factor NF- $\kappa$ B in muscle resulting in myofibre atrophy and activation of the ubiquitin-proteasome pathway (Li and Reid, 2000; Ladner et al., 2003; Cai et al., 2004) and (3) suppression of the Akt-mTOR pathway of protein synthesis (Pijet et al., 2013). In rats, infusion of lipopolysaccharide to mimic sepsis induces a



**Fig. 3.** Relationships between dysregulation of PI3k-Akt pathway in neutrophils and sarcopenia and frailty. Figure depicting proposed relationships between dysregulation of PI3k-Akt pathway within neutrophils and muscle and frailty and sarcopenia states.

significant systemic inflammatory response and increased expression of IL-6 and TNF $\alpha$  mRNA in skeletal muscle associated with loss of muscle mass and strength (Crossland et al., 2008). Moreover, dampening of the inflammatory response in muscle, by the concomitant administration of glucocorticoid, preserved muscle mass (Crossland et al., 2010). TNF $\alpha$  directly upregulates the NF $\kappa$ B pathway via I $\kappa$ B kinase (IKK) and induces MuRF-1 expression which causes myofibril degradation via the ubiquitin proteasome pathway (Li and Reid, 2000; Ladner et al., 2003).

Multiple chronic inflammatory conditions are associated with muscle loss either described as sarcopenia or cachexia: cancer, heart failure, COPD, chronic kidney disease, Crohn's disease, rheumatoid arthritis, HIV (Evans, 2010; Biolo et al., 2014). Muscle loss has been investigated at a cellular level in COPD, and whilst further research is required to confirm the data, on balance there is an increase in ubiquitin proteasome activity and a decrease in protein synthesis (Constantin et al., 2013). This suggests that the anabolic and catabolic pathways utilising the intra-cellular PI3K-Akt pathway are important in the development and maintenance of sarcopenia in chronic inflammatory states. Similar results have been replicated in other chronic inflammatory conditions.

### 3.1.2. Anti-inflammatory cytokines

IL-10, an anti-inflammatory cytokine, declines in the circulation with age in humans (Franceschi et al., 2007; Bartlett et al., 2012). The development of an IL-10 homozygous knockout mouse has provided an interesting and informative model of sarcopenia and frailty as it develops increased muscle weakness and decreased strength with age in comparison to wild type mice (Walston et al., 2008). This mouse also has significantly raised levels of IL-6 at 50 weeks of age (Walston et al., 2008). At 92 weeks of age these mice also show compromised skeletal muscle quality, with reduced skeletal muscle energy metabolism in the form of reduced ATP flux via creatine kinase, and lower free energy released during ATP hydrolysis compared to wild type mice (Akki et al., 2014). These

mice also show reduced muscle growth and regeneration after injury (Deng et al., 2012). These data offer one potential explanation for why muscle strength declines more quickly than muscle mass in sarcopenia, however there are currently few reports of associations between IL-10 and frailty or sarcopenia in humans. Only one study has compared IL-10 expression in muscle from young and old subjects and shown a modest increase, 1.4 fold, in IL-10 mRNA in healthy older males (Przybyla et al., 2006). However, an IL-10 polymorphism 1082CC, associated with high serum levels of IL-10, is over-represented in centenarians, suggesting an association with longevity at least (Franceschi and Bonafe, 2003). It is therefore important now to confirm if IL-10 expression is reduced in skeletal muscle from sarcopenic older adults to provide support for its role in muscle loss and frailty in humans.

There are few studies of other anti-inflammatory cytokines and their expression in skeletal muscle. One study found that interleukin-1 receptor antagonist (IL1-ra) mRNA was increased 7.2 fold in healthy older males in comparison to younger males (Przybyla et al., 2006) but this has not yet been confirmed by others. The authors suggested this may be a functional response to the elevated IL-1 $\beta$  mRNA also demonstrated in the healthy older males.

Fig. 2 proposes a relationship between inflammaging, sarcopenia and frailty, representing a coalescence of ideas that may underpin the potential relationship between inflammaging and sarcopenia. At present mechanistic insight cannot be given as further research is required, especially in humans and evidence of a direct causal relationship is thus also missing.

### 3.1.3. Leukocytes, sarcopenia and frailty

Age-related changes to the cells of the innate immune system may contribute indirectly to frailty and sarcopenia via their role in the age-related increase in systemic inflammation. White cell counts and neutrophil numbers after adjustment for the most common confounders are raised in populations of frail older people (Leng et al., 2007; Leng et al., 2009; Collerton et al., 2012). Higher

neutrophil counts are associated with low levels of physical activity and frailty (Fernandez-Garrido et al., 2014) and a higher white cell count in healthy 60 year olds can predict frailty ten years later (Baylis et al., 2013a). How such changes might affect frailty and sarcopenia is still poorly understood but we attempt to offer some insight here.

Neutrophils are the most abundant leukocyte in the blood and we have shown that their chemotactic ability is greatly reduced with age. Consequently migration is inefficient, the neutrophils produce more tissue damage and secondary systemic inflammation as they migrate through tissue (Niwa et al., 1989; Wenisch et al., 2000; Butcher et al., 2001; Hazeldine et al., 2014; Sapey et al., 2014). Therefore it is plausible that neutrophils play a key role in the inflammatory mechanisms seen in sarcopenia and frailty. Neutrophils are central to tissue repair and research has demonstrated in a number of models of muscle injury that neutrophils are recruited to the site of the injury within a couple of hours (Smith et al., 1998; MacIntyre et al., 2000; Quindry et al., 2003). However, migrating neutrophils also cause secondary damage to healthy muscle and studies report that muscle damage is reduced when functioning neutrophils are prevented from migrating to the damaged tissue (Jolly et al., 1986; Korthuis et al., 1988). The original studies used an ischaemia and reperfusion model but subsequent studies have utilised a muscle stretch injury model and directly visualised the muscle damage by microscopy (Brickson et al., 2003). Inefficient neutrophil migration may thus be a major contributor to increased inflammation in older adults especially at times of muscle damage (Fig. 3).

Recent data from our group has identified the mechanism underlying reduced chemotaxis in neutrophils from old donors. Inaccurate chemotaxis was associated with constitutive PI3K signalling and selective pharmacological inhibition of PI3K $\gamma$  or PI3K $\delta$  restored neutrophil migratory accuracy (Sapey et al., 2014). Moreover, the reduced neutrophil chemotaxis was associated with increased systemic inflammation in the older donors, most likely due to the tissue damage that occurs during neutrophil migration. As there are inhibitors of PI3K $\delta$  currently in clinical trial, this offers a novel route to therapy for immunosenescence and in theory this may also improve frailty and sarcopenia states.

As muscle ages it becomes more susceptible to injury and certainly as a person ages dysregulation of entire systems, for example balance and cognition, result in a greater number of injuries (Campbell et al., 1981; van Doorn et al., 2003; Shavlakadze et al., 2010; Shubert, 2011). It can be postulated that muscle injury in an older person combined with immune ageing would cause secondary damage to healthy muscle from aberrantly migrating neutrophils resulting in myocyte damage and apoptosis and loss of muscle fibres. This loss of muscle quality and mass could result in the functional losses and physical weakness of frailty. Research is now required to acquire evidence to test this hypothesis.

#### 4. Conclusions

The historical difficulties of definition, measurement and modelling in both sarcopenia and frailty in addition to the fundamental difficulties of investigating complex, multi-factorial syndromes has led to a lack of information regarding the pathophysiological causes of frailty and sarcopenia. Whilst there is some limited research into associations there is very little investigating more complex pathways attempting to link the two syndromes. The suggested link of increased systemic inflammation could explain the relationship between sarcopenia and immunosenescence, with aberrant neutrophil migration potentially contributing to inflammaging and tissue damage associated with sarcopenia and frailty. Further research on the cell pathways connecting inflammaging,

sarcopenia and frailty would help to better understand these conditions and progress to potential novel therapies for frailty and sarcopenia which could include modulation of PI3k to correct neutrophil chemotaxis.

#### Acknowledgments

Daisy Wilson is supported by a clinical research fellowship funded by the MRC-Arthritis Research UK Centre for Musculoskeletal Ageing Research. Elizabeth Sapey is funded by the Medical Research Council.

We would like to thank Professor Paul Greenhaff for his careful reading of the manuscript.

We would also like to thank Alexandria Clark for her work in improving the visual appearance of the figures.

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