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Review

Inflammaging as a common ground for the development and maintenance of sarcopenia, obesity, cardiomyopathy and dysbiosis

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ABSTRACT

Sarcopenia, obesity and their coexistence, obese sarcopenia (OBSP) as well as atherosclerosis-related cardiovascular diseases (ACVDs), including chronic heart failure (CHF), are among the greatest public health concerns in the ageing population. A clear age-dependent increased prevalence of sarcopenia and OBSP has been registered in CHF patients, suggesting mechanistic relationships. Development of OBSP could be mediated by a crosstalk between the visceral and subcutaneous adipose tissue (AT) and the skeletal muscle under conditions of low-grade local and systemic inflammation, inflammaging. The present review summarizes the emerging data supporting the idea that inflammaging may serve as a mutual mechanism governing the development of sarcopenia, OBSP and ACVDs. In support of this hypothesis, various immune cells release pro-inflammatory mediators in the skeletal muscle and myocardium. Subsequently, the endothelial structure is disrupted, and cellular processes, such as mitochondrial activity, mitophagy, and autophagy are impaired. Inflamed myocytes lose their contractile properties, which is characteristic of sarcopenia and CHF. Inflammation may increase the risk of ACVD events in a hyperlipidemia-independent manner. Significant reduction of ACVD event rates, without the lowering of plasma lipids, following a specific targeting of key pro-inflammatory cytokines confirms a key role of inflammation in ACVD pathogenesis. Gut dysbiosis, an imbalanced gut microbial community, is known to be deeply involved in the pathogenesis of age-associated sarcopenia and ACVDs by inducing and supporting inflammaging. Dysbiosis induces the production of trimethylamine-*N*-oxide (TMAO), which is implicated in atherosclerosis, thrombosis, metabolic syndrome, hypertension and poor CHF prognosis. In OBSP, AT dysfunction and inflammation induce, in concert with dysbiosis, lipotoxicity and other pathophysiological processes, thus exacerbating sarcopenia and CHF. Administration of specialized, inflammation pro-resolving mediators has been shown to ameliorate the inflammatory manifestations. Considering all these findings, we hypothesize that sarcopenia, OBSP, CHF and dysbiosis are inflammaging-oriented disorders, whereby inflammaging is common and most probably the causative mechanism driving their pathogenesis.

1. Introduction

Among the aging population of the developed world, sarcopenia, obesity and atherosclerosis-related cardio-vascular diseases (ACVDs) are major public health concerns and economic burden. Demographic trends show that the incidence and prevalence of sarcopenia, obesity and ACVDs in the elderly are increasing at unprecedented rates, setting a challenge for the health system in the immediate future (Kaeberlein

Abbreviations: ACVD, atherosclerosis-associated cardiovascular disease; Ang II, angiotensin II; AT, adipose tissue; CHF, chronic heart failure; DC, dendritic cells; EAT, epicardial adipose tissue; EMT, endothelial-to-mesenchymal transition; FFA, free fatty acid; GF, germ free; FMT, fecal microbiota transplantation; FXR, farnesoid X receptor; hsCRP, high-sensitivity C-reactive protein; HF, heart failure; HFpEF, HF patients with preserved ejection fraction; IL, interleukin; IFNγ, interferon γ; IR, insulin resistance; LPS, lipopolysaccharide; LV, left ventricular; M1, pro-inflammatory skewed macrophage; MCP-1, monocyte-chemoattractant protein-1; NF-??B, nuclear factor kappa-light-chain-enhancer of activated B cells; NMJ, neuromuscular junction; NLRP3, NOD-like receptor family pyrin domain containing 3 inflammasome; PCSK9, proprotein convertase subtilisin/kexin type 9; PEDF, pigment epithelium-derived factor; OBSP, obese sarcopenia; OPN, osteopontin; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SCFA, short-chain fatty acid; SOB, sarcopenic obesity; SPMs, pro-resolving mediators; TCR, T-cell receptor; TGFβ, transforming growth factor beta; Th, T-helper cell; TLR, toll-like receptor; TMAO, trimethylamine-*N*-oxide; Treg, T-regulatory cell; TNFα, tumor necrosis factor alpha

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et al., 2015; Kim and Choi, 2015). Obesity and sarcopenia may act synergistically, resulting in detrimental health outcomes (Barazzoni et al., 2018; Batsis and Villareal, 2018; Goisser et al., 2015; Hamer and O'Donovan, 2017; Zamboni et al., 2019). This chronic condition is called sarcopenic obesity; the concomitant accumulation of fat combined with abnormal age-dependent loss of muscle mass and strength (Morley et al., 2001).

Despite immense attempts to decipher the mechanisms of sarcopenia, obesity and thus sarcopenic obesity, therapeutic success is far from reaching its goal. The pleiotropic functions of the molecules and pathways are presumably involved in the development of these conditions, which consequentially make it challenging to develop effective treatments (Kob et al., 2015; Sakuma et al., 2015). Sarcopenia and obesity are multifactorial syndromes with various overlapping causes and feedback mechanisms. Supposedly, they are strongly interconnected and reciprocally aggravating each other (Barazzoni et al., 2018; Batsis and Villareal, 2018; GBD 2015 Obesity Collaborators; Goisser et al., 2015; Hamer and O'Donovan, 2017). Moreover, a high level of age-associated comorbidities often leads to confounding results (Batsis and Villareal, 2018; Juillière et al., 2018; NCD Risk Factor Collaboration (NCD-RisC), 2017). We have recently suggested the existence of a crosstalk between the inflamed adipose tissue (AT) and the inflamed skeletal muscle, which establishes, in turn, an age-associated, detrimental vicious cycle. Low-grade, chronic local (AT and skeletal muscle, via paracrine/autocrine regulation) and systemic inflammation (via endocrine regulation) represent inflammaging, which is therefore the major conjoining mechanism of sarcopenic obesity (Kalinkovich and Livshits, 2017). Under this condition, the seemingly vulnerable AT depots display pro-inflammatory immune cell infiltration, which is then exacerbated into systemic inflammaging (Kwon and Pessin, 2013). Ectopic accumulation of free fatty acids (FFAs) also contributes to skeletal muscle inflammation (Kelley and Goodpaster, 2015; Trouwborst et al., 2018). In addition, AT inflammation dominates over skeletal muscle inflammation, thus redirecting the vector of processes from traditional "sarcopenia → obesity" to "obesity → sarcopenia". We therefore proposed that this condition should be defined as "obese sarcopenia" (OBSP), which more accurately reflects the actual nature and order of events in the pathogenesis of this disorder (Kalinkovich and Livshits, 2017).

Atherosclerosis, a chronic inflammatory process of lipid-laden lesion growth in the vascular wall, is a major cause of myocardial infarction leading to the development of congestive heart failure (HF), and especially chronic HF (CHF). CHF, characterized by the significant deterioration of the heart-pumping function, is a major cause of morbidity and mortality in the elderly (Hackam and Anand, 2003). Its epidemiological incidence after 55 years of age doubles approximately every 10 years, and the numbers of afflicted people are expected to rise with increased overall life expectancy (Bozkurt, 2018; Cleland et al., 2019; Savarese et al., 2019; Springer et al., 2017; Tsao et al., 2018). Sarcopenia has been identified as a co-morbidity and a poor prognosis factor in patients with CHF, affecting ~ 20 % of older adults with CHF (Fülster et al., 2013; Suzuki et al., 2018; Shinmura, 2016; von Haehling et al., 2010). It has been shown that CHF patients with sarcopenia also have an increased risk for clinical complications (Steinbeck et al., 2015), which may be related to insufficient diet, which may lead to nutrient malabsorption (Saitoh et al., 2016).

A paradigm shift in our understanding of HF from a hemodynamic/neurohormonal (Packer, 1992) to a cytokine-mediated condition (Seta et al., 1996) placed chronic low-grade inflammation at the center of HF pathogenesis (Bellumkonda et al., 2017; Ferrucci and Fabbri, 2018; Paulus and Tschöpe, 2013; Van Linthout and Tschöpe, 2017; Wilson et al., 2017; Zhang et al., 2017). Noteworthy, pro-inflammatory pathways were found to be specifically up-regulated in HF patients with preserved ejection fraction (HFpEF) (Borlaug, 2014; Paulus and Tschöpe, 2013; Tromp et al., 2018), which also display a high prevalence of OBSP (Narumi et al., 2015; Saitoh et al., 2017). In addition, gut dysbiosis has been shown to be deeply involved in the development of sarcopenia (Ticinesi et al., 2019), obesity (Avolio et al., 2019) and CHF (Rogler and Rosano, 2014; Tang et al., 2019). Increased prevalence of sarcopenia (Mayhew et al., 2019), OBSP (Batsis and Villareal, 2018; Zamboni et al., 2019), CHF (Beltrami and Fumagalli, 2019) and dysbiosis (Rinninella et al., 2019) in the elderly imply a clear involvement of inflammaging in the pathogenesis of these conditions (Ferrucci and Fabbri, 2018; Frasca et al., 2017; Kalinkovich and Livshits, 2017; Prattichizzo et al., 2018; Wilson et al., 2017). This raises an important question on whether inflammaging unifies these chronic conditions mechanistically, suggesting a causative link. This review follows the recognition of this connection and extensive research efforts in deciphering the underlying mechanisms.

2. Inflammaging is a common mechanism that regulates the development of sarcopenia, CHF and obesity

2.1. Inflammaging

Since its launch in 2000, the concept of inflammaging has evolved significantly – from a chronic, systemic, low-grade inflammatory status that contributes to age-associated diseases (Franceschi et al., 2000), to "garb-aging", in which endogenous, misplaced, or altered molecules originating from damaged and/or dead cells, recognized by receptors of the innate immune system were suggested as a main triggers of inflammaging, thus considering it as an auto-inflammatory process (Franceschi et al., 2017). Further theoretical evolution suggested the existence of a combination of inflammaging with "metaflammation" (the inflammation accompanying metabolic diseases), in which dysbiosis was proposed to play an aggravating role by releasing inflammatory products (Franceschi et al., 2018). Lastly, the traditional view that inflammaging and immunosenescence, an age-associated immunocompromised condition, are responsible for most of the age-related diseases, such as recurrent infections, cancer, autoimmune disorders and chronic inflammatory diseases, has been altered. This new concept states that the coupling of immunosenescence-inflammaging might be responsible for both the shortening and extension of the human lifespan. For example, its activity may serve detrimental for responses to new antigens in most circumstances, but, conversely, may be necessary for an adequate response to known antigens (Fulop et al., 2018). Obviously, this paradoxical notion requires solid validation. Nevertheless, inflammaging is now considered to serve as a biomarker for accelerated ageing and one of the hallmarks of ageing biology (Campisi et al., 2019).

2.2. Inflammaging and sarcopenia

Depending on the diagnostic criteria, the prevalence of sarcopenia in the general population is strongly associated with age and sex, and even by most conservative estimates affects > 50 million people currently and is estimated to affect > 200 million in the next 40 years (Dhillon and Hasni, 2017). This is accompanied by the sarcopenia-related morbidity rate that comprises 5–13 % of the 60- to 70-year-old individuals, and 11–50 % of those above 80-years-old (von Haehling et al., 2010). Considered as an immanent component of frailty syndrome (Morley et al., 2001; Vanitallie, 2003), sarcopenia has been shown to be responsible for the rise in the incidence of falls and the risk of fractures in the elderly, and is therefore linked to physical disability, morbidity, increased mortality and health care costs (Filippin et al., 2015; Murphy et al., 2014; Szulc et al., 2016). Sarcopenia has been recently redefined as "a muscle disease/failure, rooted in adverse muscle changes that accrue across a lifetime and is common among adults of older age, but can also occur earlier in life" (Cruz-Jentoft et al., 2019). The inter-individual variation of muscle mass and its rate of loss have a significant genetic component and are governed by a complex interplay of genetic and epigenetic factors (Korostishevsky et al., 2016;

Livshits et al., 2016; Shafiee et al., 2018). However, the mechanisms underlying the etiology and progression of sarcopenia remain poorly understood.

The main proposed triggers of sarcopenia include decreased physical activity, malnutrition, age-related decline in the levels of systemic hormones, such as growth hormone, insulin-like growth factor-1, testosterone and estrogen (Collamati et al., 2016; Keller, 2019), disturbed production of muscle growth regulators, in paerticular myostatin, activins, irisin and bone morphogenetic proteins (Kalinkovich and Livshits, 2015), and an age-associated neuromuscular junction dysfunction (Gonzalez-Freire et al., 2014; Rudolf et al., 2014). Sarcopenia is also associated with the activation of catabolic pathways in the skeletal muscle, which are composed of three main protein degradation systems: the ubiquitin-proteasome system (UPS), the autophagy-lysosome system and apoptosis (von Haehling et al., 2017). These pathways lead to mitochondrial dysfunction, muscle fiber reorganization and denervation, myofibril degeneration and myocyte death (von Haehling et al., 2017; Gonzalez-Freire et al., 2018; Hood et al., 2019). In the mitochondria, the UPS regulates the turnover of most short-lived cytosolic proteins (Bragoszewski et al., 2017). The UPS is involved in mitophagy (Desai et al., 2018), energy metabolism (Lavie et al., 2018), proteolytic regulation of fusion/fission-mediating factors in mitochondrial membranes (Ali and McStay, 2018) and in other functional mitochondrial activities (Livnat-Levanon and Glickman, 2011). Disturbed mitochondrial protein synthesis/degradation machinery in sarcopenia is associated with an impaired signaling through the mechanistic targeting of the rapamycin (mTOR) pathway, which is the major regulator of protein synthesis in skeletal muscle. The mTOR pathway induces the activation of p70 S6K, the inhibition of 4e-binding protein (4e-BP1) and the activation of eukaryotic translation initiation factor-4e (EIF-4e), all of which increase protein translation. The activation of these pathways stimulates cell growth, involving primarily myofibrillar proteins (Reviewed in Coen et al., 2019). In addition, low muscle quality was found to be characterized by the impaired transport of amino acids, especially branched chain amino acids (BCAAs), across the muscle cell membrane (Fouré and Bendahan, 2017). At low BCAA concentrations, mTOR senses the limited substrate availability for protein synthesis/recycling and inhibits p70S6K phosphorylation, hindering normal protein recycling, thus allowing 'wear and tear' protein damage to accumulate. BCAA deficiency can reduce the expression of sirtuin 1 (*SIRT1*) and genes that regulate oxidative phosphorylation, such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), nuclear respiratory factor-1 (NRF1), and mitochondrial DNA (mtDNA) transcription factor A (TFAM), all of which lead to impaired mitochondrial biogenesis and reduced energy production in the muscle (Reviewed in Coen et al., 2019; Gonzalez-Freire et al., 2018; Hood et al., 2019). It was also shown that PGC-1α suppresses FOXO3-mediated transcription of various E3 ubiquitin ligases, thereby attenuating protein degradation and muscle atrophy during aging and sarcopenia (Brault et al., 2010). Recently, a number of unfolded protein response (UPR) pathways have been implicated in the development of sarcopenia. For example, ATF6α is a transcription factor associated with the regulation of chaperones linked to UPR pathways in the endoplasmic reticulum (ER), the absence of which results in exercise intolerance (Bohnert et al., 2016; Wu et al., 2011). Notably, mitochondrial reactive oxygen species (ROS) release was shown to inhibit protein synthesis by decreasing phosphorylation of 4e-BP1 and impairing mTOR assembly, thus inducing muscle atrophy in preclinical studies (Reviewed in Mason and Wadley, 2014). Increased mitochondrial ROS production stimulates proteolytic degradation pathways (autophagy and proteasome system) and energetic stress (reduced ATP production), which can activate the AMP kinase (AMPK)-FOXO3 pathway. In turn, this pathway triggers the UPS and the lysosome-autophagy system that significantly contribute to disturbed mitochondrial fission and muscle remodeling, displaying muscle atrophy (Romanello and Sandri, 2016).

Defective mitochondrial function is also connected to ageing-associated neuromuscular junction (NMJ) remodeling, consequently leading to motor unit loss, specifically in type II fibres, and muscle fibre atrophy (Gonzalez-Freire et al., 2014). In sarcopenic rats with altered NMJ integrity, the expression of genes and proteins implicated in mitochondrial energy metabolism is downregulated (Ibebunjo et al., 2013). Mice lacking UPS proteins, such as the ubiquitin ligases muscle atrophy f-box (Atrogin1/MAFbx) and muscle ring finger-1 (MuRF1), are resistant to muscle atrophy induced by denervation (Bodine and Baehr, 2014). Moreover, overexpression of PGC-1α, a transcription factor that promotes mitochondrial biogenesis, helps to maintain NMJ integrity during ageing (Gouspillou et al., 2013), whereas oxidative damage of NMJ promotes the loss of skeletal muscle proteostasis (Vasilaki et al., 2017).

Concerning potential involvement of chronic inflammation in the mitochondria-sarcopenia link, it was shown that ROS over-generation by mitochondria might be mediated by activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome and promotion of IL-1 secretion (Yu and Lee, 2016). In addition to ROS, some other mitochondrial components, such as mtDNA, cardiolipin, mitofusins, and cathepsins are involved in the recruitment and docking of NLRP3 inflammasome into the mitochondria (Gurung et al., 2015; Picca et al., 2018b). It is also known that NLRP3 inflammasome is activated by cell debris and misplaced self-molecules, followed by the production of IL-1, IL-18, and IL-33 (Kufer et al., 2016). In the mouse skeletal muscle, it has been shown that accelerated NLRP3-dependent caspase-1 activity within the mouse skeletal muscle results in decreased myofiber size (McBride et al., 2017), mitochondrial damage, nuclear fragmentation, tubular aggregates formation, reduced locomotor activity and increased frailty index, further deteriorating with age (Sayed et al., 2019). Deep involvement of the inflammasome pathway in sarcopenia suggests that innate immunity plays a significant role in its pathogenesis. Indeed, the expression of many innate immune receptors, such as MYD88, NLRX1, NAIP, TLR4 and NLRC5 was detected in human skeletal muscle biopsies (Pillon and Krook, 2017). In addition, skeletal muscle deficiency of the nuclear erythroid-related factor 2 (Nrf2), a key regulator of innate immunity (Mohan and Gupta, 2018), exacerbates sarcopenia progression in aging, as shown by impaired mitochondrial biogenesis and dynamics (Huang et al., 2019) and enhanced mitochondrial oxidative stress (Kitaoka et al., 2019).

A strong relationship between sarcopenia and the altered adaptive immune system is well established (Marcos-Pérez et al., 2018). For example, in a study that followed old women for 3.5-years, increased IL-6 levels predict a significantly higher risk of developing physical disability and reduced muscle strength and motor performance (Ferrucci et al., 2002). In a recent meta-analysis sarcopenia was shown to be clearly associated with significantly higher serum levels of various pro-inflammatory molecules, especially highly-sensitive C-reactive protein (hsCRP) and IL-6 levels, compared with the levels recorded in non-sarcopenic participants (Soysal et al., 2016). In another study, a 70 % increase in serum levels of IL-6 and the 75-kDa soluble TNF-α receptor II was detected in sarcopenic subjects in comparison to non-sarcopenic participants.

Alterations of the ageing adaptive immune system include both quantiative changes and cell functional deteriorations (Pansarasa et al., 2019), such as a decrease in the naïve T cell count, accompanied by a reduction in the T-cell receptor (TCR) repertoire, a decline in antibody-producing B cells and an increase in memory T cells (Ventura et al., 2017; Yanes et al., 2017).

Senescent cells (SCs), despite their cell-cycle arrest, remain viable, are resistant to apoptosis and, most importantly, are metabolically active (Sapieha and Mallette, 2018). SCs are capable of secreting numerous pro-inflammatory cytokines and chemokines, growth factors and extracellular matrix (ECM) degrading proteins (Davalos et al., 2010), thus creating the so-called senescence-associated secretory phenotype (SASP). SASP is not just a consequence of cell senescence, but also induces senescence in surrounding normal cells (Hubackova

et al., 2012), mainly via secretion of TGFβ and IL-1α, which induce DNA damage and increased expression of p53 and p21CIP1 in targets cells (Acosta et al., 2013). SASP is thought to have evolved as a signal which recruits and activates immune cells to the vicinity of SCs in order to mediate their clearance (Krizhanovsky et al., 2008). Moreover, SCs accumulate in a range of tissues with age (Biran et al., 2017) and at sites of various chronic age-associated diseases (reviewed in Habiballa et al., 2019). Importantly, abundance of SCs has been shown to causally contribute to the ageing process, since their removal resulted in significant improvements in the health span during ageing and age-related diseases (Baar et al., 2018; Roos et al., 2016; Xu et al., 2018). Of note, the skeletal muscle of mice, which were genetically engineered for accelerated ageing, showed increased expression of senescence markers, such as cyclin-dependent kinase inhibitors $p16^{Ink4a}$ and $p19^{Arf}$, as well as the SASP components Igfbp2, Mmp13 and Pai1 (Baker et al., 2008). Complementary deletion of $p16^{Ink4a}$ in this mouse model reduced expression of SASP components, increased proliferation and attenuated sarcopenia (Baker et al., 2016). Taken together, these observations indicate that inflammaging may play a central role in both induction and maintenance of sarcopenia (Collins et al., 2018; Fulop et al., 2015; Wilson et al., 2017; Wu et al., 2015).

2.3. Inflammaging and ACVDs

Like sarcopenia, the prevalence of ACVDs increases with age, even with higher rates (Benjamin, 2019; Lind et al., 2018). ACVDs in general and CHF in particular are a major cause of morbidity and mortality in the ageing (Dunlay et al., 2017; Taylor et al., 2019). Sarcopenia is common in CHF patients (Emami et al., 2018), particularly in advanced CHF stages (Carbone et al., 2019; Tyrovolas et al., 2016). Notably, sarcopenia is an independent risk factor for ACVDs (Abe et al., 2012) and a predictive prognostic factor for HF (Yamada et al., 2015). This clearly indicates the existence of a close link between these two conditions. It has been observed that age-associated sarcopenia develops early in patients with HF, and with the progress of the disease, while both conditions concurrently worsen each another (von Haehling et al., 2017). Classical atherosclerosis risk factors, such as total serum cholesterol and hsCRP are also highly significantly associated with the risk for sarcopenia (Hida et al., 2018). These findings raise a question on the existence of a common mechanism underlying the development of both diseases. Inflammaging may serve as such a mechanism. In support of this notion, an increased age-associated expression of muscle growth inhibitor myostatin and elevated levels of pro-inflammatory cytokines (mainly, TNFα, IL-1β, and IL-6), promote the generation of ROS and induce activation of NF-κB signaling. As a result, this inflammatory pathogenesis leads to mitochondrial dysfunction, muscle fibre reorganization, denervation of type II fibres, myofibril degeneration and myocyte death (von Haehling et al., 2017). This cascade of events also promotes coronary microvascular endothelial activation that contributes to the development of adverse effects, such as diastolic left ventricular (LV) dysfunction and HFpEF. Enhanced endothelial-to-mesenchymal transition (EMT) is known to be associated with cardiac fibrosis and diastolic dysfunction. Increased pro-inflammatory cytokines, such as TNFα and IL-1β, mediate EMT via renin-angiotensin activation. This, in turn, favors elevated collagen production combined with infiltration of inflammatory cells, suggesting a direct influence of inflammation on HF development (De Angelis et al., 2019). Concomitantly, HF can provoke inflammation in various tissues, including the skeletal muscle and myocardium itself, in both a direct (inflammation) and indirect (hemodynamic) manner (Van Linthout and Tschöpe, 2017). Stress-induced myocardial cells may release a variety of inflammatory mediators capable of affecting the skeletal muscle. During HF, activated neurohormonal mechanisms, such as the renin-aldosterone system and the β-adrenergic nervous system, which trigger and/or enhance inflammation in different organs including the skeletal muscle. This HF-mediated inflammation has been proposed to be related to cellular senescence, increased oxidative stress, reduced autophagy and mitophagy, increased DNA damage and mitochondrial dysfunction leading to muscle cell death. The latter activates the innate immune system to produce inflammatory cytokines, which further exacerbate the cell death-inducing processes (Bellumkonda et al., 2017).

Noteworthy, the activity of NLRP3 inflammasome was found to be enhanced in the human atrial tissue of CHF patients with long-lasting atrial fibrillation (AF), presumably via increased diastolic sarcoplasmic reticulum release of $Ca2^{+}$ (Yao et al., 2018). Altered IL-6 expression was associated with supraventricular arrhythmias including AF (Pan et al., 2018), therefore leading to increased rates of ACVD events and death in CHF patients (Aulin et al., 2015). Moreover, increased IL-6 levels (along with TNFα) have been attributed to persistent inflammation in the atrial myocardium, thus disrupting ion channel function and cardiomyocyte electrical activity. (Reviewed in Alí et al., 2019; Vonderlin et al., 2019). This suggests an important functional link between inflammation and supraventricular arrhythmias. In addition, in a large cohort study, elevated IL-6 levels were found in more than 50 % of the HF patients; these were associated with reduced LV ejection fraction, AF and poor clinical outcomes (Markousis-Mavrogenis et al., 2019).

About 30 % of patients with HF have inspiratory muscle weakness associated with exercise intolerance, suggesting that sarcopenia of the diaphragm may be one of the causes of their physical frailty (Kelley and Ferreira, 2017; Miyagi et al., 2018). The known etiology of CHF-associated diaphragm insufficiency includes the development of abnormalities in the phrenic nerve, neuromuscular junctions and myocytes. The abnormal myocytes show intrinsic changes in the quantity and quality of contractile proteins, accelerated fiber atrophy, and shifts in fiber type distribution. All of these abnormalities are likely supplementary factors in the simultaneous development of sarcopenia (Fogarty et al., 2019; Greising et al., 2018; Keller, 2019). Noteworthy, overexpression of TNFα or IL-6 has been shown to cause a significant weakening of the muscle force and atrophy of fiber types I, IIa, IIb in the diaphragm (Greising et al., 2018). Collectively, these findings suggest that inflammation and HF are not only strongly interconnected, but they also affect the skeletal muscle, thus supporting and worsening sarcopenia.

Whether inflammation is a cause or consequence of HF and or sarcopenia, however, remains uncertain (Bellumkonda et al., 2017; Van Linthout and Tschöpe, 2017; von Haehling et al., 2017; Westermann et al., 2011). The alternative view of atherosclerosis as an inflammatory disease (Hansson, 2005; Libby et al., 2011) is supported by the evidence that anti-inflammatory therapies could be effective. For example, a recent study shows that targeting IL-1β by its specific inhibitor, canakinumab, significantly reduces ACVD event rates, diminishes the circulating levels of IL-6 levels and the downstream clinical biomarker hsCRP, but does not affect lipid levels or blood pressure (Ridker, 2017). In contrast, administration of TNF or IL-6 antagonists was revealed inconsistent data in HF patients (Holte et al., 2017; Hori and Yamaguchi, 2013; Ridker, 2019), although there are ongoing discussions concerning forthcoming trials involving these inhibitors in ACVDs (Aday and Ridker, 2019). In this regard, a small-scale study with anakinra, an IL-1 receptor antagonist, revealed potential benefits of lowering inflammatory biomarkers in patients with HF (Abbate et al., 2013). Using IL-17 blockade has been shown to prevent coronary plaque expansion in psoriatic patients (Elnabawi et al., 2019). Selective NLRP3 inflammasome inhibitor MCC950 has been found to inhibit the development of atherosclerotic lesions (van der Heijden et al., 2017) and reduce infarct size, preserving LV function (van Hout et al., 2017) in animal models of atherosclerosis.

Since atherosclerosis is a disorder driven by both lipid accumulation and inflammation, an intensive concomitant targeting cholesterol production and the pro-inflammatory cytokine network has been proposed as a successful therapeutic method for successfully treating ACVDs (Ridker, 2019). An example for the proposed combinatory therapy is a combination of anti-IL-1 and anti-IL-6 drugs together with statins

(Cholesterol Treatment Trialists' Collaboration, 2019) and PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (Sabatine, 2019; Wong and Shapiro, 2019). The latter is presumably a powerful cholesterol-lowering agent (Ridker, 2019). This proposed combination could also become a new therapeutic option in treating hypertension, where a clear association of increased blood pressure and/or end-organ damage was registered with the increased serum levels of pro-inflammatory cytokines, such as IL-1β, IL-6, -8, -17, -23 and TNFα (Tanase et al., 2019).

2.4. Inflammaging, obesity and ACVDs

The strong connection between age and obesity (Pérez et al., 2016; Zamboni et al., 2019) as well as between AT and musculoskeletal (Batsis and Villareal, 2018; Collins et al., 2018; Kalinkovich and Livshits, 2017; Kob et al., 2015; Tyrovolas et al., 2016) and cardiovascular systems (Apostolopoulos et al., 2016; Carbone et al., 2019) are well established. In obesity, excessive lipids in the form of FFAs outflow the AT and accumulate ectopically in the skeletal muscle and myocardium, where they and their derivatives, such as long-chain acyl CoA, diacylglycerols, triacylglycerols, and/or ceramides can induce a lipotoxic effect (D'Souza et al., 2016; Ferrara et al., 2019; Nakamura and Sadoshima, 2019; Neeland et al., 2018; Ortega-Loubon et al., 2019; Shulman, 2014). The main lipotoxic effect is the marked impairment of the mitochondria characterized by enhanced ROS production (oxidative stress) (Marzetti et al., 2013), disturbed mitophagy (Bravo-San Pedro et al., 2017; Ferrucci et al., 2018) and reduced biogenesis. This is accompanied by significant function disturbances, such as reduced lipid β-oxidation of FFAs and lipolysis (Shulman, 2014), resulting in an insulin resistance (IR) state, dysregulated autophagy, excessive apoptosis and cell death (Gonzalez-Freire et al., 2018; Kob et al., 2015; Romanello and Sandri, 2016; Sergi et al., 2019; Tsushima et al., 2018). Interestingly, the escape of mtDNA from autophagy has been shown to cause myocardial inflammation via TLR9 activation (Oka et al., 2012; Rodríguez-Nuevo and Zorzano, 2019) and is presumably involved in skeletal muscle atrophy (Picca et al., 2018b; Pillon and Krook, 2017). Interaction of TLR9 with mtDNA activates nuclear factor kappa B (NF-κB) signaling and increases the expression of various pro-inflammatory cytokines (Yu and Bennett, 2016). Changes in mitochondrial dynamics, such as mitochondrial fusion and fission, have been considered to be closely related to IR (Filippi et al., 2017). In particular, mitochondrial tafazzin, a phospholipid acyltransferase involved in cardiolipin synthesis, was shown to promote mitochondrial fission and impair insulin signaling in the hearts of mice under high fat diet (Chang et al., 2019). Barth syndrome develops due to a mutation in the tafazzin gene, and is characterized by mitochondrial dysfunction, dilated cardiomyopathy and muscle weakness (Barth et al., 2004), thus further suggesting the coupling of cardiomyopathy and sarcopenia.

In addition, ectopic FFAs induce NLRP3 inflammasome formation to trigger caspase-1, which subsequently activates IL-1β and IL-18, promoting inflammation and IR (Wen et al., 2011). Moreover, ectopic FFAs supposedly attract immune cells that activate pro-inflammatory skewed M1 macrophages resident in the skeletal muscle and the myocardium (Rivas et al., 2016). These macrophages release TNFα, IL-1β, IL-6, MCP-1, and TGFβ, which stimulate differentiation of fibroblasts into myofibroblasts. As a result, collagen production is increased, the secretion of protease inhibitors is inhibited, and the extracellular matrix is degraded via activation of both canonical (Smad-dependent) and non-canonical (Smad-independent) signaling pathways (Bandet et al., 2019; Ferrara et al., 2019; Kitessa and Abeywardena, 2016; Montgomery et al., 2019; Nishida and Otsu, 2017; Ortega-Loubon et al., 2019). These events lead to skeletal and cardiac fibrosis (Michalska-Kasiczak et al., 2018), thus contributing to the development of sarcopenia and cardiomyopathy (Fig. 1).

It is also well known that in obesity, adipocytes undergo hypertrophy and hyperplasia, accompanied by the recruitment of M1-skewed macrophages as well as lymphocytes and mast cells. In the AT itself, these immune cells produce pro-inflammatory cytokines, including IFNγ, TNFα, IL-1β, IL-6, -7, -8, -17, -21 and IL-22 in AT (Caër et al., 2017; Castoldi et al., 2016; Exley et al., 2014; Liu and Nikolajczyk, 2019; Wensveen et al., 2015). In the AT of obese individuals, various chemokines that recruit macrophages and other immune cells have been detected (Xue et al., 2019). Other innate and adaptive immune cells, in particular, neutrophils, dendritic cells (Sundara Rajan and Longhi, 2016), and B cells, play a role in obesity-induced AT inflammation (Apostolopoulos et al., 2016; Frasca and Blomberg, 2017; Grant and Dixit, 2015). AT-resident B cells, which are localized around macrophage clusters, were shown to have a predominant pathogenic role in obesity-related IR in mice. These pathogenic B cells activate IFNγ-producing $CD4^+$ and $CD8^+$ T cells and/or IL-17-secreting Th1 cells within the visceral AT, presumably through LTB4/leukotriene-B4 receptor 1 (LTB4R1) signaling (DeFuria et al., 2013; Winer et al., 2014). B cells were also found to promote the expansion of a senescent population of visceral AT-resident $CD4^+CD153^+PD\text{-}1^+$ T cells, which, in turn, secrete osteopontin that promotes IgG production by B cells and suppresses IL-10 secretion (Shirakawa et al., 2016).

In ageing, the pro-inflammatory milieu created by immune and other senescent cells, such as fibroblasts and endothelial cells, is the source of SASP. This is characterized by the increased secretion of pro-inflammatory molecules (cytokines, chemokines, micro-RNAs) and various growth factors and proteases (Campisi, 2011). In general, SASP participates in inducing and/or exacerbating sarcopenia (Habiballa et al., 2019) and cardiomyopathy (Lewis-McDougall et al., 2019; Shimizu and Minamino, 2019). Of note, markers of SASP are highly expressed in B cells of elderly individuals, especially in the double negative (DN) $CD19^+$IgD-CD27- memory B cells (Frasca et al., 2017). This DN B cell subset, which has been reported to express SASP markers, expands in the blood of healthy elderly individuals and in patients with autoimmune and infectious diseases (Reviewed in Bernard, 2018). Importantly, DN B cells are transcriptionally active and negatively affect the microenvironment by secreting pro-inflammatory mediators, which in turn sustain and propagate the inflammatory response (Frasca et al., 2017).

In close association with AT inflammation, several potentially pro-inflammatory molecules, such as leptin, CRP, osteopontin, chemerin, resistin, PEDF and myostatin are found in abundance in obese AT subjects (Mancuso, 2016; Nicholson et al., 2018). In particular, a genetic knockdown of myostatin, which is a critical autocrine/paracrine inhibitor of skeletal muscle growth and development (McPherron et al., 1997), suppressed body fat accumulation and protected against diet-induced IR (Dong et al., 2016). Additionally, serum myostatin levels were found to be elevated in obese individuals in a correlation with IR (Amor et al., 2019), thus emphasizing the close relation between myostatin and obesity. Moreover, end-stage CHF subjects demonstrate elevated myocardial expression of myostatin (Ishida et al., 2017). Released from the myocardium, myostatin has been reported to be causal for skeletal muscle atrophy in a CHF mouse model (Heineke et al., 2010). In the myocardium, myostatin exerts a pro-fibrotic effect, associated with reduced cardiac function during ageing (Breitbart et al., 2011). In addition, serum myostatin levels were found to reflect the severity of CHF, presumably serving as a predictor of poor prognosis in CHF patients (Chen et al., 2019a, b). Interestingly, an age-associated deficiency of adiponectin in HF has been found to exacerbate LV hypertrophy and diastolic dysfunction. Furthermore, CHF patients have been shown to develop adiponectin resistance in myocardial and skeletal muscle cells. The mechanism involves an increase in oxidative stress and modulation of intracellular calcium-handling regulatory proteins (Krause et al., 2019; Sente et al., 2016; Tanaka et al., 2014). Increased myocardial oxidative stress was shown to modify epicardial AT (EAT) secretory profile by releasing more antioxidant adipokines, such as adiponectin, in an attempt to protect the heart from oxidative damage (Antonopoulos et al., 2016).

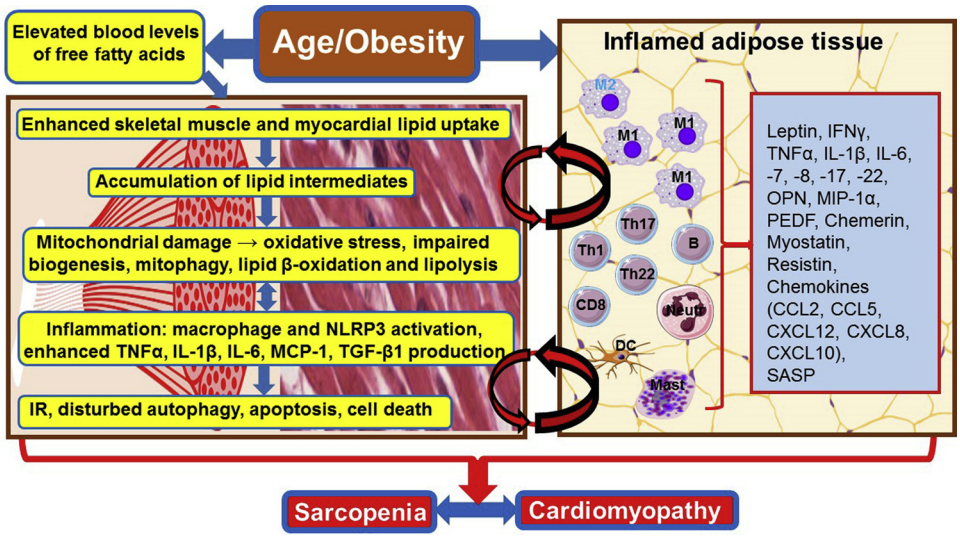

Fig. 1. Hypothesized mechanism of an age/obesity-mediated development of sarcopenia and cardiomyopathy via an inflammatory cross talk between the skeletal muscle, myocardium and adipose tissue (AT).
Ectopically accumulated fatty acids' derivatives in the skeletal muscle and myocardium trigger a sequence of events designated on the left part of the scheme. These events mainly include mitochondrial damage, inflammation, insulin resistance (IR) and cell death via lipotoxic effect on the skeletal muscle and myocardium. This results in reduced myocyte functionality, leading to sarcopenia and cardiomyopathy. Concomitantly, as shown on right hand side of the scheme, an age-associated obesity is accompanied by AT inflammation, in which pro-inflammatory skewed M1-macrophages and other immune cells secrete a variety of pro-inflammatory mediators (e.g., cytokines, adipokines, chemokines, and others). In a paracrine/autocrine manner, they support ongoing AT inflammation and, in an endocrine manner, induce and support inflammation in both the skeletal muscle and myocardium. AT inflammation plays a prevailing role in this detrimental pro-inflammatory vicious circle, which hypothetically governs the development of sarcopenia and cardiomyopathy. Leakage of the depicted pro-inflammatory mediators to the circulation induces, maintains and worsens inflammaging. Further explanations are given in the text.
Th—T-helper cell; DC—dendritic cells; OPN—osteopontin; PEDF—pigment epithelium-derived factor; Mast—mast cell; Eos—eosinophils; B—B-cell; Neutr—neutrophil; MIP-1α—macrophage inflammatory protein 1 α; MCP-1—monocyte chemoattractant protein 1; NLRP3—(NLR family pyrin domain containing 3) inflammasome; SASP—senescence-associated secretory phenotype; IFNγ—interferon γ; IL—interleukin.

EAT is a relatively small visceral fat depot with unique anatomic, biomolecular and genetic features. It regulates crucial physiological and pathological properties in the heart, such as the myocardial redox state, intracellular $Ca2^{+}$ cycling, the contractile and electrophysiological properties of cardiomyocytes, cardiac fibrosis as well as coronary atherosclerosis progression (Ansaldo et al., 2019; Ferrara et al., 2019; Iacobellis and Barbaro, 2019; Neeland et al., 2018; Packer, 2019). A study describing the underlying mechanistic relationship between EAT and cardiomyopathy (Reviewed in Antonopoulos and Antoniades, 2017; Iacobellis and Barbaro, 2019; Madonna et al., 2019) revealed a consistent, clear similarity with those described in the visceral and subcutaneous AT. However, due to the anatomical proximity to the myocardium, EAT acts as a metabolic transducer for various mediators as part of a paracrine crosstalk with the myocardium (Antonopoulos and Antoniades, 2017; Patel et al., 2017). Through this paracrine activity, EAT-derived cytokines diffuse across the interstitial fluid or the arterial wall layers to directly interact with the myocardium. Alternatively, EAT-derived cytokines could be released directly into the vasa vasorum of the coronary arterial wall (Yudkin et al., 2005; Antonopoulos and Antoniades, 2017). In obese-associated enlargement of EAT, pro-inflammatory cytokines, such as IL-1β, IL-6, IL-8, MCP-1, TNFα, leptin, plasminogen activator inhibitor-1, resistin and RANTES, diffuse into the vessel wall and the coronary circulation, whereby they exert their pathophysiological effects. These include the changes in the vascular tone and vascular remodeling, increased LV mass, abnormal right ventricle geometry, enlarged atria chemotaxis, foam cell formation, smooth muscle cell proliferation and migration as well as plaque destabilization (Antonopoulos and Antoniades, 2017; Berg et al., 2019; Greulich et al., 2012; Guzik et al., 2017). Moreover, secretion of profibrotic adipokines from EAT can induce atrial fibrosis, presumably via adipogenic differentiation of epicardial mesenchymal cells, leading to a development of fibro-fatty phenotype in the atrial myocardium (Suffee et al., 2017). Also, a positive correlation between EAT volume index, the degree of myocardial fibrosis and impaired LV systolic function has been observed (Ng et al., 2018). As for specific atherogenic activity, lipase G (*LIPG*), solute carrier family 7 member 5 (*SLC7A5*) and solute carrier family 16 member 10 (*SLC16A10*), all of which are involved in lipid metabolism and nutrient transport, were found to be among the top upregulated genes in diabetic EAT (McAninch et al., 2015). Epicardial fat is also highly enriched in secretory type II phospholipase A2 (sPLA2-IIA or PLA2 G2A), which contributes to lipid build up in the coronary arteries (Gaborit et al., 2017). The lipogenic effect of EAT has also been attributed to the increase of fatty acids in EAT (Pezeshkian and Mahtabipour, 2013). Given rapid metabolism and simple objective measurability of size, EAT may represent a usable risk factor and modifiable therapeutic target (Iacobellis, 2016; Packer, 2019; Neeland et al., 2018; Ferrara et al., 2019). Indeed, EAT was shown to be significantly affected by thiazolidinediones, which are insulin sensitizers acting as agonists of peroxisome proliferator-activated receptors, glucagon like peptide 1 receptor agonists, dipeptidyl peptidase-4 inhibitors and lipid-lowering statins (Iacobellis, 2016). For example, treatment of coronary artery disease-afflicted diabetic patients with pioglitazone, a commonly used thiazolidinedione, was associated with reduced expression of *IL-1β* and other pro-inflammatory genes in EAT (Sacks et al., 2011). Not only that the application of pleiotropic statins leads to reduction of AT inflammation (Diamantis et al., 2017) in type 2 diabetic patients (Park et al., 2010), in hyperlipidemic post-menopausal women (Alexopoulos et al., 2013) and in arterial stenosis patients (Parisi et al., 2019), it also resulted in reduced EAT thickness. In the latter study, beneficial effects of atorvastatin were significantly associated with EAT thickness and its pro-inflammatory status. Moreover, atorvastatin showed a direct anti-inflammatory effect on EAT-derived cells in vitro (Parisi et al., 2019). Simvastatin and pioglitazone significantly reduced plasma levels of IL-6, leptin, resistin, TNFα and matrix metalloproteinase-9 in patients showing signs of coronary artery disease and metabolic syndrome (Grosso et al., 2014). In this study, a combinatory application further reduced these markers along with an elevation in plasma levels of adiponectin and a decrease in hsCRP levels. Thus, modulating the EAT inflammation-oriented transcriptome with targeted pharmacological agents may open new possibilities in the therapy of cardio-metabolic diseases.

In conclusion, obesity-mediated infiltration of immune cells into the skeletal muscle and myocardium in concert with activated myocytes and cardiomyocytes induce local inflammation. In an autocrine/paracrine/endocrine manner, this affects the functionality of both the skeletal muscle and the myocardium, thereby triggering, supporting and worsening AT inflammation (Conte et al., 2019; Costamagna et al., 2015; Duchesne et al., 2017; Londhe and Guttridge, 2015; Wu and

Ballantyne, 2017). In this detrimental, vicious cycle, AT inflammation presumably plays a prevailing role, governing the development of sarcopenia and cardiomyopathy (Kalinkovich and Livshits, 2017) (Fig. 1).

3. Dysbiosis regulates the development of sarcopenia, CHF and OBSP in an inflammaging-dependent manner

3.1. Dysbiosis and age

The observations and ideas discussed above clearly indicate that inflammaging governs the major common mechanisms responsible for the development of sarcopenia and cardiomyopathy and particularly obesity. In addition, accumulating evidence indicates that dysbiosis plays a very important role in the pathogenesis of these disorders, especially among the elderly, by demonstrating characteristic changes in gut microbiota (Grosicki et al., 2018; Lakshminarayanan et al., 2014; Lynch et al., 2015; Nagpal et al., 2018). These include an extreme variability in microbiota composition among individuals, reduced intra-individual diversity and prevalence of pathogens vs commensals, all in associated with a balanced health status (Biagi et al., 2010; Claesson et al., 2012). It has been additionally found that the gut microbial composition is associated with nature and levels of circulating cytokines and parameters of health in the elderly, such as measures of frailty, comorbidity, and nutritional status (Claesson et al., 2012). In addition, the observed intestinal permeability, which leads to bacterial translocation and endotoxemia, is accompanied by enhanced systemic inflammation in a feed-forward process that increases with age (Scott et al., 2017). In concordance, dietary interventions have been shown to improve anti-bacterial immunity by reducing age-associated inflammation and macrophage immunosenescence (Clements and Carding S, 2018; Vaiserman et al., 2017). Oral supplementation with the probiotic, Bifidobacterium, restores phagocytosis and lymphocyte proportions in the circulation (Gill et al., 2001), while probiotic *Lactobacillus rhamnosus* GG supplementation exerted anti-inflammatory effects (Ludwig et al., 2018; Pagnini et al., 2018). However, there is an answered question of whether dysbiosis is a driving force of immune dysfunction or its consequence. It has been recently observed that mice under germ-free (GF) conditions are protected from age-associated inflammation, and co-housing GF mice with old conventionally-raised old mice triggers an inflammatory response, suggesting a causal relationship between age-associated inflammation and dysbiosis (Thevaranjan et al., 2017).

3.2. Dysbiosis and sarcopenia

There is some evidence that dysbiosis, in particular reduced microbiota diversity and disturbed *Bifidobacteria/Proteobacteria* ratio, affects the emergence of age-associated sarcopenia. Presumably, this is mediated via reduced bioavailability of dietary proteins, short-chain fatty acids (SCFAs) and vitamin synthesis, and disturbed biotransformation of nutrients and bile acids (Casati et al., 2019; de Sire et al., 2018; Picca et al., 2018a; Ticinesi et al., 2017). Leakage of lipopolysaccharide (LPS) from the dysbiotic gut into the circulation is accompanied by a significant elevation in TNFα and IL-6 levels in the blood (Frost et al., 2002), These pro-inflammatory cytokines are known to induce IR and affect skeletal muscle structure and functional activity (Ghosh et al.,2015; Kawamura et al., 2019; Ono and Sakamoto, 2017), mainly in an age-dependent manner (Grosicki et al., 2018), thus connecting age, dysbiosis and sarcopenia via inflammaging (Franceschi et al., 2018). Notably, supplementation of prebiotics increases the strength and endurance of muscles in older, frail adults (Buigues et al., 2016; Theou et al., 2019), and the supplementation of probiotic *L. plantarum* TWK10 (LP10) in mice increases muscle mass and muscle function after acute exercise challenge (Chen et al., 2016). Although these findings indicate dysbiosis as a potential risk factor for age-related sarcopenia, they are still inconclusive, thus demanding further research aimed at deciphering the pathways involved in the gut microbiota-sarcopenia axis.

3.3. Dysbiosis and ACVDs

The potential detrimental role of dysbiosis in HF pathogenesis and especially its involvement in chronic inflammation in CHF, has been discussed for years (Krack et al., 2005; Rogler and Rosano, 2014; Sandek et al., 2009). Numerous studies have revealed a significant age/CHF-associated decrease in microbial richness and diversity along with a pronounced elevation in various pathogenic phyla (e.g., *Ruminococcus gnavus*, *Clostridium difficile*, *Collinsella*, and others) and a decrease in health-supporting commensals (e.g., *Faecalibacterium prausnitzii, Akkermansia muciniphila* and others) (Ahmadmehrabi and Tang, 2017; Battson et al., 2018; Cui et al., 2018; Dick and Epelman, 2016; Forkosh and Ilan, 2019; Harikrishnan, 2019; Kasselman et al., 2018). This vigorous dysbiosis destroys the gut barrier integrity followed by endotoxin leakage (mainly, LPS), reduced production of SCFAs, mainly an anti-inflammatory butyrate (Bach Knudsen et al., 2018; Branca et al., 2019), impaired synthesis and signaling of bile acids (Vasavan et al., 2018), thus inducing, maintaining and exacerbating CHF-associated inflammaging (Fransen et al., 2017; Shin and Kim, 2018) (Fig. 2). In addition, HF-associated reduced cardiac output can further lead to a decrease in intestinal perfusion and mucosal ischemia, subsequently resulting in a disrupted intestinal mucosa. Structurally, intestinal wall thickening with edema was observed in patients with HF (Emami et al., 2018). The collagen content in their mucosal walls is also increased in proportion to the severity of HF (Arutyunov et al., 2008). Importantly, bowel wall thickening has been correlated with circulating levels of hsCRP and increased markers of intestinal permeability (Emami et al., 2018; Pasini et al., 2016). Intestinal mucosa disruption can in turn lead to increased gut permeability and subsequent enhanced translocation of bacteria and bacterial toxins to the blood, contributing to low-grade systemic inflammation (see below). As discussed earlier, HF-associated cardiac inflammation is featured by increased cardiac NLRP3 inflammasome activity, cardiomyocyte apoptosis and autophagy, hypertrophy, stiffness, myofibroblast differentiation, increased collagen production, EMT and subsequent cardiac remodeling and LV dysfunction (Shah and Lecis, 2019; Westermann et al., 2011).

Sprouty-related EVH1 domain-containing protein 2 (SPRED2) is an intracellular repressor of ERK-MAPK signaling that is ubiquitously expressed in various tissues, including the digestive tract and the heart. Interestingly, in SPRED2 deficiency resulted in cardiomyocyte hypertrophy, cardiac fibrosis, impaired electrical excitability, severe arrhythmias, and shortened lifespan (Ullrich et al., 2019). Mechanistically, SPRED2 deficiency-associated HF exhibited ERK hyperactivation, dysregulated autophagy (e.g., accumulation of vesicles, vacuolar structures and degenerated mitochondria), decreased expression of key autophagy regulators, such as Atg7, Atg4B and Atg16L, and increased expression of autophagosomal adaptors, such as p62/SQSTM1, NBR1 and lysosomal Cathepsin D (Ullrich et al., 2019). In another recent study (Ohkura et al., 2019), SPRED2 knockout mice, fed with a high fat diet, exhibited an augmented body weight gain, enhanced adipocyte hypertrophy, deteriorated dyslipidemia, accumulation of M1 macrophages surrounding dead adipocytes, aggravated IR and fatty liver disease. As compared with control mice, the stromal vascular cells of SPRED2 knockout mice expressed elevated levels of TNFα and the monocyte chemoattractant protein-1 (MCP-1/CCL2). These studies suggest that SPRED2 represents a potential therapeutic tool for the prevention of HF, IR and obesity.

Experimental genetic and pharmacological data as well as GF models implicate dysbiosis in the development and maintenance of hypertension (Jama et al., 2019b). Several causative mechanisms have been proposed, including an abnormal reaction to angiotensin II (Ang II)-induced cardiovascular stress (Karbach et al., 2016) and reduced prevalence of SCFAs (Ganesh et al., 2018; Marques et al., 2017). SCFAs

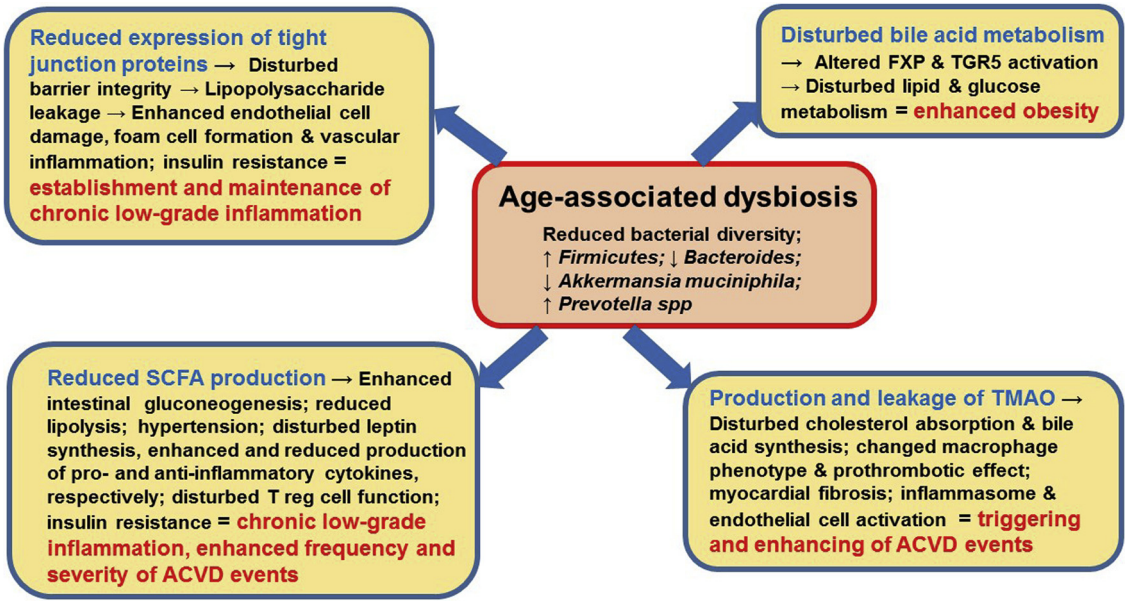

Fig. 2. Proposed mechanisms underlying the development of dysbiosis-mediated obesity and ACVDs under chronic, low-grade inflammatory settings.
Characterized by a reduced bacterial diversity and increased pathogens/commensals ratio, an age-associated dysbiosis is proposed to be responsible for multiple pathological effects. Dysbiosis, therefore, triggers, supports or worsens inflammaging, which, as we suggest, governs the development of sarcopenia, obesity, and ACVDs (mainly, CHF). In the scheme, we depict the consequences of dysbiosis, such as LPS leakage, reduced synthesis of SCFAs, increased gut permeability and disturbed bile acid metabolism, all of which lead to the induction of chronic low-grade inflammation, IR and lipotoxicity. Eventually, this is manifested by contractile defects of myocytes and cardiomyocytes that characterize sarcopenia and cardiomyopathy. Dysbiosis-mediated production of TMAO is a main process that results in a variety of detrimental ACVD events. Further explanations are given in the text.
ACVDs – atherosclerosis-mediated cardiovascular disorders; TMAO – trimethylamine-*N*-oxide; SCFA – short chain fatty acids; Treg – T regulatory cells; FXR – farnesoid X receptor; TGR5 – G-protein-coupled bile acid receptor.

normally mediate their homeostatic blood pressure effects via binding to Olfr78 and GPR41 receptors (Jin et al., 2019). Dietary intake-induced changes in the gut microbiota support a dysbiosis-hypertension connection, because they modulate blood pressure either beneficially (e.g., fibre and SCFAs) or detrimentally (e.g., salt) (Jama et al., 2019a). In a human study, fecal microbiota transplantation (FMT) from hypertensive individuals to GF mice resulted in elevated blood pressure in the host, suggesting a direct dysbiosis-induced effect (Li et al., 2017). Interestingly, FMT from normotensive rats to hypertensive rats leads to reduced blood pressure in the host, accompanied by a restored imbalance between Th17 and Treg cells in mesenteric lymph nodes. In contrast, FMT from hypertensive rats to normotensive rats results in a significant local and systemic T-cell activation, impaired endothelial function and increased blood pressure. These effects are abolished by a blockade of co-stimulation of T-cells using CTLA4-Ig and IL-17 neutralizing antibodies, suggesting an involvement of the adaptive immune system in dysbiosis-mediated hypertension (Toral et al., 2019).

Dysbiosis impacts ACVDs also through other ways, particularly via diet-derived metabolites. The most noteworthy example of this is the effect of TMAO on ACVDs. TMAO is produced from diet-derived choline and other trimethylamine (TMA) moiety-containing nutrients, which are abundant in Western food products, including meat, eggs and dairy products. These are subsequently metabolized by TMAO through the enzymatic activity of microbial choline TMA lyases (Nagatomo and Tang, 2015). Raised TMAO levels are implicated in endothelial and smooth muscle cell activation, foam cell formation, myocardial and renal fibrosis (Brown and Hazen, 2018) and hypertension (Chen et al., 2019a, b), all of which are associated with the increased risk of cardiovascular morbidity and mortality (Heianza et al., 2017; Schiattarella et al., 2017). Mechanistically, TMAO stimulates release of cytokines such as TNFα, which can aggravate myocardial fibrosis and microvascular dysfunction in the heart, independent of its pro-inflammatory, pro-atherosclerotic and neuro-hormonal derangements (Nagatomo and Tang, 2015). Moreover, TMAO is capable of activating the inflammasome multiprotein complex in human endothelial vascular cells, promoting lipid deposition and mitochondrial ROS production through the inhibition of the sirtuin 3-superoxide dismutase 2 signaling pathway (Chen et al., 2017). Notably, plasma TMAO levels are elevated with ageing. Antibiotic treatment in mice lowers TMAO levels in correlation with reversed endothelial dysfunction, arterial stiffening and oxidative stress (Brunt et al., 2019). These observations suggest that TMAO inhibition could be a promising anti-ACVD treatment strategy. Indeed, an administration of TMAO inhibitor 3,3-Dimethyl-1-butanol (DMB) in mice results in a clear anti-platelet aggregation activity (Roberts et al., 2018). In this study, the researches supplemented the diet with small quantities of two choline TMA lyase inhibitors with a potency roughly 10 000 times greater than that of DMB. Consequently, the mice display a reversed choline-induced increase in TMAO production, accompanied by a significant inhibition of platelet aggregation, platelet adherence to collagen, and clot formation.

3.4. Dysbiosis and obesity

The scientific community has significantly explored the role of the gut microbiota in obesity. Overweight individuals maintain a less diverse microbiota and express significantly higher levels of gut bacteria that promote inflammation and weight gain as compared to normal-weight individuals (Bäckhed et al., 2004; Frasca et al., 2017; Gérard, 2017; Kasselman et al., 2018; Trim et al., 2018; Tseng and Wu, 2019). Although causality in the dysbiosis-obesity axis has yet to be clarified, studies of GF mice unequivocally demonstrated that the changes in gut microbiota can trigger obesity. It has been repeatedly shown that GF mice possess significantly less fat mass than conventional mice (Bäckhed et al., 2004; Gérard, 2017; Stephens et al., 2018; Zhao, 2013). Moreover, in comparison with their conventional counterparts, GF mice show resistance to obesity when fed a high fat, sugar-rich diet, thus displaying improved insulin sensitivity and glucose tolerance (Bäckhed et al., 2007; Rabot et al., 2010).

Along with these *causative* microbiota → obesity data observed in mice, there are many *associative (correlation)* findings linking dysbiosis and obesity-associated parameters. These observational studies, however, do not clarify whether dysbiosis is a pre-requisite factor for obesity, or rather induces obesity (e.g., by a high fat diet), which then leads to dysbiosis. In this regard, FMT experiments support the notion that obesity is transmissible by modulation of gut microbiota. For example, FMT from genetically obese (*ob/ob*) mice to GF mice leads to a ~2-fold fat mass gain as compared with the reciprocal FMT from lean donors (*ob*+/− or +/+) (Turnbaugh et al., 2006). FMT from obese twins to GM mice results in an increased fat mass gain as compared with mice receiving FMT from lean twins. Of note, co-housing of recipient GM mice with mice that are fed a fiber-rich diet leads to the establishment of the lean phenotype (Ridaura et al., 2013). These observations indicate the strength of co-housing experiments: sharing bacterial communities from healthy mice is metabolically beneficial, whereas sharing bacterial communities from obese mice is metabolically harmful.

Specific bacteria strains might play specific roles in the presumed microbiota-obesity link. The previously observed elevated proportion of *Firmicutes* and reduced proportion of *Bacteroidetes* has not been confirmed in further studies in obese humans and animals (Ley et al., 2005, 2006). This reveals a significant inter-study variability in microbiota composition that may exceed differences between lean and obese individuals (Duca et al., 2014; Sze and Schloss, 2016; Walters et al., 2014). These observations suggest that the obesity-associated altered gut ecology is more complex than a simply considering the imbalance of commensal phyla, therefore a precise definition of the “obese” microbiota may not be feasible (Finucane et al., 2014; Olesen and Alm, 2016; Reijnders et al., 2016). Thus, studies focusing on the mechanistic understanding and causative association between gut microbiota and obesity become more relevant (Gérard, 2017; Meijnikman et al., 2018).

Concerning a possible link between microbiota, obesity and inflammation, it has been first shown that a high fat diet induces reduced expression of host genes encoding the intestinal tight junction proteins zonula occludens-1 and occludin (Cani and Delzenne, 2009). This results in LPS leakage from the intestinal lumen into the circulation and triggers downstream inflammation through the activation of CD14/TLR4/NF-κB axis, which is involved in the enhanced production of various pro-inflammatory cytokines eventually promoting the development of systemic inflammation, obesity and IR (Araújo et al., 2017; Glaros et al., 2013; Graham et al., 2015). Moreover, administration of LPS also induces elevated IL-6 and TNFα concentrations in right atrium increasing vulnerability of AF (Chen et al., 2017). It has been also shown that diet-induced obesity is associated with an abundance of pro-inflammatory T cells, that produce cytokines, such as IFNγ. This is accompanied by a reduction in the number and functional activity of homeostatic immune cells, such as regulatory T cells (Tregs), IL-22-producing innate lymphoid cells, Th17 cells, IgA-producing B cells (Lycke and Bemark, 2017; Winer et al., 2014) and regulatory B cells (Bregs) (García-Hernández et al., 2018). In particular, a decline in IgA in obese mice worsens IR and increases intestinal permeability via loss of mucosal factors, B cell-released cytokines, such as TGFβ1 and IL-5, along with a decreased expression of enzymes required for the synthesis of retinoid acid (Luck et al., 2019). Obesity is also associated with decreased levels of mucosal Bregs (García-Hernández et al., 2018; Mishima et al., 2019), which function to physiologically prevent inflammation by inhibition of Th1 cell activation, maintenance of the Treg cell population and induction of Th17 proliferation and differentiation, mainly via IL-10 (Moore and Loxton, 2019). Of note, Breg levels were shown to be restored to the pre-surgery level following bariatric surgery (Zhan et al., 2017). Other important mechanisms that are deeply involved in the microbiota-obesity-inflammation connection include the reduced production of SCFAs, which was shown to affect the mucosal integrity and the anti-inflammatory activity of gut-associated immune cells from both the innate and adaptive immune systems (Barrea et al., 2019; Baxter et al., 2019; Koh et al., 2016; Rooks and Garrett, 2016). In particular, dysbiosis-induced decline in SCFA production was shown to be associated with reduced number and functional activity of Tregs, leading to the development of mucosal infection (Bhaskaran et al., 2018). In addition, obesity and dysbiosis lead to disturbed production of bile acids that activate the farnesoid X receptor (FXR) and the TGR5 receptor (Ding et al., 2016; Parséus et al., 2017). These bile acids are known to exert anti-inflammatory effects in some gut-associated inflammatory disorders (Pavlidis et al., 2015; Tiratterra et al., 2018). As a result of the reduced bile acid production, the membrane integrity of various gut bacteria, including probiotic *Lactobacilli* and *Bifidobacteria,* is disrupted, halting their growth (Kurdi et al., 2006). Obesity- and dysbiosis-enhanced production of TMAO is well established (Schiattarella et al., 2017; Tang et al., 2014; van den Munckhof et al., 2018) as discussed above. All these processes are schematically presented in Fig. 2.

Concerning the application of probiotics, prebiotics or antibiotics in attempts to prevent and/or treat ACVDs, there are several encouraging preclinical data (Reviewed in Battson et al., 2018). However, these have not been confirmed so far when tested in human subjects (Aquila et al., 2019; Duan et al., 2019; Ebel et al., 2014; Kiousi et al., 2019; Ma and Li, 2018; Peng et al., 2018; Schiattarella et al., 2019), raising questions about the true applicability of such intervention in humans. Nevertheless, a recent meta-analysis of 10 studies (385,122 ACVD participants) has revealed that the intake of fermented dairy foods, especially yogurt and cheese, is significantly associated with decreased ACVD risk (Zhang et al., 2019). Thus, the notion of using dysbiosis-modifying drugs in preventing/treating ACVDs might be still clinically relevant.

4. Inflammation resolution as an emerging approach to attenuate inflammaging

The current extensive data on the paramount significance of inflammaging in the pathogenesis of sarcopenia, obesity, cardiomyopathy and dysbiosis clearly imply that targeting inflammaging would provide an efficient pleiotropic therapeutic effect. The chronic, low-grade nature of inflammaging indicates defective inflammation resolution as a potential mechanism responsible for its persistence. Being the final phase of any acute inflammation response, inflammation resolution is necessary for the restoration of tissue homeostasis, thereby limiting excessive tissue injury and preventing the development of a chronic inflammatory state (Serhan, 2017). Accordingly, unresolved (failed) inflammation can result in ongoing inflammation, fibrosis and loss of organ function (Bennett and Gilroy, 2016; Fredman and Spite, 2017; Serhan et al., 2015). Resolution of inflammation is an active and dynamically regulated process, in which specialized, pro-resolving mediators (SPMs) are involved, comprising of four families - lipoxins, resolvins, protectins, and maresins (Serhan, 2017). These small lipid molecules are physiologically derived from the metabolism of dietary polyunsaturated fatty acids. The most important property of SPMs is their ability to exert pro-resolving and anti-inflammatory effects without a systemic immune suppression of the host (Serhan, 2017). The main mechanisms of SPM-mediated inflammation resolution include the inhibition of neutrophil infiltration into tissues along with the promotion of neutrophil apoptosis by macrophages (efferocytosis) and the reduction of excessive oxidative stress (Bennett and Gilroy, 2016; Chiang and Serhan, 2017; Serhan et al., 2015). Efferocytosis, in turn, has been shown to promote the biosynthesis of SPMs (Elliott et al., 2017; Yurdagul et al., 2018(. Another important aspect of the physiological SPM activity is their capacity to stimulate tissue reparative/regenerative programs that participate in the post-inflammation restoration of tissue homeostasis (Serhan et al., 2015). This is exemplified by the restoration of the functional activities of both the innate and the adaptive immune cells (Basil and Levy, 2016; Duffney et al., 2018; Fullerton and Gilroy, 2016). In addition, the inflammation resolution by SPMs is accompanied by the inhibition of several major atherosclerosis-associated events, including platelet aggregation (Dona et al., 2008)

and pathological thrombosis (Cherpokova et al., 2019). Moreover, one of the major effects of SPMs is the phenotypic conversion of pro-inflammatory macrophages into pro-resolving macrophages that suppress inflammation and promote healing. In advanced atherosclerotic lesions, the ratio between specialized pro-resolving mediators and pro-inflammatory lipids (in particular leukotrienes) is very low, providing a molecular basis for the defective inflammation-resolution features of these lesions (Bäck et al., 2019; Fredman, 2019). Recent studies have demonstrated that SPMs are locally synthesized in vascular tissues, therefore providing a direct beneficial effect on the endothelium and its interactions with leukocytes (Conte et al., 2018). SPMs increase the production of protective adipokines, such as adiponectin in white AT that along with the enhancement of macrophage-clearing functions are shown to improve metabolic control in obese-prone conditions (Hansen et al., 2019; Sima et al., 2018; Wang and Colgan, 2017). In addition, SPMs are capable of preventing gut dysbiosis and maintaining gut permeability (Sima et al., 2018). They also promote the generation of antimicrobial peptides and the attenuation of mucosal cytokine responses through the intestinal mucosa (Wang and Colgan, 2017). Notably, SPMs are able to dampen LPS signaling, thus reducing LPS-induced inflammation and the subsequent atrophy of myotubes (Baker et al., 2018). Moreover, SPMs enhance the functional activity of muscle-infiltrating macrophages that mediate post-damage skeletal regeneration (Giannakis et al., 2019). Of interest, acute resistance exercise transiently stimulates skeletal muscle production of metabolites involved in SPM biosynthesis (Vella et al., 2019). Collectively, these exciting findings suggest that failed inflammation resolution might be involved in the pathogenesis of multiple pathologies, including atherosclerosis, obesity, dysbiosis and sarcopenia. In light of these observations, the capability of SPMs to suppress inflammation in a manner that does not compromise host defense makes them highly attractive candidates for the alleviation of detrimental inflammaging.

5. Concluding remarks

A growing number of elderly people is increasingly confronted with the limitations of modern medicine, requiring a search for new effective approaches for the prevention and treatment of age-associated disorders. The existence of bidirectional pairs (duos), such as "sarcopenia-obesity", "sarcopenia – CHF", "obesity – CHF", "obesity-dysbiosis", or " dysbiosis – CHF" is well-known. However, a thorough study of these links reveals an evolution into trios like "inflammaging-sarcopenia-obesity", "inflammaging-sarcopenia – CHF", "inflammaging-obesity – CHF, "inflammaging-dysbiosis – CHF" etc, among which inflammaging is a dominant, driving force. This review provides a volume of evidence on the existence of a unique, age-related multi-morbid quintet, comprising of inflammaging, sarcopenia, obesity, CHF, and dysbiosis. In this ensemble, inflammaging "plays first fiddle", being responsible for the development and maintenance of other components of the quintet, thus converting sarcopenia, obesity (and OBSP), CHF, and dysbiosis into *"inflammaging-oriented"* disorders (Fig. 3).

Although a succinct decision on the ***causative*** role of inflammaging in the pathogenesis of these chronic conditions has not yet reached a consensus, we believe that the evidence is substansial in supporting the casuality hypothesis. Coexistence of inflammaging with a wide variety of disorders, in addition to sarcopenia, cardiomyopathy, obesity and dysbiosis (Chung et al., 2019) clearly suggests causative relationships. In this regard, the existence of low-grade inflammation along with dysbiosis in the *preclinical* stages of several chronic diseases also supports the idea of causative relationships. Probably, the most demonstrative example of such a link is rheumatoid arthritis and some other autoimmune and non-autoimmune arthropathies (Kalinkovich et al., 2018). Gut dysbiosis was observed in preclinical type 2 diabetes mellitus (Mokkala et al., 2017). Moreover, chronic inflammation (Aggarwal et al., 2014; Libby and Crea, 2010) and a pro-inflammatory diet (Davis et al., 2019) have been suggested as independent causative risk factors for ACVDs. In a longitudinal, prospective study that monitored children, chronic oral infections were found to be significantly associated with further development of ACVD events and obesity during the middle-aged years (Pussinen et al., 2019). Finally, note that the experiments with laboratory animals repeatedly provided data that could be best interpreted as causative effects of dysbiosis on obesity (Gérard, 2017; Turnbaugh et al., 2006; Ridaura et al., 2013). Thus, these findings support the hypothesis of the causative relationships between inflammaging and inflammaging-oriented sarcopenia, cardiomyopathy, obesity and dysbiosis.

As such, targeting inflammaging is highly clinically relevant to healthy ageing. One of the key achievements that support this idea is a significantly reduced rate of recurrent ACVDs following a clinical trial that examined the specific elimination of IL-1β (Ridker, 2017). However, researchers observed a significant elevation in the incidence of fatal infection and sepsis in the treated group of patients. This shows that blockage of critical, multi-functional cytokines may suppress life-threatening host defense mechanisms. Conversely, an efficient and safe course of therapy is recommended to consider a specific elimination of senescent cells via established SASP, which considerably contribute to inflammaging (Prata et al., 2019), frailty (Justice et al., 2018), sarcopenia (da Silva et al., 2019) and obesity (Burton and Faragher, 2018). Indeed, the application of "senolytic drugs", such as dasatinib and quercetin, has been shown to attenuate frailty, to delay the onset of age-related diseases and to extend the remaining lifespan in older animals (Reviewed in Prata et al., 2019). Also, this treatment reduced circulating inflammatory mediators and alleviated metabolic and AT dysfunction in obese mice (Palmer et al., 2019), improved established vasomotor dysfunction (Roos et al., 2016), promoted vascular endothelial repair and slowed atherogenesis in aged and atherosclerotic mice (Caland et al., 2019; Childs et al., 2016). These data suggest that senolytic agents hold promise for the prevention and treatment of age-associated sarcopenia, metabolic disorders, and atherosclerosis, presumably acting via the mitigation of inflammaging.

However, the most promising therapeutic approach seems to be the use of inflammation resolving SPMs that represent a paradigm shift - from the traditional “stop,” anti-inflammatory approaches to a new tactic that promotes or mimics the mode of action of endogenous pro-resolution pathways. This approach may include a novel complementary or potentially superior traditional strategy – a regulation of inflammation and its restoration, rather than merely considering the suppression of inflammation (Doyle et al., 2018; Fullerton and Gilroy, 2016). As discussed in the review, the potential complementary candidates to attenuate inflammaging are SPMs, tailored diet manipulations, senolytic agents and anti-cytokine agents, all of which could be combined with LDL-lowering drugs. This multilevel approach may be the future of therapeutic efforts in managing age-related chronic diseases, such as inflammaging-oriented sarcopenia, obesity, ACVDs and dysbiosis.

Nevertheless, our current challenge consists of cultivating the concept of the causative role of inflammaging in the development of these conditions, and there are numerous findings favouring this concept. However, several key questions remain unanswered. What is a “healthy” microbiota and which (if any) specific alterations in the microbiota composition might represent a specific signature in age-associated chronic disorders? Which of the following is paramount - quality, quantity or activity of microbes? Although a causative role of some microbial components, such as LPS in the triggering of inflammaging, and TMAO in the induction of ACVD events can be considered as sufficiently proven, it is not obvious to what extent the data obtained in animal models are relevant to humans. Since the ultimate goal of therapeutic research is to provide a personalized strategy (precision medicine), “we need to show that differences in the microbiota can be used to predict or ameliorate disease, and not just show that differences exist” (Olesen and Alm, 2016).

The detrimental role of obesity in the development of sarcopenia

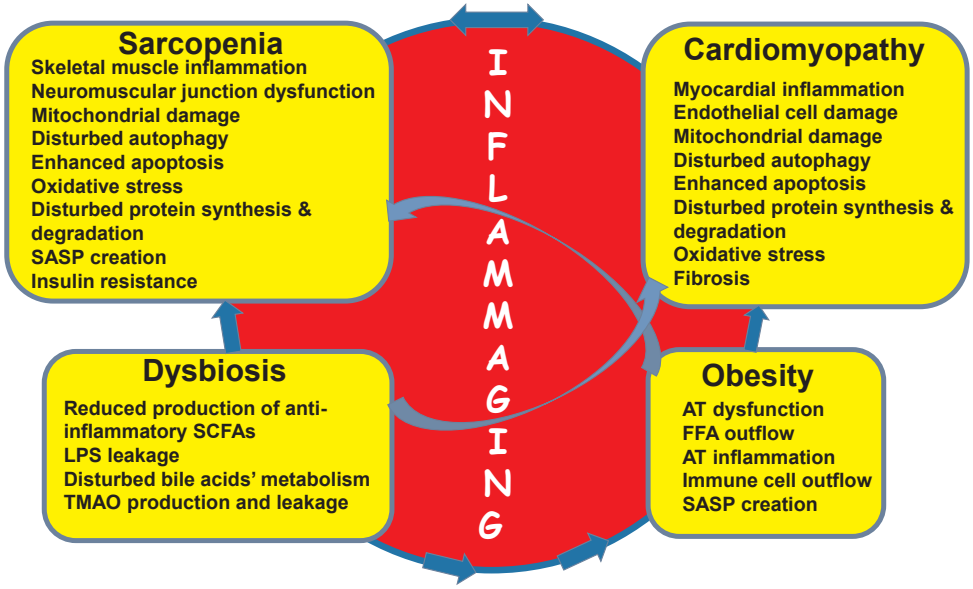

Fig. 3. Schematic representation of the hypothesis proposing inflammaging as a common mechanism that governs the development of sarcopenia, obesity, dysbiosis and cardiomyopathy.

It is well established that the prevalence of sarcopenia, obesity, dysbiosis and cardiomyopathy (in particular, CHF) is increased in ageing. Moreover, all these disorders exacerbate each other. We suggest that inflammaging is a mechanism that links all these conditions. As depicted in the scheme, chronic inflammation is the main triggering, supporting and worsening component in the pathogenesis of these diseases. Obesity is associated with AT inflammation leading to an outflow of various pro-inflammatory cells and FFAs. Ectopic accumulating of lipids and infiltration of pro-inflammatory cells in the skeletal muscle and myocardium induce a cascade of events that results in sarcopenia and cardiomyopathy. Ongoing systemic chronic inflammation is supported by an age/obesity-associated dysbiosis. Also depicted in the scheme, dysbiosis-associated mechanisms exacerbate inflammaging and may affect myocardium via TMAO production directly. Additionally, CHF-associated mechanisms, such as decreased cardiac output, may enhance dysbiosis. Based on these findings, we hypothesize that sarcopenia, obesity, CHF and dysbiosis are inflammaging-oriented disorders and inflammaging is a common mechanism governing their pathogenesis.

AT – adipose tissue; CHF – chronic heart failure; FFA – free fatty acids; TMAO –trimethylamine-*N*-oxide; SASP – senescence-associated secretory phenotype; LPS – lipopolysaccharide; SCFA – short chain fatty acids.

and cardiomyopathy, mainly due to mitochondria-associated lipotoxicity and IR induced by FFA excess, suggests that obesity prevention should be considered as the main target in the prevention/treatment of chronic musculoskeletal and heart disorders. As discussed, the anti-obesity efficacy of probiotics, prebiotics and antibiotics is exemplified by a clear reduction of inflammatory biomarkers, thus very encouraging. However, the causative obesity/sarcopenia/cardiomyopathy relationships remain to be confirmed in longitudinal, prospective, well-controlled studies.

It should be mentioned that several key questions concerning the process of inflammaging itself also remain unanswered. What are the dominant factors that drive inflammaging? Is immunosenescence a key element in inflammaging? Are the changes in immune cells intrinsic, reflecting their ageing, or rather extrinsic, i.e. derived from the surrounding aging tissues? Would senolytic drugs that demonstrated great geroprotective potential in animal models be effective in human studies? Since clinical trials that prospectively extend to the lifespan or health span of human subjects are not feasible, new paradigms for testing senolytics, SPMs or other age-associated prophylaxis/treatment approaches are required. Because these studies will aim at reducing the degree of inflammaging, they should include new surrogate endpoints of aging. Undoubtedly, reducing the degree of inflammaging, the hallmark and probably the major common ground of age-related diseases, will provide hope for better quality of life in aging people.

Competing interests

The authors declare no conflict of interest.

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