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Review

Health relevance of the modification of low grade inflammation in ageing (inflammageing) and the role of nutrition

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ABSTRACT

Ageing of the global population has become a public health concern with an important socio-economic dimension. Ageing is characterized by an increase in the concentration of inflammatory markers in the bloodstream, a phenomenon that has been termed “inflammageing”. The inflammatory response is beneficial as an acute, transient reaction to harmful conditions, facilitating the defense, repair, turnover and adaptation of many tissues. However, chronic and low grade inflammation is likely to be detrimental for many tissues and for normal functions. We provide an overview of low grade inflammation (LGI) and determine the potential drivers and the effects of the “inflamed” phenotype observed in the elderly. We discuss the role of gut microbiota and immune system crosstalk and the gut-brain axis. Then, we focus on major health complications associated with LGI in the elderly, including mental health and wellbeing, metabolic abnormalities and infections. Finally, we discuss the possibility of manipulating LGI in the elderly by nutritional interventions. We provide an overview of the evidence that exists in the elderly for omega-3 fatty acid, probiotic, prebiotic, antioxidant and polyphenol interventions as a means to influence LGI. We conclude that slowing, controlling or reversing LGI is likely to be an important way to prevent, or reduce the severity of, age-related functional decline and the onset of conditions affecting health and well-being; that there is evidence to support specific dietary interventions as a strategy to control LGI; and that a continued research focus on this field is warranted.

1. Introduction

Recent progress in the science of ageing has identified a number of key processes that are involved (López-Otín et al., 2013; Mahmoudi and Brunet, 2012), and seven such processes were discussed recently (Kennedy et al., 2014). These processes, which include inflammation, adaptation to stress, proteostasis, stem cells and regeneration, metabolism, macromolecular damage and epigenetics, are likely linked in multiple ways (Fig. 1).

Inflammation is of particular interest, because ageing is characterized by an increase in the concentration of a number of pro-inflammatory molecules in the circulation, a phenomenon that has been

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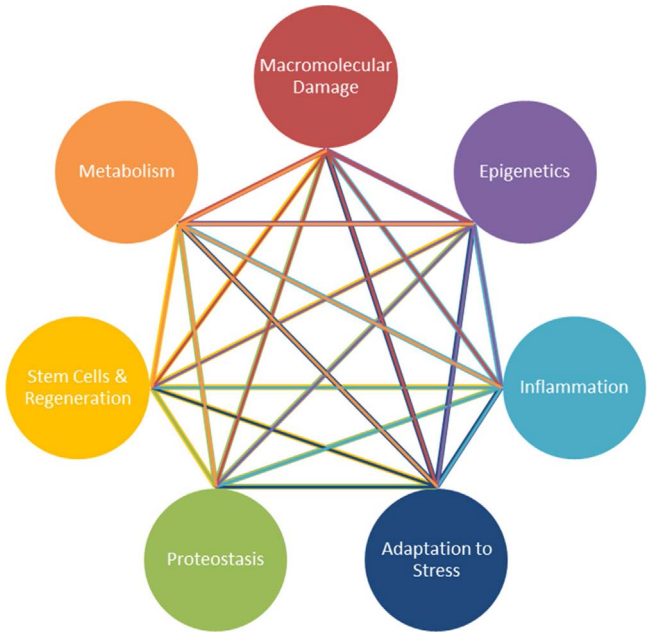

Fig. 1. The seven interacting pillars of ageing. Modified from Kennedy et al. (2014).

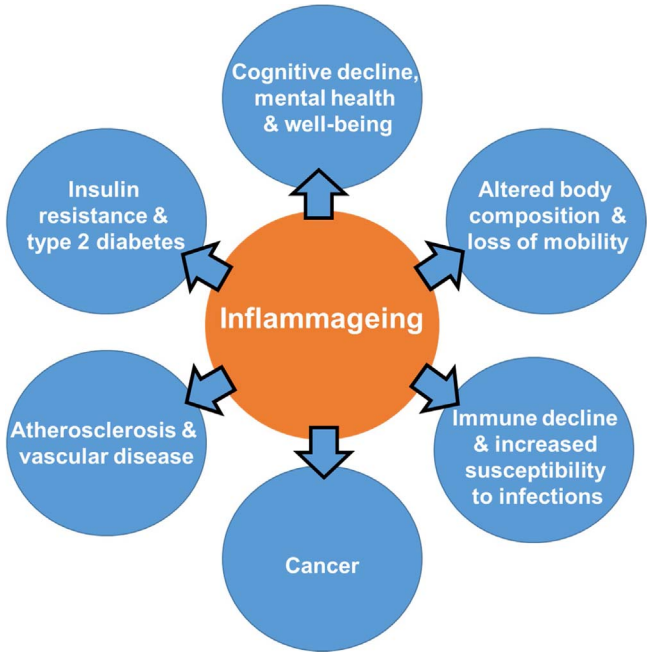

Fig. 2. Central role of inflammageing in chronic conditions of ageing.

termed “inflammageing” (Franceschi et al., 2007, 2000; Franceschi and Campisi, 2014). This article provides an overview of low grade inflammation (LGI) and identifies the potential drivers and effects of the “inflamed” phenotype observed in the elderly (i.e. of inflammageing). It discusses the role of gut microbiota and host immune system cross-talk, the gut-brain axis, and some of the major health complications associated to LGI in the elderly, including mental health and wellbeing, loss of mobility, increased susceptibility to infections and cancers (Fig. 2). Finally, the article considers the possibility of manipulating LGI in the elderly by nutritional interventions, including omega-3 fatty acids, probiotics, prebiotics and antioxidants and polyphenols.

2. Low grade inflammation (LGI) in ageing

Ageing is associated with complex changes in, and a dysregulation of, the immune system, including its inflammatory component. The ageing of the immune system, termed immunosenescence, has been suggested to be a consequence of continuous attrition caused by chronic antigenic overload and an inability of immune cell output, for example from the thymus, to keep up with the demand for naive cells (Candore et al., 2006; Pearce and Bonnet, 2009; Pawelec et al., 2010; Palmer 2013; Grubeck-Loebenstein et al., 2009; Pera et al., 2015). Another, seemingly universal, phenomenon that accompanies the ageing process is a low grade, chronic inflammatory state. This is shown by the well-described 2- to 4-fold increases in serum levels of several inflammatory mediators in the elderly (Krabbe et al., 2004). There are numerous studies showing that the circulating concentrations of many markers and mediators of inflammation are higher in old than in young adults (e.g., Wei et al., 1992; Hager et al., 1994; Fagiolo et al., 1993; Franceschi et al., 1995; Pedersen et al., 2003; Ferrucci et al., 2005). However, a significant and consistent association with age has been demonstrated for only some of these mediators, while for others, such as interleukin (IL)-1β, serum amyloid A, tumour necrosis factor (TNF)-α and IL-8, observations have been less consistent (Ballou et al., 1996; Di Iorio et al., 2003; Morrisette-Thomas et al., 2014). A recent study used principal component analysis to investigate 19 biomarkers including pro- and anti-inflammatory cytokines, cytokine receptors, chemokines and C-reactive protein (CRP) in a group of Italian subjects of different age (Morrisette-Thomas et al., 2014). This study observed that 10 out of the 19 biomarkers investigated show a significant age association. The mean levels per age class of these significantly age-associated inflammatory biomarkers plus fibrinogen (for which other evidence is reported in the literature) are summarised in Table 1. The results of this study also indicated that inflammageing does not simply reflect an increase of pro-inflammatory markers but an overall activation of inflammatory systems that probably also promotes a concomitant rise in the levels of anti-inflammatory mediators. This process may result in different outcomes depending on the nature of the stimulation, the pre-existing physiological reserve, the immune background and exposure to infections (Morrisette-Thomas et al., 2014). The term “immunobiography” has been recently suggested in an effort to capture the lifelong exposure to antigens and inflammatory stimuli (Grignolio et al., 2014). Overall, these data suggest that it is the balance between pro- and anti-inflammatory mediators that matters and this idea is consistent with the hypothesis that human longevity is paradoxically compatible with a certain degree of inflammageing, likely optimally counter-balanced by the concomitant increase/up-regulation of anti-inflammatory responses (Franceschi et al., 2007). Thus, long living persons may be protected against the harmful effects of inflammageing by the presence of high levels of anti-inflammatory molecules, such as soluble TNF receptors. Alternatively, circulating levels of pro-inflammatory molecules may not tell the whole story and the context in which these molecules are produced may be more important. For example it has been hypothesised that inflammation induced by DNA damage, but not by other stimuli (e.g. muscle contraction, antigenic stimulation), can contribute to, and be responsible for, the detrimental effects of inflammageing (Salvioli et al., 2013).

Different tissues (muscle, adipose tissue), organs (brain and liver), systems (immune system) and ecosystems (gut microbiota) may contribute to the systemic state of LGI seen in ageing through altered production of pro-inflammatory and/or anti-inflammatory mediators (Cevenini et al., 2013, 2010; Franceschi et al., 2007). This will be discussed below.

3. Involvement of LGI/inflammageing in poor health

The elevated inflammatory state that occurs with ageing can potentially trigger or facilitate the onset of the most important age-related

Table 1
Reported circulating concentrations of selected age-correlated inflammatory markers in young, old, and long living persons.

Molecule	Young adults	Late-adults/elderly	Long lived persons	Data expression	Reference
CRP (mg/dl)	nd	0.1 ± 0.2	3.8 ± 5.6	Arithmetic means of log transformed values ± SD	Arai et al. (2001)
IL1RA (pg/ml)	112 (100–125)	133 (124–141)	154 (131–180)#	Means (95% confidence intervals), 1 st row: men; 2nd row: women	Ferrucci et al. (2005)
	114 (96–135)	125 (117–134)	145 (130–160)#	means (95% confidence intervals)	Jylhä et al. (2007)
	nd	nd	340 (261–420)#		
IL-6 (pg/ml)	nd 2.1 (0.3–17.0)	2.8 ± 1.6	10.9 ± 11.2	Arithmetic means of log transformed values ± SD	Arai et al. (2001)
	0.69 (0–1.09)	3.8 (0.7–20.4)	6.1 (1.5–25.3)	Geometric mean (2.5–97.5 percentile)	Bruunsgaard et al. (1999)
	1.1 (0.7–1.9)	2.41 (0.51–115.25)	5.98 (1.16–47.93)#	Median (range)	Forsey et al. (2003)
		2.13 (1.37–4.23)	10.27 (5.32–10.99)	Median (25–75 percentile)	Giuliani et al. (2001)
IL-10 (pg/ml)	13.13 (2.15–156.60)	6.00 (1.94–81.50)	6.13 (1.77–86.79)#	Median (range)	Forsey et al. (2003)
IL-15 (pg/ml)	1. 73 ± 0.50	1. 94 ± 1.32	3. 05 ± 1.41	Mean ± SD	Gangemi et al. (2003)
IL-18 (ng/ml)	0.19 ± 0.02	0.26 ± 0.03	0.45 ± 0.05	Mean ± SEM	Gangemi et al. (2003)
MIP-1beta (CCL4) (pg/ml)	32 (6–1107)	32 (11–200)	n.d.	Median (range)	Seidler et al. (2010)
			88.63 ± 159.07§	Mean ± SD	Morrisette-Thomas et al. (2014)
sGP130 (ng/ml)	230 (195–263)	263.9 (236.3–300.4)	218 (201.3–259.7)	Median (25–75 percentile)	Giuliani et al. (2001)
sTNFR-I (ng/ml)	0.607 ± 0.129	1.0 ± 0.29	2.459 ± 0.572	Mean ± SD	Gerli et al. (2001)
sTNFR-II (ng/ml)	1.8 (1.1–3.1)	2.8 (1.4–5.6)	5.0 (2.5–10.2)	Geometric mean (2.5–97.5 percentile)	Bruunsgaard et al. (1999)
	1.227 ± 0.27	1.754 ± 0.341	3.888 ± 1.246	Mean ± SD	Gerli et al. (2001)
Fibrinogen (mg/dl)	297.19 ± 68.60	336.75 ± 89.87	394.07 ± 134.51	Mean ± SD	Spazzafumo et al., 2013

The markers listed were selected on the basis of their statistical association with age according to Morrisette-Thomas et al. (2014). MIP: macrophage inflammatory protein-1beta. §: For this marker, we reported as a value for long-lived individuals the result by Morrisette-Thomas et al. (2014) on the whole population (1010 individuals aged 21-to-96 years, two thirds of them being > 65 years-old).
nd = not determined; SD = standard deviation; SEM = standard error of the mean.
Where not indicated, long living persons are centenarians. # age > 90 years.

diseases, such as atherosclerosis and other cardiovascular diseases; metabolic syndrome, type 2 diabetes and obesity; sarcopenia and osteoporosis; neurodegeneration; major depression and impaired mental wellbeing; and cancer (Fig. 2) (Cevenini et al., 2013; Franceschi et al., 2007; Salvioli et al., 2013). There are an increasing number of studies demonstrating a significant link between a mild proinflammatory state and major diseases of the elderly such as atherosclerosis, cardiovascular diseases and type II diabetes, as well as disability and mortality (discussed in Howcroft et al., 2013; Hansson and Hermansson, 2011; Donath and Shoelson, 2011). In old people high circulating IL-6 levels are negatively associated with handgrip strength and explosive leg power (Barbieri et al., 2003), can predict the onset of disability (Ferrucci et al., 1999), and are positively associated with higher risk of mortality (Harris et al., 1999). IL-1β has been found linked with age-associated conditions such as angina, congestive heart failure and dyslipidemia (Di Iorio et al., 2003). The Emerging Risk Factors Collaboration (2010) identified through meta-analysis that a high CRP concentration is associated with higher risk of mortality as a result of vascular disease, respiratory disease and several cancers. High levels of fibrinogen were found to be associated with type 2 diabetes in old people (Spazzafumo et al., 2013). An inflammation index score that included IL-6 and soluble TNF-α receptor-1 was able to predict 10-year all-cause mortality in subjects in the Cardiovascular Health Study (Varadhan et al., 2014). Morrisette-Thomas et al. (2014) identified that the age-related pattern of pro- and anti-inflammatory molecules was strongly predictive of mortality and multiple chronic diseases including diabetes, cardiovascular disease and myocardial infarction, arthritis and kidney disease. Similarly, a longitudinal study on a cohort of 1018 Italian old persons has demonstrated that higher circulating levels of inflammation-related mediators such as IL-6, IL-1ra, TNF-α receptor II (TNFAR2) were associated with the occurrence of a higher number of chronic diseases, including hypertension, diabetes, ischemic heart disease, congestive heart failure, stroke, chronic obstructive pulmonary disease, cancer, Parkinson's disease, hip fracture, lower extremities joint disease, anemia, chronic kidney disease, peripheral arterial disease and cognitive impairment (Fabbri et al., 2015). The association was independent of age, sex, body mass index, and education. In addition, higher baseline IL-6 and a steeper increase of IL-6 levels with age were significantly and independently associated with a faster increase in multi-morbidity over time (Fabbri et al., 2015).

Studies have also suggested a role for LGI in frailty. Frailty is a geriatric syndrome characterised by a cumulative decline in physiological functions that causes an increased vulnerability to internal and external stressors. Diagnosis often involves evaluation of involuntary weight loss, exhaustion, low physical activity, slowness and weakness (Fried et al., 2001). Frailty is associated with increased vulnerability to ageing-related diseases and mortality (Woods et al., 2005). Association between inflammation markers (especially CRP and IL-6) and frailty has been described (Hubbard and Woodhouse 2010). More recently, 31 cross-sectional studies were reported in a meta-analysis which confirmed the significant association of inflammatory markers such as CRP and IL-6, elevated white blood cell counts and fibrinogen level with frailty as a health outcome (Soysal et al., 2016). The same meta-analysis also considered 4 longitudinal studies, and in this case IL-6 and CRP were not associated with frailty, casting some doubts on the role of inflammation in frailty onset. Further longitudinal studies are required to better clarify this point.

4. Potential triggers of LGI

Many possible triggers of LGI have been proposed, ranging from dysfunctional mitochondria (and consequent oxidative stress) to an imbalance in gut microbiota (termed dysbiosis). A detailed description of these mechanisms is outside the scope of this review. They are summarised in Table 2 and further details may be found in the references cited in that table. A brief discussion is reserved for cell

Table 2
Possible triggers of low grade inflammation.

Molecular mechanism	Cellular consequence	References
Dysfunctional mitochondria and oxidative stress DNA damage response	Cell senescence and SASP	Rodier et al. (2009), Passos et al. (2010), Nakahira et al. (2011)
ER stress Defective autophagy/mitophagy Defective ubiquitin/proteasome system Increased production of stress proteins and/or DAMPs	Engagement of PRRs including inflammasomes	Davis et al. (2011), Zhang et al. (2010), Franceschi and Campisi (2014), Cuervo and Wong (2014), Mishto et al. (2003), Stroikin et al. (2005), Martinez-Vicente and Cuervo (2007), Franceschi et al. (2017), Zhang et al. (2006), Menu et al. (2012)
Increased production of agalactosylated immunoglobulins (IgG-G0)	Increased complement activation; increased interaction of IgG-G0 with macrophages and dendritic cells	Malhotra et al. (1995), Yabe et al. (2010)
Increased synthesis/secretion of pro-inflammatory microRNAs (InflammaMIR)	Activation of pathways involved in inflammation, such as NF-κB, mTOR, sirtuins, TGF-β and Wnt	Olivieri et al. (2013), Marques-Rocha et al. (2015)
Imbalance in gut microbiota	Increased production of Th1-Th17 cytokines; decreased production of regulatory molecules such as SCFA or tryptophan	Biagi et al. (2010), Rampelli et al. (2013), Biagi et al. (2016)
Excess of nutrients (e.g. free fatty acids, glucose)	Metaflammation	Gregor and Hotamisligil (2011), Hotamisligil (2017)

senescence and for the increased production/release of self-molecules that can engage innate immune receptors and thus trigger the production of inflammatory mediators. Mitochondrial DNA (mtDNA) can be considered as a prototype of these molecules. It has been observed that mtDNA, as well as other mitochondrial components, when released into the bloodstream, is able to initiate inflammation by engaging pattern recognition receptors (PRRs) (Zhang et al., 2010). Plasma mtDNA level increases gradually after the fifth decade of life and has been found to be correlated with increased levels of pro-inflammatory cytokines such as TNF-α, IL-6, Chemokine (C-C motif) ligand 5 (CCL5, also known as RANTES) and IL-1receptor antagonist (Pinti et al., 2014). These data suggest that circulating mtDNA can significantly contribute to the maintenance of inflammageing. Other than mtDNA, a number of molecules are known for their capacity to activate inflammation via PRRs. These molecules are collectively indicated as damage associated molecular patterns (DAMPs). Some of them (like mtDNA) are normal cell components or products of cell metabolism that are usually sequestered into organelles or compartments inaccessible to PRRs, and can trigger PRRs when misplaced, while others are metabolic end-products or damaged or stress-induced proteins. Recently, the term "cellular garbage" has been proposed for these molecules (Franceschi et al., 2017), which include lipofuscins, advanced glycation end-products (AGEs), Tau protein aggregates, alpha-synuclein fibrils, beta-amyloid networks, misfolded or oxidized proteins, organic and inorganic crystals, ceramides, cardiolipin, succinate, peroxidized lipids, altered *N*-glycans, and high mobility group Box 1 (HMGB1) protein among others (Davis et al., 2011; Franceschi and Campisi, 2014). While their production is physiological and increases with age, their disposal by the ubiquitin-proteasome system, autophagy and/or mitophagy progressively declines with age (Cuervo and Wong, 2014; Mishto et al., 2003; Stroikin et al., 2005), leading to their intracellular accumulation especially in non-cycling cells (Martinez-Vicente and Cuervo, 2007; Stroikin et al., 2005). It has been proposed that this process can drive the onset or progression of inflammageing, and can accelerate and propagate the ageing process locally and systemically (Franceschi et al., 2017).

Another important contributor to the onset and maintenance of LGI is cell senescence, defined as an irreversible block of the cell cycle. Actually, ageing is accompanied by the accumulation of senescent cells in many, if not all, organs and tissues (Krishnamurthy et al., 2004). Senescent cells are characterised by a peculiar secretory phenotype, termed the senescence-associated secretory phenotype, or SASP, that entails the production of a number of inflammatory mediators including IL-6, IL-1β, IL-8 and other chemokines such as CXCL1, CXCL2, CCL3, CCL8, CCL13, CCL20 but also matrix metalloproteinases, serine proteases and regulators of plasminogen activators (PAI-1, PAI-2), growth factors, soluble or shed receptors, and non-protein factors such as nitric oxide and reactive oxygen species, among others (Coppé et al., 2010; Van Deursen 2014). The SASP influences the cellular microenvironment, and this can be beneficial at a young age, as it has been demonstrated that SASP is involved in development, tissue repair and wound healing (Demaria et al., 2014; Munoz-Espin et al., 2013). However, SASP can become detrimental later in life as a driver of LGI. As such, persistent senescent cells are thought to accelerate ageing and the onset of age-related diseases at least in part because of their low but chronic SASP (de Keizer, 2017). Accordingly, the selective elimination of senescent cells in mice leads to the prevention of a number of pathologies occurring with age (arthritis, loss of liver and renal function) as well as typical signs of ageing (e.g. kyphosis and fur greyness and density) (Jeon et al., 2017; Baar et al., 2017). It is not yet clear if these positive effects are strictly due to the elimination of SASP or rather of the senescent cells themselves, and more studies are needed to further clarify this point. Of course, in humans the situation can be even more complex and there is an urgent need of translating the results obtained in animal models into human studies. As an example, in the study by Jeon et al. (2017) treatment with senolytic drugs (i.e. drugs that selectively kill senescent cells) of *in vitro* cultures of chondrocytes from patients undergoing total knee replacement provoked a decreased expression of senescence and inflammatory markers and a concomitant increased expression of cartilage tissue extracellular matrix proteins.

It is also hypothesised that failure of anti-inflammatory and inflammation resolving mechanisms to neutralize inflammatory processes plays a role in the development of chronic LGI in the elderly (Franceschi et al., 2007). The association of ageing with LGI, however, cannot be completely separated from the contributions of co-morbidity, medication use and malnutrition (Ahluwalia, 2004; Lesourd, 2006; World Health Organization, 2006). Other factors which may affect and modulate circulating levels of inflammatory mediators, including obesity, infections, physical activity, age-related decline in sex hormones, and altered host-gut microbiota interaction, may also be involved in the

age-associated increase in LGI (Bruunsgaard 2002; Candore et al., 2006; Guigoz et al., 2008; Nakhai Pour et al., 2007). Furthermore, high plasma levels of IL-6 and TNF-α in the elderly were associated with increased truncal fat mass (Pedersen et al., 2003) suggesting that some of this effect might be mediated by age-associated increases in fat mass.

The terminal activators of the inflammatory response where most of the aforementioned stimuli converge are the nuclear factor kappa B (NF-κB) pathway and the inflammasome platform. Once again, a detailed description of these mechanisms is outside the scope of this review, and the readers are referred to specific publications on these topics. Briefly, NF-κB is a multimeric transcription factor that modulates gene expression by binding to specific DNA sequences, known as κB response elements, in gene promoters and enhancers (Lenardo and Baltimore, 1989; Hoffmann and Baltimore, 2006). In mammalian cells, there are five NF-κB family members, RelA (p65), RelB, c-Rel, p50/p105 (NF-κB1) and p52/p100 (NF-κB2), and different NF-κB complexes are formed as homo- and hetero-dimers. NF-κB can be activated by over 150 different stimuli, including cytokines, ultraviolet irradiation, and bacterial or viral antigens (Pahl, 1999). Moreover, it has a unique sensitivity to oxidative stress, as many of the agents activating NF-κB are either modulated by oxidative stress or are pro-oxidants themselves (Chung et al., 2002) or are oxidized molecules, such as oxidized low density lipoprotein (Robbesyn et al., 2004). In turn, there is evidence that active NF-κB participates in the control of transcription of more than 400 genes, the majority of them being involved in cell survival and inflammation (including cytokines such as IL-2, TNF-alpha and beta, IL-1β and IL-6, chemokines and their modulators, immunoreceptors, proteins involved in antigen presentation, cell adhesion molecules, acute phase proteins, stress response proteins, cell-surface receptors, regulators of apoptosis, growth factors) (Gilmore 2010).

Inflammasomes are cytoplasmatic platforms that trigger the maturation and release of pro-inflammatory cytokines such as IL-1β (Lamkanfi and Dixit, 2014). Inflammasome assembly mostly results from the oligomerization of a nucleotide-binding domain-like receptor (NLR) upon the recognition of different types of pathogen-associated molecular patterns (PAMPs) from bacteria, viruses or fungi, or DAMPs, including ATP, nucleotides, cholesterol crystals, beta-amyloid and hyaluronan (Davis et al., 2011). Other proteins such as absent in melanoma 2 (AIM2), retinoic acid-inducible gene I (RIG-I) and pyrin may be able to form inflammasome platforms. However, the NLR proteins are considered the main inflammasome sensors (de Torre-Minguela et al., 2017). They contain either a pyrin domain (PYD) or a caspase activation and recruitment domain (CARD). Inflammasomes activate pro-caspase-1 to caspase-1, that in turn leads to the maturation of pro-IL-1β and pro-IL-18 to the respective mature forms (Martinon et al., 2002; Agostini et al., 2004). In this regard, in most inflammasomes, the interaction with an adaptor protein is required to enhance the activation of caspase-1. The protein ASC (also known as Pycard) is the ubiquitous adaptor for inflammasomes, and its interaction with the active inflammasome sensor protein induces the oligomerization process essential for the final structural conformation of the inflammasome. Dysregulation of inflammasomes leads to well-recognized auto-inflammatory diseases such as the cryopyrin-associated periodic syndrome (CAPS) for the NLRP3 inflammasome and the familial Mediterranean fever (FMF) and pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND) for the pyrin inflammasome. However, inflammasomes are involved in the pathophysiology of many other illnesses, including chronic inflammatory diseases, degenerative processes, fibrosis, or metabolic diseases (de Torre-Minguela et al., 2017).

Finally, different pro- and anti-inflammatory stimuli may be derived from the intestinal microbiota. The microbial composition and the diversity of the intestinal ecosystem of centenarians is different from that of younger individuals and is associated with an increased inflammatory state, represented by high levels of inflammatory cytokines such as IL-6 and −8 (Biagi et al., 2010). Specific aspects of crosstalk between gut microbiota and the host seem to be involved in inflammageing.

5. Gut microbiota-host cross-talk

In numerous immune-mediated disorders ranging from inflammatory or metabolic diseases all the way to neuropsychiatric disorders, reported common features are an altered gut microbiota (often called dysbiosis) characterised by a reduced diversity with fewer butyrate-producing Firmicutes and more gram negative pathobionts, together with a low grade to overt inflammatory status of the host. Such dysbiosis has been identified in the contexts of frailty in the elderly (van Tongeren et al., 2005), Crohn's disease (De Cruz et al., 2012; Docktor et al., 2012), ulcerative colitis (Lepage et al., 2011), obesity (Furet et al., 2010; Le Chatelier et al., 2013; Cotillard et al., 2013), type-2 diabetes (Burcelin et al., 2011; Qin et al., 2012), allergy (Abrahamsson et al., 2012; Hanski et al., 2012; Russell et al., 2012), colorectal cancer (Chen et al., 2012; Sobhani et al., 2011), irritable bowel syndrome (Carroll et al., 2012; Chassard et al., 2012; Rajilic-Stojanovic et al., 2011), non-alcoholic fatty liver disease (Henao-Mejia et al., 2012; Machado and Cortez-Pinto, 2012) and cardiovascular disorders (Karlsson et al., 2012; Lam et al., 2012). However, viewing dysbiosis as a mere deviation in gut microbiota composition is over-simplistic because it ignores the key aspect of cross-talk with the host. The very frequent association of dysbiosis with an altered inflammatory tone suggests an alteration in the crosstalk between commensal bacteria on the one side and intestinal epithelium including immune cells of the gut associated lymphoid tissue on the other side. Indeed, when investigating changes in bacterial taxa and modulation of human gene expression at the level of the mucosa (from transcriptome of biopsies), Lepage et al. showed that the most obvious alteration of gut physiology, when going from the healthy context to unaffected- and then to affected twins suffering from ulcerative colitis, was an extinction of bacteria-host crosstalk illustrated by a dramatic reduction in correlations between bacterial taxa and modulated human genes (Lepage et al., 2011). The interplay between the gut microbiota and the host immune system appears highly relevant in the elderly. Minor infections, nutritional or therapeutic stressors, and immunosenescence can induce changes in the inflammatory tone that will inevitably alter the physico-chemical conditions of the intestine. Irrespective of whether the primary event is alteration of mucosal barrier integrity or dysbiosis of the microbiota itself, the result will be a shift of the ecological context towards a new equilibrium due to forces that exceed the ecological robustness of the microbiota, forcing maladaptation. It only takes a few specific changes such as a reduced proportion of protective commensals among those recognized to exert barrier-protective and/or anti-inflammatory properties including *Akkermansia muciniphila* (Everard et al., 2013), *Faecalibacterium prausnitzii* (Fujimoto et al., 2013; Sokol et al., 2008), *Bacteroides fragilis* (Round and Mazmanian, 2009; Shen et al., 2012) and/or the proliferation of immuno-aggressive pathobionts that had been previously maintained subdominant (Chow and Mazmanian, 2010) for microbiota-host crosstalk to become far less protective and to instead promote a state of chronic LGI. The return to the initial stable state may even be far more demanding than what triggered the critical transition, leaving the ecosystem in an auto-aggravating vicious circle.

The current knowledge of the age-related changes in the gut microbiota phylogenetic composition has been reviewed elsewhere (Arboleya et al., 2016; Biagi et al., 2011; Cheng et al., 2011; O'Toole and Jeffery, 2015). What emerges from the available data is a larger variability of gut microbiota composition among elderly with a concomitant reduced biodiversity and compromised stability, with an increase in pathobionts and a decrease in healthy promoting bacteria such as bifidobacteria (Arboleya et al., 2016; Biagi et al., 2013; Biagi et al., 2010; OToole and Jeffery, 2015).

Despite the obvious importance of functional interactions of the gut microbiota towards the host's intestinal epithelium and immune system

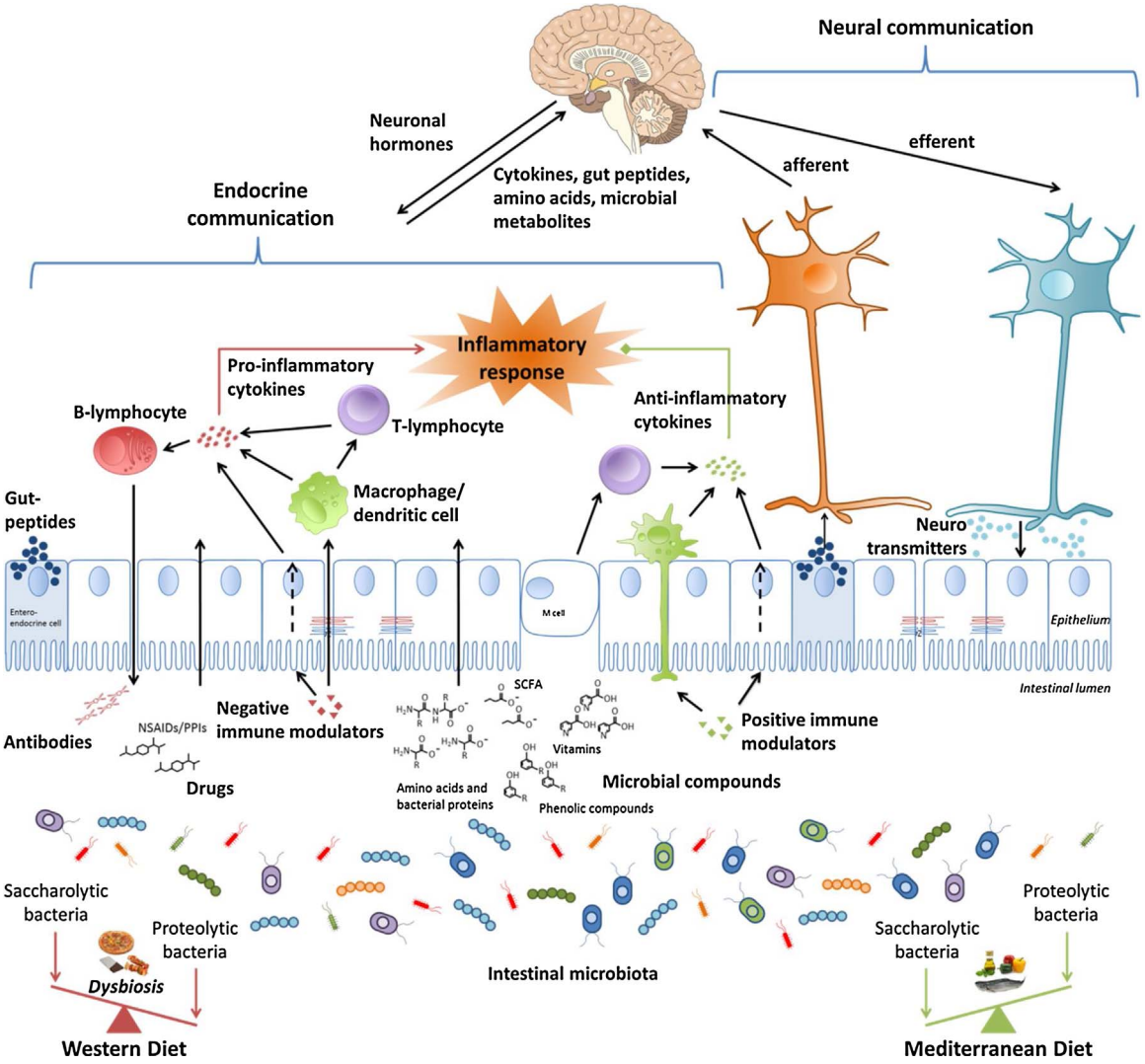

Fig. 3. Overview of general mechanisms by which the gut microbiota affects host intestinal epithelium, immune-inflammatory response and brain. The epithelial layer consists of a single layer of epithelial cells that are sealed by tight junction proteins preventing paracellular passage. The connective tissue close to the epithelial cells (lamina propria) contains a large number of immune cells, both of the innate immune system (e.g., macrophages, dendritic cells, mast cells) and the adaptive immune system (e.g., T cells, antibody-producing B cell derived plasma cells). In addition, cells of the central and enteric nervous system are innervated in the lamina propria. Factors affecting intestinal barrier function include food-derived allergens, (pathogenic and commensal) bacteria and microbial compounds (lipopolysaccharides, metabolites such as short chain fatty acids (SCFA), tryptophan-related metabolites, neurotransmitters and peptides) as well as drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs). When activated by immune modulators, lymphocytes release anti- and/or pro-inflammatory cytokines which trigger or regulate an inflammatory response. In addition, the released cytokines signal the brain to activate immunomodulatory mechanisms like the cholinergic anti-inflammatory pathway, the hypothalamo-pituitary-adrenal (HPA) axis as well as the sympathetic nervous system (SNS). Furthermore, intestinal neurotransmitters or their precursors may modulate functions of the central nervous systems. The neuronal efferent activation may also impact directly the epithelium and the gut microbiota composition. Modified from König et al. (2016) and Collins et al. (2012).

(König et al., 2016) (Fig. 3), the precise mechanisms involved remain largely unknown (Round and Mazmanian, 2009). Intestinal microbiota activity results in the generation of catecholamines in the gut with an impact on gut physiology (Asano et al., 2012). The impact of various metabolites including short chain fatty acids (SCFAs) produced in the colon, and especially butyrate, has been the subject of much recent research. SCFAs affect the intestinal mucosa (Donohoe et al., 2011) as well as peripheral tissues, influencing host metabolism (Tremaroli and Bäckhed, 2012). Additionally, alterations in the gut microbial population and changes in gut permeability may contribute directly to chronic LGI. For example, increased gut permeability has been shown to lead to the diffusion of lipopolysaccharide (LPS) into the circulation, thus promoting the development of chronic low-grade endotoxemia and the activation of inflammatory processes. An important discovery has been the link between the gut microbiota and host behaviour via gut-brain signalling. Transferring gut microbiota into germ-free mice could affect complex behaviour (Bercik et al., 2011; Heijtz et al., 2011), opening novel avenues for human research and providing opportunities for interventions that alter gut microbiota to have cognitive and behavioural effects.

6. LGI mediated alteration of brain, immune and metabolic functions

6.1. Brain function

A large dataset documents the effects of inflammatory processes on the central nervous system and brain function. Pro-inflammatory cytokines (e.g., IL-6, IL-1β, TNF-α) released peripherally by activated immune cells have access to the brain through non-exclusive humoral, neural and cellular pathways (Capuron and Miller, 2011). The mechanisms that are involved include: 1) the entry of peripheral cytokines into the brain through leaky regions of the blood brain barrier such as the circum ventricular organs and plexus choroids; 2) an active

transport via cytokine-specific transport molecules; 3) the release of molecular second messengers by activated endothelial cells; 4) the activation of afferent nerve fibres (e.g., vagus nerve) that translate the immune-inflammatory message into a neural response; and 5) the infiltration of peripheral immune cells by chemo-attractant dependent processes (Banks, 2015; Capuron and Miller, 2011; Konsman et al., 2002; Watkins et al., 1995). Within the brain, pro-inflammatory cytokines are responsible for a large number of neurochemical and neurobiological changes impacting different systems. Moreover, the gut and the brain are highly connected through endocrine, immune and neural pathways (Collins et al., 2012) (Fig. 3), and there is now strong evidence for a role of this gut-brain axis in the regulation of major brain functions, including mood and cognitive functions (Cryan and Dinan, 2012; Grenham et al., 2011).

6.1.1. Neuroendocrine changes

Pro-inflammatory cytokines potently modulate the activity of the neuroendocrine system (Besedovsky and Del Rey, 1996). Under normal conditions, the activation of inflammatory signals is associated with the stimulation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to the production of corticoid hormones, including cortisol, with strong immunoregulatory/anti-inflammatory effects necessary to counteract and resolve inflammation (Besedovsky and Del Rey, 1996). Nevertheless, when inflammatory processes become chronically activated, as observed during repeated administration of cytokines or in certain illnesses or non-pathological conditions associated with chronic LGI (e.g., ageing), dysregulation of the HPA axis may occur, thus leading to an exacerbation of inflammation. These effects are likely to rely on disruption in glucocorticoid receptor (GR) expression/function and in modified GR signalling processes (Pace et al., 2007; Pariante and Miller, 2001; Raison and Miller, 2003).

6.1.2. Effects on neurotransmitter function

A large number of studies have shown that pro-inflammatory cytokines have potent effects on neurotransmitter metabolism and function (Kitagami et al., 2003; Lacosta et al., 2000). One mechanism underlying this effect relies on alterations in enzymatic pathways that are involved in the metabolism of monoamines. Pro-inflammatory cytokines are potent inducers of the enzymes indoleamine-2,3-dioxygenase (IDO) and guanosine-triphosphate-cyclohydrolase-1 (GTP-CH1) in monocytes, macrophages and dendritic cells (Capuron and Miller, 2011) (Fig. 4). When induced by inflammatory factors, IDO is responsible for the catabolism of tryptophan, the primary amino-acid precursor of serotonin, to kynurenine and then to quinolinic acid (Byrne et al., 1986; Widner et al., 2000). In vivo, the ratio of kynurenine/tryptophan reflects tryptophan breakdown and is considered to be a reliable estimate of IDO activity (Widner et al., 1997). This mechanism was found to result in potent immunomodulatory activities, as it contributes to immunosuppression through the inhibition of T cell functions, the activation of regulatory T cells, and the inhibition of natural killer cells (Mandi and Vecsei, 2012; de la Fuente et al., 2012). Relevant to brain function and mental wellbeing, IDO-induced tryptophan breakdown is believed to contribute to reduced serotonin availability and synthesis within the central nervous system. Moreover, products of the degradation of tryptophan and kynurenine, including quinolinic acid, exert potential neurotoxic effects by promoting glutamate release through the activation of brain N-methyl-D-aspartate (NMDA) receptors (Schwarcz and Pellicciari, 2002). The induction of GTP-CH1 by inflammatory cytokines may also promote substantial alterations in serotonin biosynthesis and in noradrenalin and dopamine metabolism. GTP-CH1 produces 7,8-dihydroneopterin-triphosphate (NH_2PPP) that is normally used for the production of tetrahydrobiopterin (BH4), the cofactor of the enzymatic reactions, including phenylalanine hydroxylase (PAH) and tyrosine hydroxylase (TH), which lead to the biosynthesis of dopamine, noradrenalin and serotonin. During inflammation, however, NH_2PPP is preferentially converted in neopterin to the detriment of BH4 in human immune cells. Concomitantly, the inflammation-derived production of nitric oxide consumes BH4. This leads to profound decreases in BH4 activity together with alterations in related neurotransmitter biosynthesis (Neurauter et al., 2008). Interestingly, older age was found to be associated with increased IDO activity together with impaired PAH activity (Capuron et al., 2011a, 2011b, 2014). Given the role of monoamines in the regulation of mood and behaviour, cytokine-induced alterations in monoamine metabolism, together with the production of downstream neuroactive metabolites, are likely to contribute to significant impairment in wellbeing and mental health in the elderly. This will be further discussed below.

6.1.3. Effects on brain plasticity and circuitry

There is much evidence for the impact of inflammatory processes on brain plasticity and neurocircuitry. Accordingly, a large amount of preclinical data indicate that pro-inflammatory cytokines significantly

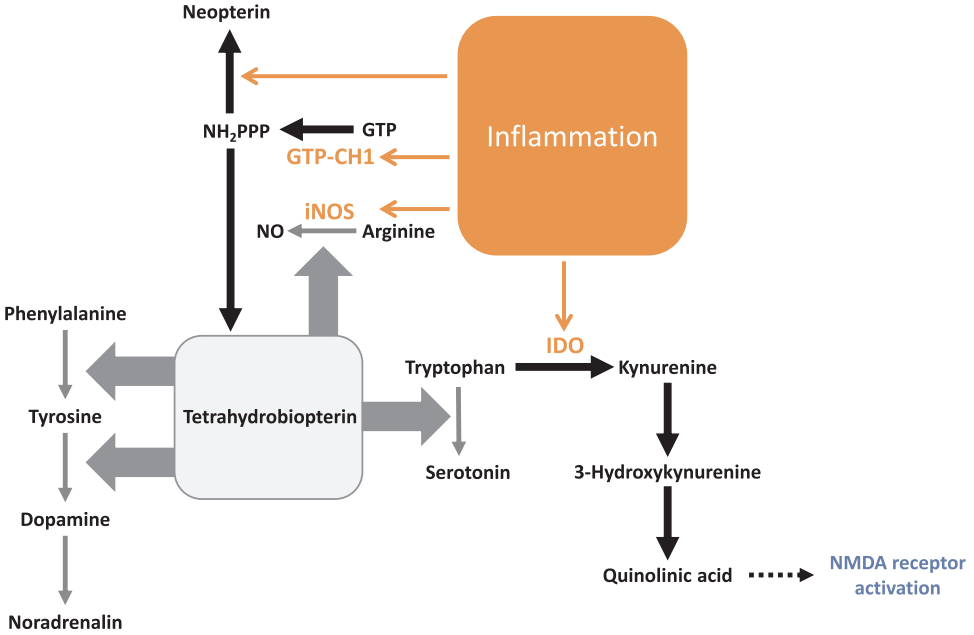

Fig. 4. Effects of inflammation on monoamine metabolism. Inflammation leads to induction of indoleamine-2,3-dioxygenase (IDO), guanosine-triphosphate-cyclohydrolase-1 (GTP-CH1) and inducible nitric oxide synthase (iNOS). IDO converts tryptophan to kynurenine which is converted to quinolinic acid. This decreases serotonin production from tryptophan, while quinolinic acid activates N-methyl-D-aspartate (NMDA) receptors. GTP-CH1 produces 7,8-dihydroneopterin-triphosphate (NH_2PPP) that is normally used for the production of tetrahydrobiopterin, the cofactor of the enzymatic reactions that lead to the biosynthesis of serotonin, dopamine and noradrenalin. During inflammation, however, NH_2PPP is preferentially converted to neopterin. Concomitantly, the inflammation-derived production of nitric oxide as a result of induction of iNOS consumes tetrahydrobiopterin. Orange arrows indicate reactions induced by inflammation, while grey arrows indicate enzymes that use tetrahydrobiopterin as a cofactor. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

modulate neural plasticity and neurogenesis (Borsini et al., 2015; Koo and Duman, 2008; Yirmiya and Goshen, 2011; Zunszain et al., 2012). Neuroimageing findings in patients chronically treated with cytokines (primarily, interferon-α) have documented important changes in brain basal metabolism together with alterations in brain frontal activity, basal ganglia circuitry and dopamine function (Capuron et al., 2012, 2007, 2005). Similar findings were reported in healthy subjects subjected to an acute immune stimulus such as vaccination (Brydon et al., 2008; Eisenberger et al., 2010; Harrison et al., 2009).

6.1.4. Hypothalamic inflammation

The hypothalamus participates in the regulation of homeostasis, which includes appetite and body weight. In particular, the extreme lateral part of the ventromedial nucleus of the hypothalamus governs the control of food intake. The prevalent hypothesis is that hormones such as leptin and cholecystokinin (among others) act on the hypothalamus through a feedback inhibitory mechanisms, in turn leading to satiety and lower food intake. A causal link between hypothalamic dysfunctions and overnutrition was first proposed by Zhang et al. (2008), who pointed to IKKB/NF-κB as the crucial connection between the two phenomena. Such hypothalamic alterations play major roles in ageing and lifespan control (Zhang et al., 2013). A unifying theory that links hypothalamic inflammation with obesity, type 2 diabetes and, in turn, ageing was proposed by Yan et al. (2014) and accruing data are suggesting causality (Valdearcos et al., 2015). In accordance with this, sensitivity to diet-induced obesity was found to correlate with hypothalamic inflammation and reactive gliosis in laboratory rodents (Dorfman and Thaler, 2015). As shown by Zhang et al. (2008) one potential culprit is excess caloric intake (in particular saturated fat) and the hypothalamic effects of a high saturated fat diet are long-lasting (Wang et al., 2012) and not easily reversible by dietary corrections. Oxidative stress (now renamed redox code) has also been implicated in hypothalamic inflammation.

The cardiometabolic consequences of hypothalamic inflammation are manifold and include impaired insulin secretion and glucose metabolism, in turn leading to higher risk of hepatic steatosis, gluconeogenesis, and insulin resistance. Within the scope of this review (i.e., ageing) it is noteworthy that the combination of age and diet-induced obesity greatly increases the risk of neurodegeneration. Mechanistically, some authors suggest that disruption of hypothalamic neural stems cells, as induced by hyperphagia and consequent obesity, impairs remodelling and plasticity, in turn enhancing neurodegeneration and cognitive decline (Li et al., 2012; Sousa-Ferreira et al., 2014; McNay et al., 2012).

One current research limitation is that it is difficult to discriminate hypothalamic metabolic inflammation and mere hypothalamic dysfunction, leaving the issue of the true contribution of either one to cardiometabolism unaddressed. Finally, obesogenic diets (e.g. high-fat diets, high-sugar diets, Western diets, or cafeteria diets) do not induce neuroinflammation to the same extent in different brain structures in rodents and obesity-induced cognitive dysfunction has been also found in the absence of neuroinflammation (Guillemot-Legris and Muccioli, 2017) making it difficult to disentangle the intricate interplay.

6.1.5. Relevance of immune-to-brain interactions for wellbeing and mental health

Through their effects on neurobiological systems and brain circuitry, pro-inflammatory cytokines contribute to the development of behavioural symptoms, referred to as sickness behaviour (Dantzer et al., 2008). Characterised by symptoms of fatigue, cognitive impairment, motor slowing, emotional disturbance, anhedonia, anorexia, sleep alterations and increased sensitivity to pain, sickness behaviour develops in humans and laboratory animals afflicted with infections. Relevant to its mediation by inflammatory processes, this behavioural syndrome is inducible by several pro-inflammatory cytokines and cytokine-inducers (e.g. LPS) administered peripherally and its development may be prevented by the intra-cerebral administration of cytokine receptor antagonists (Dantzer et al., 2008). Sickness behaviour is usually moderated and transient and it represents an integrated and adapted response of the brain to an infection in order to promote the efficacy of the immune response. Nevertheless, during a chronic and/or deregulated immune response, sickness behaviour may become more severe and evolve into clinically relevant behavioural symptoms, including depression (Capuron and Miller, 2011).

The most compelling evidence of the neuropsychiatric and depressogenic effects of cytokines comes from the model of cytokine therapy in medically ill patients. Using this model, it was shown that chronic treatment with the cytokine interferon (IFN)-α in patients with cancer or chronic hepatitis C leads to the development of depression in 30–50% of cases (Capuron et al., 2002; Musselman et al., 2001). This effect, which may be prevented by the prophylactic administration of antidepressants (Musselman et al., 2001), relies primarily on the impact of the cytokine (and related inflammatory cascade) on brain neurochemistry and circuitry (Capuron and Miller, 2011). In particular, it was found that the development of the mood and cognitive features of cytokine-induced depression involves deregulations of the HPA axis, IDO-mediated alterations in tryptophan metabolism together with changes in the activity of brain frontal areas (Capuron et al., 2005, 2003a, 2003b). On the other hand, the development of the neurovegetative features of IFN-α-induced depression was found to relate to changes in basal ganglia activity together with alterations in dopamine function probably through disruption of BH4-dependant dopamine biosynthesis (Capuron et al., 2012, 2005). Although they were obtained in a model of exogenously-induced inflammation, these findings provide important information related to the development of behavioural symptoms occurring in conditions of endogenous chronic activation of the immune system. Consistent with this, recent data obtained in subjects with chronic LGI, either related to the ageing process or to metabolic disorders (e.g. obesity, metabolic syndrome), indicate that inflammation represents a key mediator of impaired wellbeing, notably in the form of behavioural symptoms and emotional distress (Capuron et al., 2011a, 2011b, 2008; Capuron and Miller, 2011). With respect to mechanisms, it was found that age-related LGI (i.e. inflammageing) associates with significant changes in tryptophan and tyrosine metabolism that correlate with alterations in quality of life and mental wellbeing in the healthy elderly (Capuron et al., 2011a, 2011b). Together, these data indicate that systemic inflammatory processes have profound effects within the central nervous system and on the neurobiological substrates involved in the regulation of behaviour. Consistent with this, there is now compelling evidence for a role of immune-to-brain and gut-to-brain interactions in mental health and psychological wellbeing.

6.2. Immune function

6.2.1. Immunosenescence is associated with LGI

Age-related changes in immune function, also called immunosenescence, have been explored extensively in animal models and humans (Muller et al., 2012). The field has benefited from important technological developments like multicolour flow cytometry that have enabled characterization of phenotype and function of many immune cell subsets. The most important age-related dysregulations of both innate and adaptive branches of the immune system have been largely described and recently reviewed (Agarwal and Busse, 2010; Muller and Pawelec, 2014). Such dysregulations comprise for example B and T lymphocyte repertoire attrition, polarization towards a Th2 type cell-mediated immune response, and alteration of myeloid cell recruitment and phagocytosis as depicted in Fig. 5, that collectively lead to higher susceptibility to many age-related diseases (Agarwal and Busse, 2010; Gayoso et al., 2011; Solana et al., 2012; Boyd et al., 2013; Muller and Pawelec, 2014). In parallel, and as described earlier, studies of elderly cohorts consistently observe small but significant elevations in markers of inflammation including CRP and several cytokines, leading to the

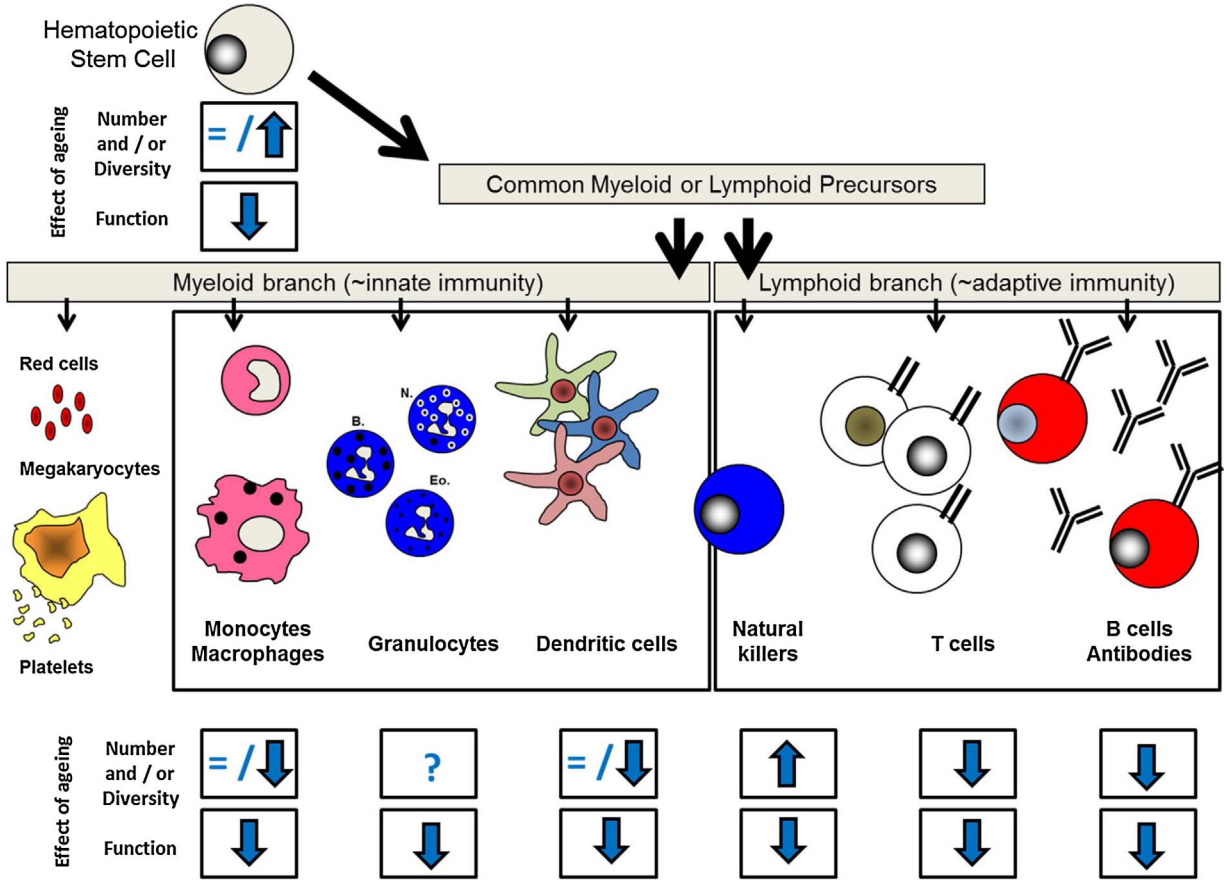

Fig. 5. Summary of age-related alterations in innate and adaptive immune cells. Hematopoiesis leads to the formation of all blood cellular components derived from hematopoietic stem cells residing in the bone marrow. Hematopoietic stem cell derived common myeloid and lymphoid progenitors cannot self-renew but through highly regulated differentiation pathways generate a variety of innate and adaptive immune cells, respectively. Both arms of the immune system need to co-operate to provide optimal immune protection to the host. Ageing leads to profound changes that affect both the innate and adaptive arms of the immune system reflected by number and functional alterations highlighted with blue arrows (as reviewed in Muller and Pawelec (2014)). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

concept of "inflammageing" (De Martinis et al., 2005; Cevenini et al., 2013). Immune decline and LGI status are prominent features of ageing and age-related diseases including for instance atherosclerosis, cancer, periodontitis and respiratory infections. Here respiratory tract infections and cancers are discussed further.

6.2.2. Role of LGI in impairment of immune competence toward infections during ageing

The incidence of lower respiratory tract infections increases significantly with advanced age such that pneumonia is a leading cause of illness and death in the elderly (Goodwin et al., 2006; Meyer, 2010). LGI exists in the lung of apparently healthy elderly, with increased neutrophils and IL-8 in the bronchoalveolar lavage fluid compared to younger adults (Meyer et al., 1998). LGI leads to anatomical and physiological changes that characterise the senescent lung and could predispose elderly individuals to lower respiratory tract infections (Meyer, 2010). As infections are a major cause of morbidity and mortality in older adults, vaccination is recommended for over 60- or 65-year old adults against influenza, pertussis and pneumococcal infections according to country public health policies. Nevertheless, the benefits of such vaccination are limited in this population because of the inability of the immune system to mount a protective response toward new antigens *i.e.* to reach seroprotective levels with specific antibodies. Regarding influenza vaccination, elderly produced considerably lower neutralizing antibody titers against influenza than younger adults (Goodwin et al., 2006; Fulop et al., 2009; Grubeck-Loebenstein et al., 2009; Pera et al., 2015). Whether this decline in the ability of the immune system to efficiently produce a protective immune response toward a pathogen could be linked to LGI is a key question addressed by few studies. Trzonkowski et al. (2004) showed that elevated serum levels of TNF-α, IL-6 and cortisol were found in depressed elderly patients compared to age-matched healthy controls and the elevated inflammatory state was associated with lower antibody response to influenza vaccination compared to the healthy group. Insights on the impact of LGI on immune competence come also from data obtained in obese subjects, as obesity is associated with elevated levels of circulating inflammatory markers (Calder et al., 2011). Obesity has been found to be a risk factor for several infections and to be a predictor for worse outcome for the H1N1 infection pandemic (Jain and Chaves, 2011). Furthermore, obese subjects were poorer responders to Hepatitis B vaccine compared to normal weight controls (Weber et al., 1985, 1986) and were less able to mount a specific $CD8^+$ T cell response after influenza vaccination even if the specific antibody response was not decreased (Sheridan et al., 2012). However, such associations were not seen in people with type 2 diabetes (Sheridan et al., 2015). In a cohort of elderly vaccinated with influenza vaccine, the non-responder group was characterised by elevated levels of pro-inflammatory cytokines, such as IL-6, before vaccination (Trzonkowski et al., 2009). Similarly, inflammation is associated with impaired antibody response to influenza vaccine in HIV infected and non-infected ageing women (Parmigiani et al., 2013) and in young African adult subjects, pro-inflammatory monocytes at baseline prior to vaccination negatively correlated with yellow fever-neutralizing antibody titers after vaccination (Muyanja et al., 2014). Whether general extrapolation of such data from young adults to the elderly population is appropriate requires further analyses as conflicting reports exist. For instance, it was

demonstrated that CXCR5$^+$ and PD-1$^+$ follicular T-helper cells predicted influenza vaccine responses in young adults but not in the elderly (Herati et al., 2014).

6.2.3. Role of LGI in impairment of immune competence toward cancer with ageing

Increased risk of cancers with increasing age is well documented by nationwide health surveys or epidemiological studies. Approximately 60% of all new diagnosed malignancies are in persons aged over 65 years, as are 70% of all deaths due to cancer (Yancik, 1997; Jemal et al., 2002; Siegel et al., 2015). However, a causal link between the incidence of common cancers and LGI is still controversial. A critical role of the immune system in prevention against cancer has been established. Many tumour immune-surveillance mechanisms have been documented to eradicate malignant cells, and tumour have developed strategies to escape immune control (Kim et al., 2005, 2007). Like in the elderly, this might explain why immunosuppressed and immune-deficient humans are at high risk of cancer (Corthay, 2014). Furthermore, causality exists between some human inflammatory diseases and malignancies such as between inflammatory bowel disease and colorectal cancer (Bernstein, 2008), periodontitis and oral cancer (Wen et al., 2014), hepatitis and hepato-cellular carcinoma (Fallot et al., 2012), and air pollution and smoking-induced lung inflammation and lung cancer (Boffetta, 2006; Bozinovski et al., 2015). Indeed, it is commonly accepted that persistent inflammation may promote genetic instability and subsequent cancerogenesis (Colotta et al., 2009). Hence, cancer-related inflammation represents a target for diagnostic, preventive and therapeutic strategies. It is now evident that a specific inflammatory environment promotes the seeding and malignant progression of tumour cells in distant vital organs. For example, in human breast cancers, poor prognosis is correlated with a high serum IL-6 level (Salgado et al., 2003; Knüpfer and Preiß, 2007), increased number of intra-tumour CD68$^+$ macrophages and high expression of chemo-attractants like CCL2 (Bonapace et al., 2014). Supporting evidence shows that in a rodent model of breast cancer, when CCL2 and IL-6 are neutralized, better outcome is obtained (Bonapace et al., 2014). Genetic studies also lead to the same conclusion on the link between inflammation and cancers. For instance, individuals with an IL-6 “high-producer” genotype (–174 G/C IL-6 gene polymorphism) have a worse evolution of their breast cancer (Markkula et al., 2014) or chronic liver disease and hepatocellular carcinoma (Liu et al., 2014). It is therefore reasonable to think that LGI may jeopardize tumour immune surveillance or favour carcinogenesis, tumour growth and/or spreading. Thus, targeting LGI in the elderly may be of interest for cancer prevention. There are already some human epidemiological studies favouring this hypothesis. Indeed, long term use of anti-inflammatory drugs like aspirin or COX-2 inhibitors is associated with prevention against some malignancies like colorectal or breast cancers (Fraser et al., 2014; Ishikawa et al., 2014), but their use is hampered by adverse effects. Cancer prevention by vaccination is also less effective in the elderly than in young adults because of various age-related changes of the immune system discussed above and recently reviewed (Gravekamp, 2013). Whether LGI may reduce the efficacy of cancer vaccines remains to be established. Anti-inflammatory agents mainly used in experimental models increased the response to cancer vaccines (Provinciali et al., 2010). These experimental data suggest the possibility to improve protective immune response in the elderly by employing pharmacological or natural anti-inflammatory compounds.

6.3. Metabolic functions: from the gut to the liver, brain and muscle

Changes in the intestinal barrier occur with ageing and can be associated to modifications of the gut microbiota composition (Nicoletti, 2015). Interestingly, similar modifications of the intestinal barrier can be observed in obesity and other nutritional disorders, which may help to understand the mechanisms involving the gut microbiota in gut barrier alterations and related health effects.

Obesity and related diseases are a pathophysiological context in which LGI has been considered as a key driver of metabolic alterations in the liver and muscle (inflammatory mediators play a role in inducing insulin resistance for example) and in cardiovascular dysfunction. The secretion of proinflammatory cytokines by expanded adipose tissue plays a key role in systemic inflammation as reviewed elsewhere (Calder et al., 2011). Several experimental approaches and observational studies in humans suggest that some elements normally present in the gut may, in some conditions, be distributed systemically. This can be illustrated taking into account the role of LPS, a component of the cell wall of gram-negative bacteria, as a factor contributing to systemic inflammation and metabolic disorders. The human gut microbiota harbours hundreds of billions of bacteria, and contains about 1 g LPS, which, in physiological conditions, are kept “at bay” through the combined processes involved in gut barrier function. In the context of nutritional obesity, it has been described that eating a high fat meal promotes the absorption of LPS (Laugerette et al., 2014), thereby creating a transient elevated post-prandial serum LPS level. In overfeeding and weight gain, the relative variations of LPS binding protein (LBP) and sCD14, play a role in LPS handling (Laugerette et al., 2014). In addition to the absorption through the chylomicron pathway, alterations of gut barrier function may also promote an increase in LPS level in the blood. When reaching the tissues, LPS binds to the specific pattern recognition receptor (PRR) toll-like receptor 4 (TLR4), located on the outer membrane of most human cells, thereby promoting inflammation (cytokine production, recruitment of acute inflammatory cells and so on) (Beutler, 2004). In 2007, it was shown for the first time that the gut microbiota contributes to the onset of hepatic insulin resistance via mechanisms associated with a relatively “small” increase in plasma LPS, defined as metabolic endotoxemia (Cani et al., 2007). In experimental obesity, metabolic endotoxemia is associated with an altered gut microbiota composition and with increased intestinal permeability, which results in increased plasma LPS levels (Cani et al., 2007, 2008). An increase in LPS or LBP levels in humans has been correlated with disturbances in glucose homeostasis. A better understanding of the role of the gut cells in the management of metabolic diseases is crucial. Intestinal epithelial cells are in constant interaction with intestinal luminal contents and can contribute to host defence through several mechanisms. MyD88 plays a major role in the regulation of immunity (Deguine and Barton, 2014). A targeted deletion of MyD88 at the level of intestinal epithelial cells confers protection against diet-induced metabolic disorders indicating that gut microbiota has a key role in regulating the host metabolic response (Everard et al., 2014). The findings suggest that the intestinal innate immune system and, more specifically, MyD88, acts as a master switch that controls gut microbiota and sets the tone of the intestinal host response (i.e., antimicrobial peptide production, gut barrier defence and permeability) and host metabolism (i.e., energy expenditure, metabolic inflammation, glucose homeostasis and fat mass) during diet-induced obesity. Other cellular and molecular components of the “gut barrier” can be altered in models of obesity, including mucus production, tight junction protein expression and localization, the endocannabinoid system and so on. Importantly, the alterations of gut functions that occur in obesity are clearly related to changes in the gut microbiota composition. One example is a key role played by *Akkermansia muciniphila*, a bacterium known to regulate mucus production, which is present in decreased numbers in situations associated with obesity, inflammation and glucose homeostasis disturbances (Dao et al., 2015). Thus, the gut barrier − including the equilibrium of the microbiota ecosystem − appears as an important target for the development of diseases related to obesity, and for a number of metabolic disorders commonly found in elderly as reviewed elsewhere (Bischoff et al., 2014). It is clear that in various pathophysiological contexts, disturbances of the gut barrier function, including gut microbial dysbiosis, lead to pro-inflammatory processes

that may have an impact on health at a distance of the gut, and disturb liver, adipose tissue and even brain functions (see earlier sections and Fig. 3).

7. The rationale for targeting LGI to improve health in the elderly

The National Institute on Aging (NIA) launched the Interventions Testing Program (ITP) in 2000 to evaluate pro-longevity drugs in genetically heterogeneous mice (Warner et al., 2000). Non-steroidal anti-inflammatory drugs (NSAIDs) belong to the first molecules tested and aspirin provided positive results in male mice only (Strong et al., 2008). A lack of effect in female mice was associated with sex differences in drug disposition and metabolism. Several groups are currently interested in existing safe therapeutics like NSAIDs to extend longevity (lifespan and health span). Positive effects were found with low dose aspirin or ibuprofen in different organisms e.g. *S. cerevisiae, C. elegans and D. melanogaster* (Ayyadevara et al., 2013; Danilov et al., 2015; He et al., 2014; Wan et al., 2013). However, it is unlikely that these beneficial effects were solely due to anti-inflammatory roles of NSAIDs. Multiple mechanisms of action have been proposed in those studies reporting parallel reduction in fecundity and insulin like signalling and/or activation of dietary restriction pathways and antioxidant defences. For primary prevention of cardiovascular diseases, particularly in at risk diabetic patients, initial evidence also supported use of low dose NSAIDs classically with aspirin in a range of 75–325 mg/day for cardioprotection (Colwell, 2003; Pignone et al., 2010). However, this approach has been criticized and recently challenged by expert opinions (Cleland et al., 2013) and negative findings from large clinical trials like Aspirin for Asymptomatic Atherosclerosis Scottish Trial (Fowkes et al., 2010) or the Japanese Primary Prevention Project (Ikeda et al., 2014). Ethically speaking it is difficult to confirm such findings in trials with healthy humans asked to take long-term medication for a “potential” risk of age-related disease. However, observational studies and some pharmaceutical interventions with patients eligible to receive long-term anti-inflammatory and/or antiplatelet treatment with NSAIDs exist. These demonstrate some efficacy in reducing the risk or severity of some age-related diseases. For instance, McGeer and colleagues showed in a meta-analysis of epidemiological studies that long term use of NSAIDs in arthritis patients has a protective effect against Alzheimer’s disease (AD) (McGeer et al., 1996). However, many uncertainties remain regarding the drugs or combination of drugs used or precise exposure assessment with studies based on self reporting. A recent systematic review confirmed that use of NSAIDs was significantly associated with a reduced risk of AD compared to no use of NSAIDs, especially in long term users, defined as > 24 months (Wang et al., 2015). Corticosteroids had no effects on AD prevention in the same study suggesting again that the anti-inflammatory role of NSAIDs is likely not involved.

Regarding cognitive decline, contrasting reports exist. Aspirin or non-aspirin NSAID use (at least twice a week for more than three months) was not significantly associated with either dementia incidence or cognitive decline in a retrospective study of the elderly (Wichmann et al., 2016) despite earlier findings based on an observational study with participants followed annually for six years (Rozzini et al., 1996). Thus, there is some scientific evidence to support the idea that strategies able to reduce LGI in elderly people could play a role in decreasing the incidence or severity of age-related pathologies. A concept of dietary low-dose aspirin fortification was even proposed as a cost-effective public health intervention (Mohapatra and Hota, 2013). Thus, the notion to lower LGI as way of improving health in the elderly is attractive. Achieving LGI attenuation or prevention with nutrition could be an important strategy to reduce incidence or severity of age-related functional decline and disease.

8. Diet, specific dietary components and LGI

8.1. Dietary patterns and specific foods

The role of dietary patterns, specific foods and individual nutrients and non-nutrients in influencing LGI has been extensively reviewed in the context of overweight and obesity (Calder et al., 2011). Most information on the role of dietary patterns and specific foods comes from observational studies, while information on nutrients and food-borne non-nutrients comes from both observational studies and intervention trials. However, these studies have not necessarily been conducted in elderly subjects. Healthy eating patterns as described by the healthy eating index, the alternative healthy eating index, vegetarian diets, and the Mediterranean diet (MD) are all associated with lower circulating concentrations of inflammatory markers including CRP and several cytokines (for references see Calder et al., 2011; Schwingshackl and Hoffmann, 2014). For example, in a study by Fung et al. (Fung et al., 2005) the alternative healthy eating index and the alternative MD score were both negatively associated with CRP, IL-6, sE-selectin, and sICAM-1 concentrations, and these associations persisted upon adjustment for potential confounder variables including BMI. Likewise, in a subsample of the Nurses' Health Study, MD index was inversely associated with markers of inflammation (circulating IL-6, CRP, sICAM-1, sVCAM-1, sE-selectin) (Fung et al., 2005). Similar findings were reported in the ATTICA study where subjects with greater adherence to the MD (those in the highest tertile) had 17% lower IL-6 and 20% lower CRP concentrations, as compared to those in the lowest tertile in analyses that adjusted for other cardiovascular risk factors (Chrysohoou et al., 2004).

Among the components of a healthy diet, higher intake of whole grains, vegetables and fruits, nuts, and fish are all associated with lower inflammation (see Calder et al., 2011 for references). This focusses attention on polyphenolic compounds, plant-derived antioxidants, fibres and prebiotics, and omega-3 fatty acids as being possible nutritional strategies to reduce LGI. Because of the interaction between gut microbiota and the inflammatory system (see earlier), probiotics may also be an important strategy.

8.2. Specific dietary components

8.2.1. Omega-3 fatty acids

Increased intake of long-chain omega-3 polyunsaturated fatty acids (PUFAs) results in increased proportions of those fatty acids in inflammatory cell phospholipids (Calder, 2015). The incorporation of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) into human inflammatory cells is partly at the expense of arachidonic acid resulting in less substrate available for synthesis of the classic inflammatory eicosanoids like prostaglandin E_2. Through altered eicosanoid production omega-3 PUFAs could affect inflammation and inflammatory processes, although they also exert non-eicosanoid mediated actions on cell signalling and gene expression (Calder, 2015). Thus, EPA and DHA are considered to have anti-inflammatory effects.

Data from subgroups of the Physicians’ Health Study and the Nurses’ Health Study showed inverse associations between dietary intake of EPA + DHA and concentrations of CRP, sTNFR1 and sTNFRII (Pischon et al., 2003) and CRP, sICAM-1, sVCAM-1 and sE-selectin (Lopez-Garcia et al., 2004a). The concentration of either EPA or DHA in granulocyte membranes was inversely associated with CRP concentration in one study (Madsen et al., 2003); the association with DHA was stronger than that with EPA. Serum non-esterified EPA and DHA were both inversely associated with concentrations of sVCAM-1 and sICAM-1 in patients at risk of coronary heart disease (Yli-Jama et al., 2002); EPA was also inversely associated with sE-selectin concentration. Plasma cholesteryl ester EPA was inversely associated with CRP concentration in overweight subjects (Klein-Platat et al., 2005). In an elderly Italian population plasma EPA was inversely associated with IL-6 concentration and positively associated with

Table 3
Selected interventional studies investigating the effect of marine *n*-3 polyunsaturated fatty acid intake on markers of low grade inflammation in adults.

Subjects	N (sex)	Age (years)	Intake (source; duration)	Effect on low grade inflammation	Reference
Healthy	58 (M) in 4 groups	21–87 (Mean 56)	0, 1.06, 2.13, 3.19 g/d EPA + DHA (fish oil capsules; up to 52 weeks)	= TNF-α, IL-1β, IL-1ra	Blok et al. (1997)
Healthy and Hyperlipidaemic	20 Healthy (M/F) 39 Hyperlipidaemic (M/F)	Mean ~ 51	0, 3.6 g/d EPA + DHA (ethyl ester capsules; up to 6 weeks)	= sICAM-1, sVCAM-1 ↓ sE-selectin	Abe et al. (1998)
Healthy and Type 2 diabetics	21 Healthy (M) 29 Diabetics (M)	Mean ~ 55	2.0 g/d EPA + DHA (fish oil capsules; 3 weeks)	= sICAM-1, sVCAM-1, sE-selectin, PAI-1 activity, PAI-1 antigen	Sampson et al. (2001)
Healthy	24 (M/F) in 3 groups	55–75	0, 0.7 g/d DHA (DHA rich algal oil capsules; 12 weeks), 1 g/d EPA + DHA (fish oil capsules; 12 weeks)	EPA + DHA: = sICAM-1, sE-selectin ↓ sVCAM-1 DHA: = sICAM-1, sVCAM-1, sE-selectin	Thies et al. (2001)
Obese	48 (M) in 4 groups (2 received *n*-3 PUFAs)	53 ± 9	0, 3.5 g/d EPA + DHA (ethyl ester capsules; 6 weeks)	= CRP, IL-6, TNF-α	Chan et al. (2002)
Elderly at risk of CHD	171 (M) in 4 groups (2 received *n*-3 PUFAs)	70 ± 3	0, 2.4 g/d EPA + DHA (fish oil capsules; 18 months)	=sICAM-1, sVCAM-1, sE-selectin, tissue plasminogen activator antigen ↓ vWF, thrombomodulin	Berstad et al. (2003)
Healthy on hormone-replacement therapy	30 (F) in 3 groups	Mean 60	0, 1.09, 2.18 g/d EPA + DHA (fish oil capsules; 5 weeks)	↓ CRP, IL-6	Ciubotaru et al., (2003)
Healthy	60 (M/F) in 3 groups	21–57 (Mean 38)	0, 2.0, 6.6 g/d EPA + DHA (fish oil capsules; 12 weeks)	=CRP	Madsen et al., (2007a)
Myocardial infarction survivors	300 (M/F) in 2 groups	28–87 (Mean 65)	0, 3.5 g/d EPA + DHA (ethyl ester capsules; 12 months)	= sICAM-1, sVCAM-1, sE-selectin	Grundt et al., (2003)
Type-2 diabetics	59 (M/F) in 3 groups	40–65 (mean 61)	0, 4 g/d EPA, 4 g/d DHA (EPA or DHA ethyl ester capsules; 6 weeks)	= CRP, IL-6, TNF-α, von Willibrand factor, tissue plasminogen activator antigen, PAI-1 antigen, sP-selectin	Mori et al. (2003) and Woodman et al. (2003)
Healthy	60 (M/F) in 3 groups	Mean ~ 38	0, 1.6, 5.8 g/d EPA + DHA (Concentrated fish oil capsules; 3 years)	Low dose: = sVCAM-1, sP-selectin ↓ sICAM-1 (especially in women) High dose: = sICAM-1, sVCAM-1 ↓ sP-selectin	Eschen et al. (2004)
Obese	11 (M)	Not given	1.1 g/d EPA + DHA (fish oil capsules; 6 weeks)	= CRP, IL-6, sTNFR1, sTNFR2, PAI-1	Jellema et al. (2004)
Hyperlipidaemia	563 (M) in 4 groups (2 received n-3 PUFAs)	64–76 (mean 70)	0, 2.4 g/d EPA + DHA (fish oil capsules; 3 years)	= sVCAM-1, sE-selectin, von Willibrand factor, tissue plasminogen activator antigen ↓ sICAM-1, thrombomodulin	Hjerkinn et al. (2005)
Healthy	93 young (M) and 62 older (M) in 4 groups	24 ± 1 61 ± 1	0, 1.35, 2.7, 4.05 g/d EPA + DHA (EPA-rich oil; 12 weeks)	= sICAM-1, sVCAM-1 ↑ sE-selectin (young only)	Cazzola et al. (2007)
Healthy	141 (M/F) in 2 groups	Mean ~ 47	0, 0.96 g/d EPA + DHA (fish oil in soy milk; 12 weeks)	= CRP, sTNFR1, sTNFR2	Fujioka et al. (2006)
Overweight and insulin resistant	116 (F) in 3 groups	21–69 (Mean 45)	0, 0 + weight loss programme, 4.2 g/d EPA + DHA + weight loss programme (Concentrated fish oil capsules; 24 weeks)	↑ adiponectin = CRP, TNF-α, IL 6.	Krebs et al. (2006)

(*continued on next page*)

Table 3 (*continued*)

Subjects	N (sex)	Age (years)	Intake (source; duration)	Effect on low grade inflammation	Reference
Healthy	80 (M/F) in 2 groups	Mean ~ 30	0, 1.5 g/d DHA (DHA-rich algal oil; 4 weeks)	= CRP, fibrinogen, PAI-1 activity, von Willibrand factor	Sanders et al. (2006)
Overweight type 2 diabetics	27 (F) in 2 groups	Mean 55	0, 1.8 g/d EPA + DHA (fish oil capsules; 8 weeks)	= IL-6, TNF-α, SAA, adiponectin ↓ PAI-1 activity, inflammatory gene expression in adipose tissue	Kabir et al. (2007)
Overweight and obese	30 (F) in 2 groups	Not given	0, 4.2 g/d EPA + DHA (DHA-rich triglyceride capsules; 12 weeks; cross-over)	=sialic acid, fibrinogen, PAI-1 activity ↓ CRP, IL-6	Browning et al. (2007)
Insulin resistant with chronic renal failure and on haemodialysis	35 (M/F) in 4 groups (2 received *n*-3 PUFAs)	54 ± 12	2.4 g/d EPA + DHA (fish oil capsules; 8 weeks)	↓ CRP, IL-6, TNF-□	Rasic-Milutinovic et al. (2007)
Chronic renal failure	46 (M/F) in 2 groups	59 ± 11	0, 2.4 g/d EPA + DHA (fish oil capsules; 8 weeks)	≅CRP	Madsen et al. (2007b)
Myocardial infaction survivors	41 (M/F) in 2 groups	63 ± 7	0, 5.2 g/d EPA + DHA (EPA-rich triglyceride capsules; 12 weeks)	=CRP	Rask-Madsen et al. (1992)
Overweight	86 (M/F) in 2 groups		0, 1 g/d EPA + DHA (Enriched foods; 6 months)	= CRP	Murphy et al. (2007)
Metabolic syndrome	23 (M/F) in 2 groups	Mean ~ 50	0, 1.8 g/d EPA (EPA capsules; 12 weeks)	↓ sICAM-1, sVCAM-1	Yamada et al. (2008)
Healthy	20 (M) in 2 groups	35–60 (Mean 45)	0, 1.8 g/d EPA + DHA (EPA-rich oil; 8 weeks)	= CRP, IL-6, sVCAM-1, sE-selectin, sP-selectin ↓ sICAM-1	Yusof et al. (2008)
Moderately hyperlipidaemic	34 (M) in 2 groups	39–66	0, 3 g/d DHA (DHA-rich algal oil; ~ 90 d)	= SAA, TNF-α, IL-1β, IL-8, IL-10, sVCAM-1, sICAM-1, sE-selectin ↓ Leukocytes, CRP, IL-6, granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factort	Kelley et al. (2009)
Healthy	77 (M/F) in 2 groups	50–70	0, 1.5 g/d EPA + DHA (fish oil capsules; 12 weeks)	= nineteen cytokines, chemokines and adhesion molecules	Pot et al. (2009)
Elderly at risk of CHD	563 (M) in 4 groups (2 received *n*-3 PUFAs)	Mean 70	0, 2.4 g/d EPA + DHA (fish oil capsules; 3 years)	=CRP, IL-6, TNF-α, adiponectin ↓ IL-18	Troseid et al. (2009)

Abbreviations used: CRP, C-reactive protein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; F, female; ICAM, intercellular adhesion molecule; IL, interleukin; M, male; PAI, plasminogen activator inhibitor; R, receptor; ra, receptor antagonist; SAA, serum amyloid A; TNF, tumour necrosis factor; VCAM, vascular cell adhesion molecule.
↓ indicates decreased; = indicates no effect on; ↑ indicates increased.

the concentrations of the anti-inflammatory cytokines IL-10 and TGF-β (Ferrucci et al., 2006). Furthermore plasma DHA was inversely associated with IL-6 and TNF-α concentrations and was also positively associated with the concentrations of IL-10 and TGF-β (Ferrucci et al., 2006). Thus, observational studies in a range of subgroups of the adult population, including the elderly, consistently suggest that both EPA and DHA are anti-inflammatory.

Studies of long chain omega-3 PUFAs in various adult groups are summarised in Table 3. Many of these studies were conducted in elderly subjects or included elderly subjects within the population group being studied (Table 3). Studies have shown that long chain omega-3 PUFAs lower the concentrations of CRP (Browning et al., 2007; Ciubotaru et al., 2003; Rasic-Milutinovic et al., 2007), IL-6 (Browning et al., 2007; Ciubotaru et al., 2003; Rasic-Milutinovic et al., 2007), TNF-α (Rasic-Milutinovic et al., 2007), IL-18 (Troseid et al., 2009), sICAM-1 (Eschen et al., 2004; Hjerkinn et al., 2005; Yamada et al., 2008; Yusof et al., 2008), sVCAM-1(Thies et al., 2001; Yamada et al., 2008), and sE-selectin (Abe et al., 1998). One study showed an increase in adiponectin concentration when a weight loss programme and 4.2 g/d EPA + DHA were combined in overweight, insulin resistant women (Krebs et al., 2006). Thus, there is quite a lot of evidence for anti-inflammatory effects of supplemental long chain omega-3 PUFAs. However, some studies have failed to replicate these findings (see Table 3).

Thus, although the common view is that EPA + DHA given at sufficient doses are anti-inflammatory, the evidence from measurements of markers of LGI is not entirely consistent. The lack of consistency may be related to differences in: duration of treatment; sample size; characteristics of the populations studied (e.g. age, healthy vs. diseased, type of disease, smokers vs. non-smokers); background diet; dose of EPA + DHA used; relative contribution of EPA and DHA, since they may have different anti-inflammatory potencies; chemical formulation (e.g. triglyceride vs. ethyl ester); degree of oxidative stress present; and genetic differences among individuals studied.

8.2.2. Probiotics

The influence of probiotics on aspects of LGI in the elderly has been little studied (only 7 studies were found, Table 4). Perhaps the most comprehensive study so far showed that in elderly subjects (aged > 65 years) regular use of *Lactobacillus delbrueckii* subsp. *bulgaricus* 8481 over 6 months increased the number of recent thymus emigrant $CD31^+$ T-cells, decreased the number of $CD8^+CD28^{null}$ T-cells, and prevented cytomegalovirus reactivation (Moro-García et al., 2013), indicating that probiotic consumption could counteract some hallmarks of immunosenescence related to T-cell immunity. In addition, in the probiotic group decreased serum IL-8 and increased beta-defensin 2 levels were observed, but there was no effect on serum IL-6 or TNF-α concentrations (Moro-García et al., 2013), indicating a non-generalised effect on LGI in elderly subjects. Although these results indicate that probiotics could have an effect on both LGI and immunosenescence, whether these changes translate to clinical benefit is not known. Several supplementation studies have assessed the influence of probiotics on innate immune function in elderly subjects. Probiotics (*L. rhamnosus* HN001, *B. lactis* HN019, *B. lactis* Bi-07 or *L. acidophilus* NCFM, *L. casei* Shirota) were shown to improve the *ex vivo* cytotoxicity of natural killer cells against model tumour cells and the phagocytic activity of monocytes and granulocytes against *E. coli* (Elmadfa et al., 2010; Gill et al., 2001; Maneerat et al., 2013; Sheih et al., 2001; Takeda and Okumura, 2007). However, in other studies these effects were not observed (Fukushima et al., 2007; Schiffrin et al., 2009). Unfortunately, only one of these studies analysed inflammatory markers in blood samples and found no effects of probiotic compared with control (Maneerat et al., 2013), making identification of associations between innate immune function and inflammatory status difficult.

Similarly, in vaccination trials and respiratory illness studies, inflammatory markers have not been analysed to make any inferences on the role of probiotics in controlling LGI. Two studies have shown

Table 4
Summary of intervention trials with probiotics in elderly humans reporting on inflammatory outcomes.

Population	Age (y) and n	Probiotic tested	Effect on blood or fecal inflammatory markers	Reference
Institutionalized elderly	Mean 76; n = 25	4 week intervention with *B. bifidum* and *L. acidophilus* 8×10^9 CFU each per day	No effect on plasma TNF-α	De Simone et al. (1992)
Free-living elderly using NSAIDs	Mean 71; n = 51	2 week intervention with synbiotic containing *L. acidophilus* 2×10^{10} CFU per day	Fecal PGE_2 (↑ 9%); No effects on fecal TNF-α or calprotectin	Ouwehand et al. (2009)
Free-living elderly with suspected small intestinal bacterial overgrowth	Mean 77 (range 61–94); n = 279	4 week intervention with *L. johnsonii* 2×10^9 CFU per day	Plasma endotoxin (↓ 92%), sCD14 (↓ 6%), and LBP (↓ 23%); No effect on blood CRP	Schiffrin et al. (2009)
Free-living elderly	Mean 76 (range 69–95); n = 1072	12 week intervention with *L. casei* 2×10^{10} CFU per day	No effects on blood CRP, IL-1, IL-6, IFNα, IFNβ, IFNγ, IL-8, IL10, IL-12 or TNF-α < βp >	Guillemard et al. (2010)
Free-living elderly	Mean 70 (range 65–84); n = 60	12 week intervention with two *L. plantarum* strains Up to 5×10^9 CFU per day	No effects on plasma IL-1 or IL-10; Plasma TGF-β (↓, value not given)	Mañe et al. (2011)
Free-living elderly	Range 55–74; n = 30	4 week intervention with *L. casei* Shirota 13×10^9CFU per day	No effects on blood CRP or C5a; IL-10/IL-12 ratio (↑ 54%) for LPS-stimulated PBMC	Dong et al. (2013)
Free-living elderly	Mean 70 (range 65–90); n = 61	24 week intervention with *L. delbrueckii* and *S. thermophilus* 9×10^7 CFU per day	Plasma IL-8 (↓, value not given) and hBD-2 (↑, value not given); No effects on blood IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12 or TNF-α.	Moro-García et al. (2013)

Note; only studies conducted in elderly subjects are included.
Abbreviations used: C5a, complement factor 5a; CFU, colony forming unit; CRP, C-reactive protein; hBD-1, human beta defensin 2; IFN, interferon; IL, interleukin; LBP, LPS binding protein; LPS, lipopolysaccharide; PBMC, peripheral blood mononuclear cell; PGE_2, prostaglandin E; sCD14, soluble cluster of differentiation 14; TGF, transforming growth factor; TNF, tumor necrosis factor.

improved responses against influenza vaccination in the elderly by *L. casei* DN-114001 and *L. plantarum* CECT7315/7316 (Boge et al., 2009; Bosch et al., 2012). However, another study using *L. casei* Shirota and involving 737 healthy older subjects (aged > 65 years) did not show any improvements in vaccination response (Van Puyenbroeck et al., 2012). Further evidence of clinical benefits and immune system stimulation by probiotics in elderly subjects comes from respiratory infection studies where duration but not the incidence of episodes decreased with *L. casei* DN-114001 treatment (Guillemard et al., 2010; Turchet et al., 2002) or *L. acidophilus* La1 treatment (Fukushima et al., 2007). Another study on elderly consuming *L. bulgaricus* OLL1073R-1 and *S. thermophilus* OLS3059 showed that the rate of common cold infections was decreased (Makino et al., 2010).

Existing trials have shown poor or inconsistent evidence on efficacy of probiotics on inflammatory and immunosenescence markers (and on immune function in general), but there is still lack of research in this area and the true associations between probiotics, LGI and immune function cannot be established. Although some evidence exists on the anti-inflammatory effect of probiotics in other age groups, it is important to note that these results cannot be directly extrapolated to elderly subjects due to changes in the immune system that occur with ageing. Indeed, just as the toll-like receptor response to pathogens seems to change with age, it was recently shown that immune cells from the elderly and young respond differently to probiotics, at least *in vitro* (You et al., 2016)

8.2.3. Prebiotics and fibres

Prebiotics and fibres are best defined as dietary compounds that promote favourable intestinal colonization by bacteria and/or bacterial release of anti-inflammatory fermentation products (Slavin, 2013). Few human trials of prebiotics or fibres have been done specifically in the elderly and none of them targeted LGI *per se*. Table 5 summarizes the details of studies in which prebiotics or fibres have been investigated in groups of adults including older adults, although the focus of most of these studies was not on the elderly. The table shows that most of these interventions were conducted in an “at risk” population (i.e. type-2 diabetic and/or obese individuals) and the age range was often not restricted to the elderly *per se*. The interventions consistently lower the concentrations of several inflammatory markers and particularly CRP (8 studies out of 10 where it was measured). Therefore, it is highly plausible that microbiota modulation by prebiotic fibres reduces LGI.

8.2.4. Antioxidants- and polyphenol-rich foods

The interplay between inflammation and oxidative stress has not been clearly elucidated, although it appears that there is a bidirectional interaction between the two as discussed elsewhere (Calder et al., 2009). Hence, it has been common to test the anti-inflammatory effects of antioxidants such as antioxidant vitamins and (poly)phenols. The most relevant studies are summarised in Table 6. Again many of these studies are not restricted to the elderly.

8.2.4.1. Vitamin E. In a retrospective study by Schwab et al. (2015), adults (mean age 56 years) with the highest (i.e. > 78 mg/d) quintile of vitamin E consumption (achieved through supplement use) had significantly lower plasma CRP concentrations compared with non-users. In a study by Wu et al. (2006) conducted with 40 healthy male and female elderly subjects (> 65 years) vitamin E administered either at 100, 200, or 400 mg/d together with fish oil for three months was able to blunt the inflammatory response of stimulated blood mononuclear cells (PMBCs). This effect was more pronounced at the 200 mg/d dose, with no dose-response effect noted.

8.2.4.2. Lycopene. Riso et al. (2006) administered 5.7 mg/d of lycopene as part of a formulated soft drink and reported significantly lower TNF-α production by challenged whole blood from healthy humans aged ~26 years. Kim et al. (2011) administered 6 or 15 mg/d lycopene for eight weeks to healthy men aged 22–57 years. Both doses significantly decreased plasma concentrations of the adhesion proteins sICAM-1 and sVCAM-1 and the latter dose also decreased CRP concentration.

8.2.4.3. Astaxanthin. One trial (Park et al., 2010) involved administering 0, 2, or 8 mg astaxanthin daily for eight weeks to healthy young adult females. Plasma CRP concentration was significantly lower at week 8 in subjects given 2 mg/day of astaxanthin.

8.2.4.4. Vitamin D. Although it is not an antioxidant, vitamin D is included here because of its emerging multiple roles in a number of disorders involving inflammation. Within the context of inflammation, significant associations between low vitamin D status and markers of inflammation (i.e. IL-6, CRP, and the ratios of IL-6 to IL-10 and of CRP to IL-10) have been reported in an observational investigation of 957 adults from Northern Ireland (Laird et al., 2014). Of note, the authors suggest that altered markers of inflammation might also translate into sub-optimal immune function, in agreement with epidemiological findings (Lang et al., 2013). Indeed, the biochemical bases of immune-modulatory and anti-inflammatory roles of Vitamin D are quite strong, in that macrophages can synthesise the active form of vitamin D and possess a Vitamin D receptor (Yin and Agrawal, 2014). One RCT (Zittermann et al., 2009) was undertaken in healthy yet overweight subjects with mean 25(OH)D concentrations of 30 nmol/L (12 ng/mL), who received vitamin D (83 μg/d) or placebo for 12 months, while concomitantly following a weight-reduction programme. A borderline significant anti-inflammatory effect was noted in that TNF-α concentration decreased by 10% in the treatment group and by 3% in the placebo group. IL-6 concentrations were not modified by the treatment. No effects of Vitamin D supplementation on inflammation were reported by three other RCTs (Ponda et al., 2012; Stricker et al., 2012; Yiu et al., 2013) (see Table 6 for details). In summary, even though the elderly are often vitamin D deficient and there is a rationale for using vitamin D as an anti-inflammatory agent, strong clinical evidence of its effects is lacking and dose-response randomized trials are still necessary to identify threshold effects.

8.2.4.5. (Poly)phenols. Plant (poly)phenols have been suggested as anti-inflammatory molecules (Calder et al., 2009), but robust human evidence of such actions is scarce. Here we review the most common dietary sources of (poly)phenols and their anti-inflammatory actions.

Tea is rich in (poly)phenolic molecules, most of which are catechins. There is strong evidence in experimental models and in animals that suggest anti-inflammatory effects of tea and tea components, particularly epigallocatechin gallate (EGCG) (Deka and Vita, 2011). Some intervention trials have been undertaken in humans and these have yielded mixed results. Neyestani et al. (2010) reported a decrease in CRP concentration following consumption of black tea extract for four weeks in 46 patients with type 2 diabetes mellitus. Steptoe et al. (2007) also reported a decrease in CRP concentration and in pro-inflammatory monocyte-platelet aggregates following four weeks of black tea consumption in healthy men aged 18–55 years. The study by Stote et al. (2012) mentioned below (see Section on cocoa) included green tea as a comparator. The anti-inflammatory effects of green tea were similar to those of cocoa and the former also lowered fibrinogen concentration. Basu et al. (2011) conducted a randomized controlled trial in 35 obese subjects with metabolic syndrome. Subjects were given either green tea (4 cups/d), green tea extract (2 capsules matched for EGCG content and 4 cups water/d), or no treatment (4 cups water/d). The only marker of inflammation that was modified by both green tea beverage and extract was serum amyloid A. Another pertinent study is that of Oyama et al. (2010), who administered green tea to male smokers and reported lowered CRP concentration. Of note, several high-quality trials showed no anti-inflammatory effects of tea in patients with risk factors or coronary artery disease (reviewed by Deka and Vita, 2011). In summary, the available evidence does not suggest a strong anti-

Table 5
Selection of intervention trials in adults with prebiotics or fibres and reporting on inflammatory outcomes.

Population	Age (y) and n	Prebiotic or fibres tested	Effect on serum inflammatory markers	Reference
Obese men at high risk of coronary artery disease	Mean 63.3 (range: 46–76); n = 31	3 week intervention with high fiber (> 40 g/day) and low fat diet *ad libitum* combined with physical activity	CRP (↓39%), MPO (↓20%), sICAM-1 (↓20%), sP-selectin (↓8%), MMP-9 (↓ 19%)	Roberts et al. (2006a, 2006c)
Type 2 diabetic men	Mean 64.6 (range 55–74); n = 13	3 week intervention with high fiber (> 40 g/day) and low fat diet *ad libitum* combined with physical activity	CRP (↓19%), sICAM-1 (↓24%), sE-selectin (↓16%)	Roberts et al. (2006b)
Older community dwelling and/or nursing home subjects at risk of malnutrition	Mean 84 (range 70–99); n = 74	12 week intervention with oral nutritional supplement containing fructooligosaccharides (1.95-3.9 g/day)	sCD14 (↓14%)	Schiffrin et al. (2007)
Healthy men and postmenopausal women	Mean 55.4 (range 50–70); n = 34	10 week intervention with 6 week intervention with raisins (1 cup/day) and/or additional walking (10–30 min/day)	TNF-α (↓40%), sICAM-1 (↓, value not given)	Puglisi et al. (2008)
Obese and lean women	Mean 55.4 (range 30–70); n = 35	5 different test meals in cross-over study with one meal rich in starch and fibers (19 g/meal)	Post-prandial IL-6 (↓, value not given) in both obese and lean women	Manning et al. (2008)
Healthy postmenopausal women from Women's Health Initiative observational study	Mean 62.2 (range 50–79); n = 1958	Association study relating serum inflammatory markers and dietary fiber intake (calculated based on FFQ analysis)	IL-6 (↓ up to 22%) and sTNFRII (↓ up to 8%) for highest total fiber consumers (median value 24.7 g/day)	Ma et al. (2008)
Hypercholesterolemic men and postmenopausal women	Mean 56.9 (range 44–75); n = 62	10 week intervention with flaxseed supplement 40 g/day (~13 g fiber/day)	CRP (↓19%) in subgroup of patients with hypertension	Bloedon et al. (2008)
General population from an observational study	Mean 54.6 (range 40–69); n = 880	Association study relating serum inflammatory markers and fiber intake patterns	PAI-1 (↑186%) in food groups eating mostly low fiber bread and cereals (4 servings/day)	Liese et al. (2009)
Adults with impaired glucose metabolism	Mean 58.7 (range 40–70); n = 104	12 week intervention with a whole grain enriched diet (~26.5 g fiber/day)	CRP (↓20%)	de Mello et al. (2011)
General population from an observational study	Mean 54 (range 40–70); n = 104	Association study relating serum inflammatory markers and total or cereal fiber intake	IL-4 (↓ up to 70%), IL-5 (↓ up to 78%), IL-8 (↓ up to 80%), IL-12 (↓ up to 83%), IL-13 (↓ up to 69%), IFN-γ (↓ up to 84%), TNF-α (↓ up to 75%), eotaxin (↓ up to 46%) for highest cereal fiber consumers (median value > 8.81 g/day)	Chuang et al. (2011)
Moderately hypercholesterolemic men and postmenopausal women	Mean 54 (range 40–70); n = 175	4 week intervention with oat fiber or apple pectin combined with different source of protein (~33.8 g fiber/day)	No effects on CRP, IL-6, adiponectin or sICAM-1	Sirtori et al. (2012)
Overweight healthy men and women	Mean 51.6 (range 45–65); n = 79	4 week intervention with wheat aleurone-rich food (~27 g aleurone/day)	CRP (↓16% compared to baseline and up to 25% compared to the control group after 4 week intervention)	Price et al. (2012)
Prehypertensive, hypertensive and hypercholestererolemic subjects	Mean 54 (range 43–65); n = 113	4 week intervention with cocoa, hazelnuts, phytosterols and soluble fiber (20 g/day) cream	CRP (↓33%)	Sola et al. (2012)
Healthy volunteers	Mean 36 (range 18–69); n = 34	4 week intervention with whole apple vs. processed apple products providing a total pectin range of 0.03–2.87 g/day	No effect on CRP	Ravn-Haren et al. (2013)
Type 2 diabetic men and women	Mean 53.1 (range 35–70); n = 124	6 week intervention with synbiotic (inulin)	CRP (↓52%)	Asemi et al. (2014)
Type 2 diabetic men and women	Mean 48.2 (range 20–65); n = 49	8 week intervention with inulin (10 g/day)	CRP (↓35%), TNF-α (↓23%), LPS (↓27%)	Dehghan et al. (2014)

Abbreviations used: CRP, C-reactive protein; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; MMP, matrix metalloproteinase; MPO, myeloperoxidase; PAI, plasminogen activation inhibitor; sCD14, soluble cluster of differentiation 14; sTNFR, soluble TNF receptor; TNF, tumour necrosis factor.

Table 6
Summary of effect of antioxidants or antioxidant rich foods on inflammatory outcomes in adults.

Nutrient	Study detail	Outcome	Reference
Vitamin E	Retrospective	Intake > 78 mg/d (via supplements) ↓CRP	Schwab et al. (2015)
	40 healthy males and females aged > 65 y, 100 mg/d, 200 mg/d, or 400 mg/d for 3 months	↓ inflammatory response of stimulated PBMCs, max effect at 200 mg/d, no dose-response	Wu et al. (2006)
Lycopene	Healthy humans, aged ~26 y, 5.7 mg/d	↓ 34% TNF-α production by challenged whole blood	Riso et al. (2006)
	Healthy men, aged 22–57 y, 6 or 15 mg/d for 8 weeks	↓ plasma sICAM-1, sVCAM-1 and CRP	Kim et al. (2011)
Astaxanthin	Healthy adult females, 0, 2, or 8 mg/d, 8 weeks	↓ CRP in the 2 mg/d group	Park et al. (2010)
Vitamin D	Overweight subjects, mean plasma 25(OH)D = 30 nmol/L. Placebo or 83 μg/d for 1 y.	No significant effects	Zittermann et al. (2009)
	Type 2 diabetics, 5000 IU/day, 12 weeks	No significant effects	Yiu et al. (2013)
	62 peripheral arterial disease patients, single oral supplementation of 100,000 IU vitamin D3 or placebo, 1 mo	No significant effects	Stricker et al. (2012)
	150 adults with elevated risk for CVD, 50000 IU of vitamin D3/week or placebo, 8 weeks	No significant effects	Ponda et al. (2012)
Tea	46 type 2 diabetes mellitus patients, black tea extract, 4 weeks	↓ CRP	Neyestani et al. (2010)
	Healthy men, aged 18–55 y, black tea (~100 mg flavonols) vs. placebo	↓ CRP	Steptoe et al. (2007)
	35 obese metabolic syndrome subjects, green tea (~230 mg catechins/cup, 4 cups/d), green tea extract (2 capsules matched for EGCG content and 4 cups water/d), vs 4 cups water/d,	↓ SAA	Basu et al. (2011)
	Male smokers, green tea (80 or 580 mg catechins) vs water	↓ CRP	Oyama et al. (2010)
Cocoa	28 healthy volunteers, dark chocolate (providing 700 mg of flavonoids/d), 1 week	↓ CRP in women not men	Hamed et al. (2008)
	42 high CV-risk volunteers, aged ~70 y, 40 g cocoa powder 495 mg total polyphenols) with 500 mL skim milk/d or only 500 mL skim milk/d, 4 weeks	↓ adhesion molecules	Monagas et al. (2009)
	Four cocoa beverages (30–900 mg flavanol/d)	↓ CRP independent of dose	Stote et al. (2012)
Olive oil phenols	Olive mill waste water extract, 5 or 25 mg hydroxytyrosol/d, 1 week	No effect	Crespo et al. (2015)

Abbreviations used: CRP, C-reactive protein; ICAM, intercellular adhesion molecule; PBMC, peripheral blood mononuclear cell; SAA, serum amyloid A; TNF, tumour necrosis factor; VCAM, vascular cell adhesion molecule.

inflammatory effect of tea consumption, despite promising *in vitro* and animal studies.

In an *ex vivo* study, Heptinstall et al. (2006) showed inhibitory effects on leukocyte activation of four flavanol-rich cocoa beverages. Hamed et al. (2008) undertook a pilot trial in which 28 healthy volunteers were given dark chocolate (providing 700 mg of flavonoids/day) for one week: reduced CRP concentrations were seen in women but not men. Monagas et al. (2009) carried out a randomized trial in which 42 subjects aged 70 years and at high risk of cardiovascular disease received 40 g cocoa powder with 500 mL skim milk/d or only 500 mL skim milk/d for 4 wk. Anti-inflammatory effects, in terms of lower concentrations of adhesion molecules, were reported in the cocoa powder plus skim milk group. Stote et al. (2012) administered obese adults with four cocoa beverages containing 30–900 mg flavanol per day and reported lower CRP concentrations, independent of the dose. One of the major issues in (poly)phenol research is the unavoidable lack of standardization of the administered agent. In this respect, a recent study by Dower et al. (2015) appears of particular interest because the authors administered pure epicatechin (100 mg/d) and quercetin (160 mg/d) to apparently healthy (pre)hypertensive men and women in a placebo-controlled study. Plasma biomarkers of endothelial dysfunction and inflammation were reduced by this regimen; these results help to shed light on the cocoa components that are likely to be responsible for its healthful effects. Epicatechin and quercetin are also abundant in other (poly)phenol-rich foods and beverages such as green tea. However, a study (Sarria et al., 2015) in which a (poly)phenol-rich cocoa beverage was administered to free-living healthy and moderately hypercholesterolemic subjects was unable to modulate inflammatory markers, which were, conversely, positively influenced by a similar, yet (poly)phenol poor and fibre-rich cocoa drink. In summary, cocoa and its products appear to exert anti-inflammatory effects in humans but much research is still needed to clarify 1) whether these effects are limited to healthy adult volunteers or can be extended to the elderly and to patients with cardiometabolic disease; 2) the cocoa components chiefly responsible for the observed affects; 3) the dose of cocoa extracts to be administered, and; 4) whether cocoa (poly)phenols and other components stand out with respect to other similar molecules isolated from other foodstuffs.

Olives and their derivatives, such as extra virgin olive oil, olive oil and olive mill waste water (OMWW) are rich in phenolic compounds, which other vegetable oils do not contain. *In vitro*, hydroxytyrosol has been shown to have anti-inflammatory properties (Zhang et al., 2009), via its inhibition of cyclo- and lipoxygenase enzymes (de la Puerta et al., 1999; Kohyama et al., 1997). *In vivo*, OMWW was shown to lower circulating concentrations of CRP in adults with ostrearthritis (Bitler et al., 2007). Bogani et al. (2007) evaluated the effects of moderate, real life intakes of extra virgin (i.e. phenol-rich) olive oil, vs. olive oil (i.e. phenol poor) and corn oil (i.e. phenol devoid), in a Latin square design post-prandial human trial. They reported significantly lower post-prandial leukotriene B_4 accumulation in plasma in the extra virgin olive oil arm as compared with the other two (Bogani et al., 2007). In a randomized, placebo-controlled trial, Crespo et al. (2015) tested the activities of a hydroxytyrosol-rich OMWW extract on a large array of inflammation markers, including CRP and six cytokines in plasma; no significant differences were recorded. In summary, olive phenolics may be anti-inflammatory agents, but the extent and precise nature of their activities remain to be fully elucidated.

9. Future perspectives

A large variety of mediators, cells, and interconnected tissues, organs and systems participate in causing, responding to and regulating inflammation. Therefore, single-target therapies aimed at combating LGI and its related morbidities may not be fully effective if they do not consider the underlying complex network of interactions. A possible approach to face this complexity is the use of so-called network theory. Network theory investigates the global topology and structural patterns of the interactions among the constituents (e.g. social groups,

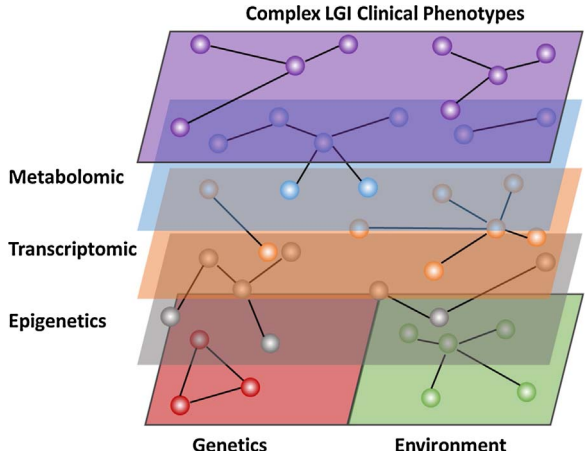

Fig. 6. A possible multiplex architecture for LGI. Each circle (node) represents an individual, with multiple interactions (lines) to other individuals. In a multiplex network, the same set of individuals have different types of interactions in each layer. Each layer corresponds to a given type of biomarker measurement, and a link might be a similar measure between two individuals. Only a few layers are represented for the sake of simplicity. Reproduced from Castellani et al. (2015).

infrastructures, biological networks) (Albert and Barabási, 2002; Newman, 2003). Network theory may be used to model ecological, immunological and neurological interactions involving multiple cells or organs. Recently, LGI has been described within the framework of such a multilayer network (Castellani et al., 2015). In such an approach, each individual person is considered with regard to the connections with others at many different levels (genetic, epigenetic, transcriptomic, metabolomic and phenotypic) with the aim of providing new multidimensional biomarkers capable of distinguishing between healthy versus unhealthy states (Fig. 6). Such an integrated analysis can help to shed light on the onset and evolution of many age-related diseases sharing an inflammatory pathogenesis, as well as of comorbidities and multi-morbidities. Finally, when integrating large-scale datasets from "omics" analyses, it should be possible to reconstruct the individual's own history and make predictions on the disease progression. Therefore, this approach is likely appropriate in order to pave a way for the coming of an era of more personalized advice.

10. Summary, discussion and conclusions

The absolute number and the proportion of older people is increasing in most countries, with a continued increase in life expectancy. However, many older people are living with one or more morbidities. Ageing is associated with alterations in a number of physiological systems and with a generalised decline in function, although some individuals age without showing these features. One common characteristic of ageing is a decline in innate and acquired immune function, termed immunosenescence, which increases susceptibility to infection. This immune decline is paralleled by an increase in the concentrations of a number of prototypical pro-inflammatory mediators in the bloodstream including acute phase proteins (CRP and serum amyloid A), cytokines (TNF-α, IL-6 and IL-8) and adhesion molecules (sICAM-1 and sVCAM-1), amongst others. This age-related increase in LGI is termed inflammageing and this is seen to contribute to many of the common declines in function, health and well-being that accompany ageing (Fig. 2). Indeed, there are many studies reporting strong links between inflammation, morbidity and mortality. Thus, it is highly relevant to healthy ageing and to improving well-being to prevent, slow or reverse the process of inflammageing. A reduction in LGI is highly likely to be a healthy and desirable strategy, without an adverse effect on the individual. Therefore, it is very important to understand those factors that trigger LGI, and the pathways involved, and to identify strategies to prevent, slow or even reverse it. Common triggers for LGI are debris arising from cellular damage and an imbalance in gut microbiota. The latter may interact directly with the host's inflammatory system through increasing exposure to agents such as LPS, but there are also more subtle forms of cross-talk between gut microbiota, the intestinal epithelium and the gut-associated and systemic immune systems. Indeed the interactions of the gut microbiota with the host extend beyond the immune system and its inflammatory component and include metabolic organs such as the adipose tissue and liver and also the brain. Many of these interactions are bidirectional (Fig. 3). The result of this is that gut dysbiosis plays a role in sub-optimal metabolism, immune function and brain function and contributes to poor health and impaired well-being associated with ageing. The many bidirectional interactions make the processes difficult to disentangle in order to study them as single entities and point to the highly complex biological processes involved. Nevertheless, because dietary components contribute to determining gut microbiota composition and diversity, there

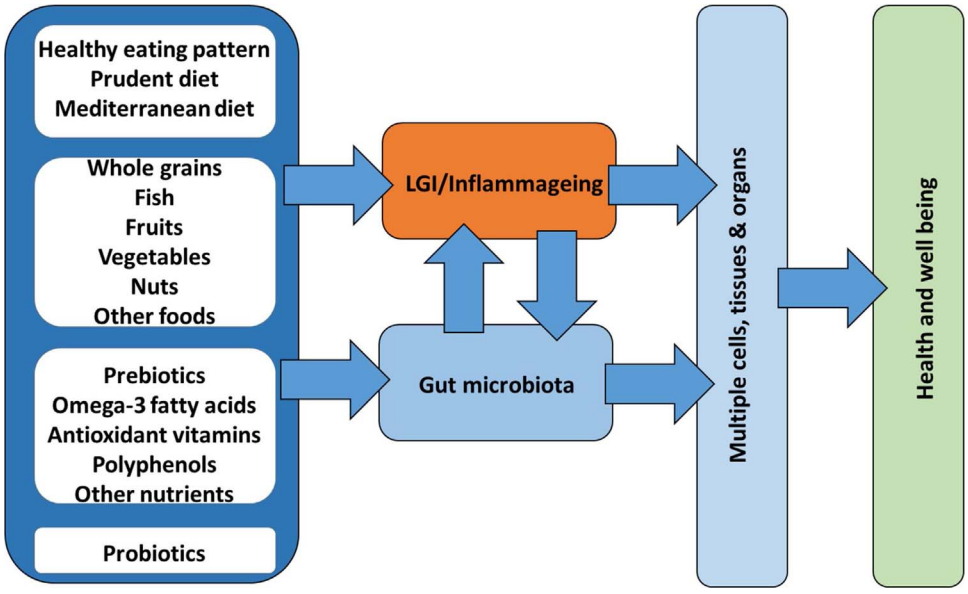

Fig. 7. Scheme linking diets and specific dietary components to health and well-being through modulation of gut microbiota and low grade inflammation (LGI).

is likely a key role for nutrition in influencing health and well-being through microbiota-mediated effects (Fig. 7). These may involve a reduction in LGI due to altered gut microbiota or they may involve other aspects of microbiota-host crosstalk. In addition, many dietary components may affect inflammation directly (Fig. 7). In this regard healthy diets, including the Mediterranean diet, are associated with lower concentrations of the inflammatory mediators that are hallmarks of LGI, like CRP and TNF-α (Chrysohoou et al., 2004; Dai et al., 2008; Lopez-Garcia et al., 2004b) and conversely a Western-style diet is associated with higher concentrations of these mediators (Lopez-Garcia et al., 2004b). Among the components of a healthy diet, higher intake of whole grains, vegetables and fruits, nuts, and fish are all associated with lower inflammation (Calder et al., 2011). This focusses attention on polyphenolic compounds, plant-derived antioxidants, fibres and prebiotics, and omega-3 fatty acids as being possible nutritional strategies to reduce LGI (Fig. 7). Because of the interaction between gut microbiota and the inflammatory system, probiotics may also be an important strategy (Fig. 7). There is evidence to favour each of these approaches as a way to reduce inflammation, although the strength of the evidence is variable. In particular, relatively few studies have investigated the effects of dietary modification to target gut microbiota and/or LGI in elderly subjects, particularly those who are relatively disease free. Therefore, it is recommended to conduct more research on dietary modification of gut microbiota, LGI and functional outcomes in elderly people, where possible using markers and biomarkers that are considered robust and strong study designs (Calder et al., 2013). Ultimately, it may be anticipated that strong evidence for specific dietary patterns, foods, nutrients and non-nutrients to improve LGI could be used as the basis for heath claims and/or dietary recommendations.

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