Introduction to inflammation

Traditionally, inflammation has been regarded as an immediate protective response to insults such as infections and traumatic injuries. This acute process is associated with cardinal clinical signs that includes the acute development of warmth, redness, swelling, pain, and if severe, a loss of function at a relatively localized site of injury or infection. Inflammation, either acute or chronic, is a protective response that destroys, dilutes or walls off the injurious agent and at the same time precipitates a series of events that heal and reconstitute damaged tissue, either by regeneration of native parenchymal cells or by filling the defect with fibroblastic (scar) tissue. Physiological inflammatory responses, like many other immune responses, are highly regulated with prompt initiation and timely resolution; too little or too late would not provide
Inflammation and its role in ageing and disease

effective protection and uncontrolled or unresolved would be harmful and potentially lead to many acute and chronic diseases.

Over the past several years, an alternative and more indolent form of inflammation has been recognized and is now frequently referred to as ‘chronic’ inflammation. It is not often recognized by cardinal signs and symptoms, rather it was first identified in large population studies of older adults where individuals often were found to have elevated serum levels of inflammatory cytokines. This low-grade, systemic, and unresolved, chronic inflammation clearly showed by 2–4-fold increase in circulating levels of inflammatory mediators including cytokines (IL-6, TNF-α, IL-β, and so on) and acute phase proteins (such as C-reactive protein, CRP) in older adult population (Fig. 44.1). Individuals with higher levels of inflammatory mediators were found to be at much higher risk of most adverse health outcomes, including frailty, mobility disability, sarcopenia, worsening chronic disease states, and mortality. Accumulating evidence suggests that chronic inflammation can have a wide variety of aetiologies and pathophysiological consequences in older adults. Chronic inflammation differs acute inflammation in that it likely has a multifactorial origin not related to acute infection or injury. Rather, it is likely to be a response to chronic antigens, stressors and tissue damage accumulated during ageing and chronic disease processes, altered body composition with increasing fat mass, from senescent cells, as well as immunesenescence. The clinical and biological importance of age-related chronic inflammation is that it may play a key activating and propagating role in the pathogenesis of many, if not all, age-related diseases. It may even have significant contribution to the ageing process itself (Chung et al., 2009). While monitoring serum CRP levels are widely utilized in clinical practice (Guarner & Rubio-Ruiz, 2015) and inflammatory indices of other cytokines may be helpful in predicting adverse health outcome or clinical risk stratification (Varadhan et al., 2014), to date there is no clinically accepted test to diagnose chronic inflammation. No pharmacological treatment such as that with non-steroidal anti-inflammatory drugs (NSAIDS) has proven clinical efficacy for chronic inflammation. The following sections provide aetiological and epidemiological details regarding the causes and consequences and potential treatments of chronic inflammation in older adults.
Inflammation and its role in ageing and disease

**Inflammation in ageing: the basic biology**

Generally speaking, inflammatory responses require the following four essential components (Currais, 2015; Medzhitov, 2008; Chovatiya & Medzhitov, 2014). The first requirement is that inducers to invoke the responses, either endogenous or exogenous, are needed. These may include microbial factors such as pathogen-associated molecular patterns (PAMPs), insulting substances in the environment such as toxic compounds and allergens, energy metabolism byproducts such as reactive oxygen species (ROS), and molecules or breakdown products released from tissue damage or cell apoptosis/necroptosis such as damage-associated molecular patterns (DAMPs) and newly identified senescence-associated secretory phenotype (SASP). The second requirement is for sensors to detect the insulting stimuli, including Toll-like receptors (TLRs) and other immune receptors as well as inflammasome. Thirdly, mediators to act on target cells and tissues are required. These include cytokines, chemokines (CXCL10, and so on), lipid mediators (eicosanoids, and so on), vasoactive amines (histamine and serotonin) and peptides (e.g. substance P, kinins), and proteolytic enzymes (e.g. cathepsins, matrix metalloproteinases). Finally, effectors that bring about various downstream cellular and molecular events and outcomes are required. These may include clotting cascade factors or factors that trigger fibrotic tissue changes such as TGF-β.

Age-related immune functional decline and dysregulation, or immunosenescence, is an essential underlying mechanism for age-related
chronic inflammation. This is because both the innate and adaptive immunity, particularly leukocytes (neutrophils, lymphocytes, monocytes and macrophages, and so on) and cytokines which are the major cellular and molecular components of the inflammation system, play an indispensable role in sensing, initiating, and mediating inflammatory responses. They also serve as key regulators of inflammation and its resolution. In fact, age-related chronic inflammation is considered as an integral part of the spectrum of immunosenescence. Other factors including smoking, decreased production of sex steroid, and increased amount of fat tissue have also been considered as significant contributors. Moreover, recent work suggests that important biological basis includes chronic and cumulative antigenic stress. This can be caused by harmful products produced by the microbial constituents of the human body, such as oral or gut microbiota, which can leak into surrounding tissues and the circulation (Biagi et al., 2011). Persistent cytomegalovirus (CMV) infection is another source of chronic antigenic stress to the ageing immune system. Cellular senescence, a cellular response to damage and stress that is similar to but distinctive from apoptosis or necroptosis likely contributes to age-related chronic inflammation through SASP inflammatory secretions. SASP can also modify tissue microenvironment and alter the function of nearby normal or transformed cells. Damaged organelle and associated macromolecules as well as harmful metabolites that accumulate during ageing due to increased production and/or inadequate elimination may also contribute. Damaged organelles can mimic bacterial products and function as endogenous DAMPs to activate innate immunity. For example, mitochondria known as phylogenetically bacterial symbionts of early eukaryotic cells, once injured, produce mitochondrial DAMPs. Harmful metabolites include ROS, extracellular ATP, fatty acids, urate crystals, ceramides, cardiolipin, amyloid, succinate, peroxidized lipids, and advanced glycation end-products (AGEs). Increased activation of the coagulation system during ageing may be a contributing factor as coagulation has many shared components and strong interactions with the inflammation system, including the ability of thrombin to activate NF-κB inflammatory pathway. In addition, d-dimers, clotting breakdown products track very closely with inflammatory pathway activation in serum measurements. Finally, defective or inappropriate regulation of the complement pathway as part of the immune functional dysregulation may occur in clinical conditions that leads to specific disease states such as macular degeneration, the leading cause of blindness in older adults (Galka et al., 2014).

Molecular inflammation theory of ageing builds upon free radical theory of ageing and further hypothesizes that Reduction-oxidation (redox) derangement that occurs during ageing is the major risk factor for molecular inflammation through activation of redox-sensitive transcription factors such NF-κB and upregulation of expression of pro-inflammatory cytokines (IL-6, TNF-α and IL-1β); this molecular inflammation, in turn, is a major mechanism that underlies ageing and
may serve as a link between normal ageing and age-related pathologies (Fig. 44.2) (Chung et al., 2009).

**Fig. 44.2**

Major molecular inflammatory pathways hypothesized by molecular inflammation theory of ageing. (RS = reactive species; MAPK = mitogen-activated protein kinases; NIK = NF-xB-induced kinases; IKK = IxB kinase; AMs = adhesion molecules; iNOS = induciable NO synthase; COX-2 = cyclooxygenase.)


Inflamm-ageing postulates that age-related chronic inflammation is provoked by a continuous antigenic load and stress, and macrophages serve as central actor not only in the inflammatory response and immunity, but also in the stress response. It further argues that inflamm-ageing represents the biologic background (first hit) for the susceptibility to age-related diseases and disabilities. A second hit such as unfavourable genetic trait is likely necessary to develop clinically overt age-related diseases (Franceschi et al., 2000). Inflamm-ageing emphasizes the potential role of chronic inflammation in the pathogenesis of many age-related conditions (Fig. 44.3) (De Martinis et al., 2006). It also proposes a wide range of sources for age-related chronic inflammation and imbalance between pro- and anti-inflammatory mechanisms (Franceschi & Campisi, 2014).
Inflammation and its role in ageing and disease

Fig. 44.3
Inflamm-ageing: cytokine network and age-related diseases. Cytokines mainly involved in the pathogenesis and progression of specific disease entities are shown.


**Inflammation in frailty and late-life functional decline**

Frailty is widely recognized as an important and common clinical syndrome in older adults characterized by decreased physiological reserve involving multiple physiologic systems and increased vulnerability to serious adverse health outcomes including falls, disability, and mortality. According to the most commonly used Fried criteria (Fried *et al.*, 2001), frailty syndrome is defined by the presence of three or more of the following clinical and functional characteristics: weakness (measured by grip strength), low physical activity, slowed motor performance (measured by walking speed), exhaustion, and unintentional weight loss. A large body of literature provides supportive evidence for the role of heightened systemic inflammation that is above and beyond age-related chronic inflammation in the pathogenesis of frailty (Li *et al.*, 2011). For example, several studies demonstrated significant associations between frailty and elevated serum levels of IL-6, CRP, and TNF-α in community-dwelling older adults. Studies also showed direct associations between frailty and increased total WBC count, albeit still under the upper limit of the normal range, and counts of specific subpopulations including neutrophils and monocytes. Among T lymphocyte subpopulations, frailty is associated with increased counts of CD8+CD28− T-cells and CCR5+ T-
cells, the latter of which has a type 1 pro-inflammatory phenotype. *Ex vivo* studies showed not only a frailty associated increase in LPS-stimulated IL-6 production by peripheral blood mononuclear cells (PBMCs), but also upregulation in expression of inflammatory pathway-specific genes by purified peripheral monocytes. Moreover, constitutive upregulation in monocyctic expression of CXCL-10, a potent pro-inflammatory chemokine, was highly correlated with elevation in serum IL-6 levels in frailty. Elevated serum levels of neopterin, a well-known molecular marker for immune activation mediated by monocytes and macrophages, were associated with frailty in community-dwelling older adults, independent of IL-6 levels. Moreover, chronic inflammation may contribute to frailty through its detrimental effects on other physiologic organ systems. For example, studies have shown that circulating IL-6 levels have inverse associations with haemoglobin concentration and serum insulin-like growth factor-1 (IGF-1) levels in frail older adults, but not in non-frail controls; low haemoglobin and IGF-1 levels were each independently associated with frailty, as well. In addition, WBC counts were inversely associated with IGF-1 levels. Taken together, it is suggested that chronic inflammation plays a key role in the pathogenesis of frailty, directly or through other intermediate pathophysiologic processes (Chen *et al.*, 2014; Yao *et al.*, 2011).

Age-related changes or pathologies in the muscle, bone, and joints are also major contributing factors to late-life functional decline. Chronic inflammation is known to have significant impact on muscle and bone health during ageing (Curtis *et al.*, 2015). Chronic inflammation contributes significantly to decreased muscle mass (sarcopenia) and strength which is also a cardinal component of the geriatric syndrome of frailty. For example, increased IL-6 is directly linked to decreased muscle strength and power in older adults, among other biological effects (Maggio *et al.*, 2006). Chronic inflammation is also known for its role in the pathogenesis of osteoporosis, a major risk factor for fractures leading to disability in older adults. For example, IL-6 aggravates systemic inflammation with age and increases hepatic CRP production. This increased systemic level of CRP has been shown to lower bone-mineral density in healthy women. CRP has consistently been found to be related to increased fracture risk in older women. In addition, IL-6 is an important stimulator of osteoclast differentiation, maturation, and activation together with IL-1β and TNF-α. Clinically, osteoarthritis, a highly prevalent inflammatory and degenerative joint disease in older adults, can cause significant late-life functional decline.

**Inflammation in neurodegenerative diseases**

Neurodegenerative diseases such as Alzheimer’s disease (AD) and Parkinson’s disease (PD) are highly prevalent with significant adverse impact on the health and quality of life for older adults and their families. As such, neuroinflammation has increasingly become an active area of ageing research. Neuroinflammation is defined as the activation of brain
Inflammation and its role in ageing and disease

Inflammation and its role in ageing and disease

innate immune system in response to an inflammatory challenge, resulting in many cellular and molecular changes within the brain, including activation of glial cells, most notably astrocytes and microglia (Hein & O’Banion, 2009). Traditionally, inflammatory challenges include injuries such as direct brain insults (such as encephalitis or ischaemia) and peripheral insults (such as infections), and often accompanied by disruption of the blood–brain barrier and increased leukocyte infiltration. During ageing, however, neuroinflammation often occurs without such classical inflammatory challenges. Instead, it may occur by exposure to endogenous stressors, such as mitochondrial dysfunction, ROS and reactive nitrogen species (RNS), and SASP, displaying features of age-related chronic inflammation or inflammaging described in the previous sections.

One unique feature of neuroinflammation is its intimate relationship of neuronal overexcitation with microglia activation and inflammatory response, which is a reciprocal stimulation in nature. While glutamate excitotoxicity leads to microglia activation, primary immune response induced by microglia may, in turn, leads to excitotoxicity. Astrocytes are frequently coactivated with microglial cells, and also contribute to both excitotoxicity and microglia activation through mechanisms of impaired glutamate uptake, inflammatory signals, and oxidative stress. With participation of other elements including immune cells and inflammasones, such neuroinflammatory processes may be amplified through stimulation of positive feedback loops between neurons, astrocytes, and microglia, to expand the level and area of inflammation. It may represent a potential target for effective intervention in the treatment of age-related neurodegenerative diseases (Currais, 2015; Hardeland et al., 2015).

In the normal aging brain, neuroinflammation may exist as a time-limited form of homeostasis. It can be accelerated and aggravated under some neuropathological conditions to form a sustained, progressive low-grade inflammation, which occurs in almost all neurodegenerative disorders, such as AD, PD, Huntington’s disease, and amyotrophic lateral sclerosis (Urrutia et al., 2014). In the early phase of these conditions, neuroinflammation may be subtle and not distinguishable from what is observed in the normal ageing brain. In the case of AD, for example, progressive neuroinflammation includes accumulation of toxic products (such as Aβ peptides, oligomers and plaques), microglial proliferation and phagocytosis after their activation, and progressive formation of pro-inflammatory signal molecules. Such progressive neuroinflammation in the AD brain is known as a prodromal indicator of AD (Giunta et al., 2008). It typically lacks neutrophil infiltration or oedema, but preserves certain classic features including microglia activation, release of CRP and pro-inflammatory cytokines (IL-6, TNF-α, IL-1β, IL-15, and IL-18), and lymphocyte recruitment. IL-18 may be important here as it is not only a key mediator of inflammation in neurodegeneration, but is also shown to promote Aβ formation (Sutinen et al., 2012). Elevated levels of IL-6 and
TNF-α are also demonstrable both in the central nervous system and in the peripheral circulation, suggesting dysregulation and interaction of inflammatory pathways inside and outside the brain (Hardeland et al., 2015; Michaud et al., 2013).

**Inflammation in cardiovascular diseases**

Vascular ageing, a consequence of cellular senescence, is an early and important event towards atherosclerosis and clinical cardiovascular disease (CVD). It entails complex structural and functional changes in the vasculature independent of hypertension, diabetes, hypercholesterolemia, or other risk factors, leading to increased arterial stiffness and endothelial dysfunction. Cumulative senescent cells of endothelium and other types in the vasculature during ageing are likely an important source of age-related chronic inflammation. Inflammation in turn contributes to an inflammatory microenvironment as demonstrated by high local levels of cytokines, especially TNF-α, IL-1β, and IL-6, as well as CRP and fibrinogen, and facilitate the development, and worsening of vascular ageing and dysfunction. The interaction of such inflammation and oxidative stress occurs when redox-sensitive transcriptional factors such as NF-κB are activated by ROS and increases production of cytokines (TNF-α, IL-1β, and IL-6) and adhesion molecules (ICAM, VCAM), further amplifying vascular inflammation and ageing. The relationship between vascular ageing and inflammation is further evidenced by an age-related upregulation of TNF-α expression in coronary arteries, leading to increased cell apoptosis and endothelial dysfunction. In addition, administration of recombinant TNF-α can recapitulate many features of vascular ageing, including endothelial dysfunction, oxidative stress, increased apoptosis and pro-inflammatory cytokine production. Clinically, temporal arteritis, a prototypic inflammatory vasculitis, is a condition diagnosed almost exclusively in older adults (El Assar et al., 2012; Donato et al., 2015).

Age-related chronic inflammation is one of the common denominators along with hypercholesterolemia and oxidative stress injury for atherosclerosis/atherothrombosis, the central pathophysiological process that is dynamic and progressive leading to clinically overt and severe CVD, such as myocardial infarction and stroke. In the early phase, monocytes are attracted/adhered to vascular endothelium and migrate into the vessel wall by altered expression of cellular adhesion molecules (e.g. selectins, ICAM-1, VCAM-1) and inflammatory factors (e.g. IL-1β, TNF-α, and CRP), leading to progressive accumulation of macrophages and their uptake of oxidized low-density lipoprotein (LDL). The intima accumulation of LDL induces LDL oxidative stress, which is responsible for endothelial dysfunction, more subendothelial infiltration of inflammatory cells (macrophages and T-cells) by chemoattractants, release of pro-inflammatory cytokines (mainly TNF-α and IL-6), and further expression of adhesion molecules and pro-coagulant agents. They in turn contribute to initiation, progression, and eventual rupture of
Inflammation and its role in ageing and disease

atherosclerotic plaques. During the formation of atherosclerotic plaques, continuous release of inflammatory cytokines and activation of proteolytic enzymes can weaken the fibrous cap and ultimately lead to plaque rupture and clot formation, a source of acute thrombotic complications to trigger myocardial infarction and other serious cardiovascular events (Puntmann et al., 2011).

Taken together, age-related chronic inflammation and its mediators are considered as key drivers in the initiation and progression of atherosclerosis/atherothrombosis and plaque formation, from early asymptomatic stage of vascular and myocardial injury, increased vascular stiffness, to clinical CVD and late-stage myocardial remodelling with dilatation and wall thinning. High serum level of inflammatory markers such as CRP is considered not only as a CVD risk factor but also a predictor for disease progression, and is now routinely monitored in clinical practice (Guarner & Rubio-Ruiz, 2015).

Inflammation in age-related metabolic dysfunctions

Age-related chronic inflammation has a close link with metabolic syndrome and its components (obesity, dyslipidemia, insulin resistance, and type 2 diabetes, and so on), promoting and worsening each other in a vicious cycle. These metabolic conditions display a pervasive, low-grade chronic inflammation, orchestrated by metabolic cells in response to abnormal nutrient and energy metabolisms during ageing. This process is defined as metabolic inflammation, also known as ‘metaflammation’ (Cevenini et al., 2013). Excessive levels of nutrients such as glucose and free fatty acids in older adults may induce inflammatory responses by increased local release of cytokines, chemokines, and adipokines in insulin-sensitive tissues, such as pancreatic islets and adipose tissue, liver, and muscle, which in turn, may cause insulin resistance and other metabolic abnormalities (Ye & Keller, 2010). In addition, activated macrophages and T-cells may invade adipose tissues in the viscera and under the skin accumulated during ageing where these pro-inflammatory cells can induce activation of multiple signalling networks including NF-κB and production of a variety of inflammatory factors (Guarner & Rubio-Ruiz, 2015).

Obesity is a common component of the metabolic syndrome with increased prevalence in virtually all age groups worldwide. Adipose tissues and residing macrophages produce adipokines and induce metabolic inflammation, leading to insulin resistance. The liver plays a pivotal role in the metabolism of nutrients, and the main hepatic complications of obesity and metabolic syndrome are hepatic steatosis and steatohepatitis with clinical manifestation of increases in levels of inflammation, cellular stress and fibrosis (Guarner & Rubio-Ruiz, 2015).
Type 2 diabetes mellitus, one of the most common age-related metabolic diseases, is characterized by insulin resistance in combination with reduced insulin secretion. Age-related chronic inflammation may play a key role in the pathogenesis of this condition. Infiltration of T-cells and macrophages and local production of pro-inflammatory cytokines including IL-1β, TNF-α, and IFN-γ may destroy pancreatic islet β-cells (Khodabandehloo et al., 2016). Other related cellular pathological processes including apoptosis, mitochondrial oxidative damage, and endoplasmic reticulum stress may also be important in contributing pancreatic islet β-cell destruction and insulin deficiency. In the periphery, chronic inflammation may play a critical role in the development of insulin resistance in a wide range of tissues and organs. Adipose tissue is a prime example where residing macrophages and adipokines initiate metabolic inflammation which, in turn induces insulin resistance. The pro-inflammatory axis, consisting of NF-kB and its upstream kinase IKKβ, has also been identified as a critical mediator responsible for metabolic inflammation in type-2 diabetes and other metabolic abnormalities (Nandipati et al., 2017).

Inflammation modulation by caloric restriction and physical exercise

Caloric restriction, in the absence of malnutrition, is known to delay ageing through multiple mechanisms (Ye & Keller, 2010). While maintenance of proper cellular redox balance and suppression of oxidative damage to lipids, DNA, and proteins are thought to be the underlying mechanisms, great attention has recently been devoted to investigations into CR's anti-inflammatory properties. CR has been shown to attenuate the age-related increase of systemic levels of inflammatory mediators including TNF-α, IL-1β, IL-6, and CRP (Phillips & Leeuwenburgh, 2005; Kalani et al., 2006). For example, age-associated rise of plasma TNF-a is shown to be attenuated by lifelong, moderate (40%) CR in rats (You et al., 2007). Moreover, Kalani et al. (Kalani et al., 2006) have demonstrated the capacity of long-term 40% CR to attenuate the increase in circulating levels of CRP with age, reporting even greater reduction by combining mild (8%) CR with lifelong, voluntary exercise. Taken together, these studies suggest that the age-delaying effect of CR is due, at least in part, to its inflammation modulating properties.

Exercise training is well-known for its health benefits. The impact of physical activity on inflammation can vary, depending on the frequency, intensity, volume of exercise, as well as individual’s endurance capacity. For example, strenuous exercise may increase local and systemic production of pro-inflammatory cytokines, likely resulted from muscle damage and subsequent inflammation. However, moderate regular physical activity has been shown to reduce levels of TNF-α, IL-6, and CRP in healthy older adults (Colbert et al., 2004). In addition, aerobic exercise can decrease serum IL-6 levels and increase levels of IL-10, a potent anti-inflammatory cytokine, in healthy older men (Jankord & Jemiolo, 2004). In
Inflammation and its role in ageing and disease

old rats, lifelong, voluntary wheel running reduces plasma levels of CRP, but not those of IL-6 (You et al., 2007); a four-week exercise training by treadmill running has led to reduced expression of TNF-R1 in the extensor digitorum longus muscle (Marzetti et al., 2008).

While mechanisms underlying the beneficial effects of CR and physical exercise are likely complex and not fully elucidated, their anti-inflammatory properties indicate CR and exercise training as two well-known interventions that can mitigate age-related chronic inflammation and its adverse health impact. They also suggest the potential for future development of novel therapeutic modalities that target age-related chronic inflammation for the prevention and treatment of age-related diseases, and even delaying ageing itself.

Conclusions

Age-related chronic inflammation, like typical acute and chronic inflammatory responses, has complex basic biology involving numerous inducers, sensors, mediators, and effectors. It differs from traditionally defined inflammation in that it is a low-grade, systemic, unresolved, and smouldering chronic inflammation occurring during ageing. Its clinical and biological significance is emphasized by its role in the pathogenesis of almost all age-related diseases, and perhaps in the ageing process itself. Frailty and late-life function decline, neurodegenerative diseases, cardiovascular diseases, and age-related metabolic diseases are only a few broadly defined categories of age-related conditions as examples. Age-related chronic inflammation has been shown to play an important role in the pathogenesis and progression of cancer, anaemia, kidney diseases, and many other conditions in older adults. It also has detrimental effects on wound healing, responses to therapies and vaccination, and functional recovery among older patients.

It is worthwhile noting that the development of age-related chronic inflammation as well as its progression and adverse impact can be very different among older individuals due to significant heterogeneity of the older adult population. Clinically, inflammatory markers such as CRP and IL-6 levels have increasingly been incorporated as routine laboratory parameters for diagnosis and monitoring of CVD and other chronic conditions. Whether any intervention specifically targeting age-related chronic inflammation will yield health benefit with minimal or manageable side effects for older patients is currently unknown. The anti-inflammatory properties of CR and physical exercise are worthwhile paying attention to as they may point to the possibility for future development of effective interventions to prevent or delay age-related chronic inflammation and mitigate its adverse health impact for older adults.
Inflammation and its role in ageing and disease

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Inflammation and its role in ageing and disease


Inflammation and its role in ageing and disease


