Chapter 4
Chronic Inflammation and Aging (Inflammaging)

Aging is an inherent mode of action present in all living cells (Campisi et al. 2019). Indeed, organ functions decrease with age. Despite the interactions between the age-related diseases and the aging process require further elucidation, most of the studies revealed that aging is implicated in the development of many age-related diseases (Franceschi et al. 2018; Tan et al. 2018a; Krisko and Radman 2019). One of the most common aspects of the inflammation hypothesis of aging is that age-related diseases undergo several pathways related to the inflammatory process, which may lead to the progression and development of a variety of age-related diseases (DeBalsi et al. 2017). For instance, many age-related diseases including arthritis, osteoporosis, dementia, CVD, cancer, metabolic syndrome, diabetes have been recognized as inflammatory disorders (Tan et al. 2015; Franceschi et al. 2018; Tan and Norhaizan 2021) (Fig. 4.1).

Mitochondrial and free radical theories are the two most common theories related to aging. These theories described that a vicious cycle is produced within the mitochondria, while the ROS is markedly generated and thus promotes the damage potential (Romano et al. 2010). Oxidative stress is existing in all living beings at the system, tissue, cellular, molecular, and genetic levels. This is often manifested as a progressive increase or accumulation of detrimental changes in tissues and cells with advancing age (Knupp and Miura 2018). It has been demonstrated that ROS levels increased with age and usually accumulates in major organ systems such as skeletal muscle, brain, heart, and liver (Olgar et al. 2018; Zhou et al. 2018; Hunt et al. 2019; Stefanatos and Sanz 2018) either due to reduced detoxification or increased production. In this regard, aging is considered as a progressive reduction in the biological function of the tissues and thereby increased the vulnerability to the diseases (Kregel and Zhang 2007). The widely accepted theory, namely "oxidative stress hypothesis", describes that increases in ROS resulted in pathological conditions and observable signs related to aging as well as functional alterations, and ultimately death (Hagen 2003). Despite ETC damage and mitochondrial DNA

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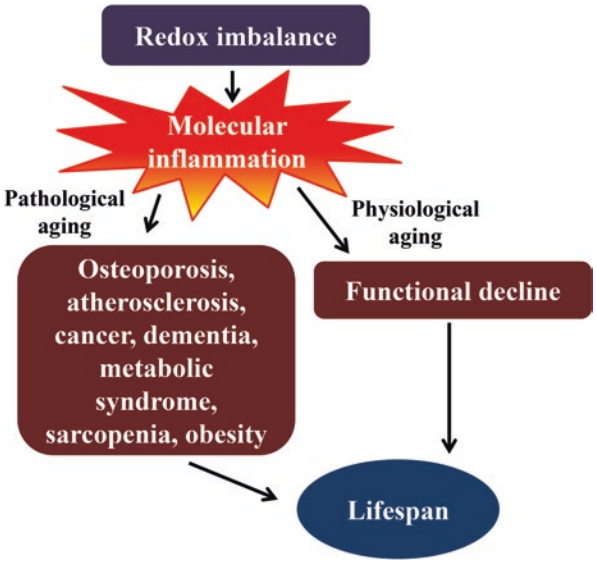

Fig. 4.1 The effects of inflammation in pathophysiological process

damage that may responsible for aging, the stimulation of redox-sensitive transcriptional factors or mediation of cellular signal response to stress by age-related oxidative stress upregulate the proinflammatory gene expression, and thereby enhances the ROS levels (Kregel and Zhang 2007).

4.1 Sources of Chronic Inflammation during Aging

Chronic, low-grade inflammation is thought to be a predominant contributor to a broad spectrum of natural processes and age-related pathologies in aging tissues, for instance, musculoskeletal and nervous systems (Libby and Kobold 2019; Cervo et al. 2020; Lin et al. 2020). In general, some tissues in the elderly are chronically inflamed (Gnani et al. 2019; Ziegler et al. 2019). Inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-1beta (IL-1β), and interleukin-6 (IL-6) has been recognized as one of the contributor to diminish the anabolic signaling cascade such as erythropoietin and insulin signaling pathway, and thereby leading to an increased risk of developing sarcopenia (Beyer et al. 2012). Figure 4.2 summarizes the sources of chronic inflammation in aging.

Aging promotes the production of COX-derived reactive species and enhances the release of inducible nitric oxide synthase (iNOS), COX-2, TNF-α, IL-6, and IL-1β (Wojdasiewicz et al. 2014; Begg et al. 2020). Other proinflammatory proteins, for instance, P-, E-selectin, intercellular cell adhesion molecule-1 (ICAM-1), and VCAM-1 are also upregulated during the aging process (Zou et al. 2006). The

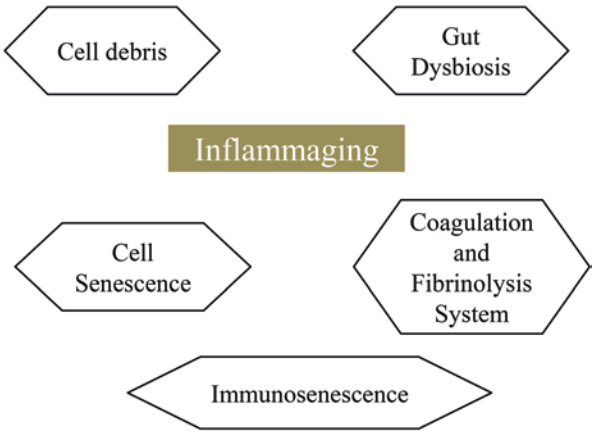

Fig. 4.2 Sources of chronic inflammation in aging

nuclear factor-kappa B (*NF-κB*) transcriptional activity is regarded as the master regulator of the inflammatory process and can be stimulated by oxidative stimuli (Park and Hong 2016; Liu et al. 2017). The stimulation of *NF-κB*-dependent genes is a key transcriptional factor for the systemic inflammatory process (Jakkampudi et al. 2016). During activation, proinflammatory genes encode proinflammatory proteins, for instance, chemokines, growth factors, and cytokines (Drago et al. 2015). The NF-κB activity is mediated by upstream signaling, for instance, mitogen-activated protein kinase (MAPK) and IκB kinase (IKK). The IκB subunits of NF-κB/IκB are phosphorylated by activated IKK complexes and thus stimulating the degradation of IκB, which subsequently lead to the activation of NF-κB. IKK activity is activated by NF-κB during aging (Tilstra et al. 2011), and subsequently promotes the activation of p38 MAPK, c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK) activities that control *NF-κB*-dependent gene expression during an inflammatory response (Jnawali et al. 2014). A previous study revealed that aging promotes p38 MAPK, JNK, and ERK signaling pathways with an increase in ROS production (Ito et al. 2010).

Under normal circumstances, stimulation of NF-κB in response to oxidative stimuli is short-lived, and the reaction is halted with resolution. Nonetheless, when the input signal is not well-maintained during aging, chronic proinflammatory conditions may create a conducive environment for many chronic diseases (Rea et al. 2018). Several NF-κB-induced proteins such as COX-2, IL-6, and TNF-α are potent NF-κB activators that form an auto-activating loop (Oeckinghaus and Ghosh 2009). Substantial studies evaluated the changes of redox-sensitive transcriptional factors such as NF-κB in rodent models (Hansen et al. 2002; Kim et al. 2002; George et al. 2009). The study revealed that old rodents have consistently expressed high NF-κB activities in a variety of tissues, for instance, brain, kidney, liver, and heart compared to the young rodents (Korhonen et al. 1997; Radák et al. 2004; Ungvari et al. 2007; Lim et al. 2012). Data from the human study have also demonstrated that

circulating levels of proinflammatory cytokines such as IL-1ra, IL-6, and TNF-α are increased during aging (Bruunsgaard 2006). In addition, aging is also linked to the high inflammatory cell counts (monocytes and neutrophils) and increased levels of C-reactive protein (CRP) (Ritzel et al. 2018; Wong and Wagner 2018; Álvarez-Sánchez et al. 2020). High IL-6 plasma levels were shown a greater likelihood of morbidity, disability, and mortality in the elderly (Puzianowska-Kuznicka et al. 2016). High levels of CRP, IL-1β, and IL-6 are linked to many diseases in the elderly (Ng et al. 2018; Poole and Steptoe 2020). Plasma levels of TNF-α are positively linked to the high levels of CRP and IL-6, implied that an interrelated stimulation of inflammatory cascade (Oe et al. 2015).

Numerous studies have evaluated the relationship between insulin resistance and obesity, but there is no definitive resolution to date. A previous study showed that inflammation could be a possible underlying link between these metabolic ailments (Fiordelisi et al. 2019; Greten and Grivennikov 2019; Diedisheim et al. 2020). Excessive caloric consumption increased adiposity and thus leads to macrophage infiltration into adipose tissues that promote local chronic inflammation which potentiates insulin resistance (Poli et al. 2017; Tan et al. 2018b). Overexpression of *Mcp1* promotes insulin resistance, inflammation, and macrophage infiltration (Kanda et al. 2006; Patsouris et al. 2014; Gogh et al. 2016). Furthermore, knockout of *Mcp1* and its receptor (*Ccr2*) impairs migration of macrophages, and thus increases insulin sensitivity and reduces inflammation (Tamura et al. 2008; Sawyer et al. 2014).

4.1.1 Immunoglobulin or Cell Debris Production

Immunoglobulin or debris accumulation caused by an inappropriate cell elimination system in aging, which induces innate immune activity stimulation and thereby leading to inflammation (Sanada et al. 2018). In particular, glycosylation is the most often posttranslational modification of protein (Carnino et al. 2020). The protein-linked sugar chain plays a crucial role in the "fine-tuning" of molecules and cells (Ohtsubo and Marth 2006; Dall'Olio et al. 2013). High-throughput studies of the N-glycome, a sugar chain N-linked to asparagine, demonstrated a potential biomarker for natural aging, for instance, N-glycans devoid of galactose residues on the branch, in human studies (Parekh et al. 1988; Vanhooren et al. 2007; Ruhaak et al. 2011). This agalactosylated biantennary structure primarily decorates Asn297 of the Fc portion of IgG (IgG-G0) and is present in patients with inflammatory/autoimmune diseases or progeria syndromes (Dall'Olio et al. 2013). Accelerated aging syndromes or progerias are partially recapitulated normal aging (Dreesen and Stewart 2011). Progerias are predominantly triggered by defects in DNA repair systems or an alteration of the nuclear envelope (Burla et al. 2018). Indeed, IgG-G0 shows a proinflammatory effect via a few mechanisms including formation of autoantibody aggregates, binding to Fcγ receptors, and lectin pathway of complement

(Gudelj et al. 2018). Further, the age-related production of IgG-G0 can stimulate the immune system and hence result in inflammaging (Barrientos et al. 2020). By contrast, mitochondrial dysfunction has also drawn attention among scientists (Manolis et al. 2021). Mitochondria-derived damage-associated molecular patterns (DAMPs) such as cell-free circulating mitochondrial DNA have been extensively studied due to the involvement in chronic diseases and aging (Zhang et al. 2010; Dall'Olio et al. 2013). Through their bacterial ancestry, these molecules may promote the inflammatory response via interaction with receptors similar to those involved in pathogen-related response (Sanada et al. 2018).

4.1.2 The Microbiota and Gut Mucosa in Elderly

The ability of gut mucosa to sequester bacteria deteriorates with age (Shoemark and Allen 2015). Periodontal disease has been reported to cause chronic low-grade inflammation (Loos and Van Dyke 2020). The study found that the diversity of gut microbiota is reduced in older people (Claesson et al. 2011; Kinross and Nicholson 2012). In particular, the anti-inflammatory microbiota, for example, *F. prausnitzii*, *Bifidobacterium* spp., and *Clostridium* cluster XIVa, are reduced in the elderly (Toward et al. 2012). A study by Okada et al. (2009) further supported that the *Bifidobacterium* species is negatively linked to the serum IL-1β and TNF-α levels. By contrast, pathogenic and inflammatory microbiota, such as *Enterobacter* spp., *Enterococcus* spp., *Staphylococcus* spp., and *Streptococcus* spp., are increased with age (Toward et al. 2012). Alteration in gut microbiota diversity may increase the susceptibility to infectious agents by pathobionts colonization (Mosca et al. 2016).

4.1.3 Cell Senescence

Cellular senescence is an irreversible cell cycle arrest mediated by a few mechanisms such as inflammatory cytokines, mitogen stimuli, genotoxic stress, and telomere shortening, which can lead to the stimulation of the cyclin-dependent kinase inhibitor p16 and/or p53 tumor suppressor (de Magalhães and Passos 2018).

Senescence is a cellular response to damage and stress (Franceschi and Campisi 2014). It was evident that the number of senescent cells is increased with age, in which these organs secrete many inflammatory cytokines and produce low-grade inflammation. Senescent cells are linked to age-related diseases or aging through the secretion of proinflammatory cytokines that alter the function of normal cells or the tissue microenvironment (Baker et al. 2011). The phenotype of senescent cells is known as senescence-associated secretory phenotype (SASP), which is suggested as the primary origin of inflammaging in age-related diseases and aging (Sanada et al. 2009; Tchkonia et al. 2013; He and Sharpless 2017). The previous study showed that the elimination of senescent cells in prematurely aged mice ameliorates

the progression of age-related diseases (Coppé et al. 2010). Such findings indicate that the mediation of proinflammatory pathways linked to the acquisition of SASP, reprogramming of senescent cells, and elimination of senescent cells could be used as a potential anti-aging approach for extending healthspan and ameliorating the metabolic ailments (van Deursen 2014).

4.1.4 Immunosenescence

Immunosenescence is characterized by the chronic inflammatory response, due to the age-related dysregulation of an innate immune system (Shaw et al. 2013). Immunosenescence impairs wound healing, reduces the response to vaccinations, and increases the susceptibility to malignancy (Aw et al. 2007; Gruver et al. 2007). Aging modifies the immune system and thus contributes to inflammaging (Fulop et al. 2018). Indeed, the immunosenescence process can be accelerated by chronic inflammatory disease (Barbé-Tuana et al. 2020). The mechanisms underlying the persistent aging-associated basal inflammation are not fully understood, but it is hypothesized that the changes in functions and numbers of innate immune cells contribute to these phenomena. Most of the studies so far indicated that unusual downstream signaling pathway of pattern recognition receptors (PRRs) stimulation, activation of PRRs by endogenous ligands related to cellular damage, and changes in the PRRs levels may lead to the induction of chronic cytokine secretion (Hung and Suzuki 2017; Zhu et al. 2019). In this regard, dysregulation of immunological imprinting modulated by innate immunity as well as cell senescence may contribute to chronic low-grade inflammation. In addition, adaptive immunity declines with age; while innate immunity showed minute changes in mild hyperactivity (Santoro et al. 2018). However, the innate immune response might activate when adaptive immunosenescence progresses. Collectively, the age-related changes could be attributed to the intrinsic changes in immune cells and lifelong exposure to pathogens and antigens (Stephenson et al. 2018).

4.1.5 Coagulation and Fibrinolysis System

Activation coagulation and fibrinolysis system in the elderly increased inflammation by modulating the protease-activated receptor (PAR) (Chu 2010; Hess and Grant 2011; Sanada et al. 2016), and thereby lead to an increased risk for lung fibrosis and atherosclerosis (Biagi et al. 2011). Coagulation is considered as part of the inflammation system. The inflammatory process is linked to the potentially aggravating phenomenon of obesity (Tan et al. 2018b). Age-related obesity is predominantly due to the increased adiposity, especially visceral fat deposits, during aging via redistribution of fat deposits with age (Villarroya et al. 2018). Indeed, most of the proinflammatory cytokines are generated by resident macrophages and

adipocytes in adipose tissues, and thereby leading to systemic inflammation (Makki et al. 2013). Elevation of proinflammatory status is more likely to increase the susceptibility of several age-related diseases (Ackermann et al. 2020; Tu et al. 2020; Tahir et al. 2021). For instance, osteopenia and sarcopenia are characterized as the normal aging processes, which are good examples of the involvement of inflammation in the normal aging process to pathogenesis (Fig. 4.1).

Research evidence indicates that plasma concentrations of coagulation factor IX, VIII, VII, and V were increased in healthy subjects in conjunction with the physiological processes of aging (Chu 2011; Favaloro et al. 2014). The fibrinogen levels (coagulation factor I), a predominant risk factor for thrombotic disorders, are increased with age (Gligorijević et al. 2018). In particular, the coagulation factor X is overexpressed in human atherosclerotic plaques, such as inflammatory cells, smooth muscle cells, and endothelial cells (Sanada et al. 2017). Based on the evidence, increased plasma levels and local coagulation factors during physiological aging may increase the risk of CVD progression in the elderly. The previous study showed that the direct coagulation factor rivaroxaban, Xa inhibitor, decreased the risk of the composite endpoint of death from stroke, myocardial infarction, and CVD in patients with acute coronary syndrome (Mega et al. 2012). Despite the molecular mechanisms underlying the coagulation factor and reduced risk of CVD require further elucidation, most of the experimental studies indicate that stimulation of coagulation cascade following fibrinogen activation may elevate the thrombosis (Palta et al. 2014). Further, increased levels of thrombin and coagulation factor Xa may improve the inflammatory response via modulation of PAR-1/2 signaling (Spronk et al. 2014). Notably, PAR-1/2 signaling triggered by fibrinolytic factor plasmin and coagulation factor Xa (FXa) was shown to elevate the insulin-like growth factor binding protein-5 (IGFBP-5) levels (Kamio et al. 2008; Carmo et al. 2014; Sanada et al. 2016, 2017). A study by Kojima et al. (2012) found that IGFBP-5 mediates IL-6 expression to trigger ROS generation, and thereby leading to the DNA damage and senescence of fibroblast cells. Further, IGFBP-5 also stimulates a fibrotic phenotype by stimulating nuclear early growth response-1 (EGR-1) translocation and MAPK signaling that interacts with IGFBP-5 and upregulates inflammatory and fibrotic transcriptional activity (Yasuoka et al. 2009). In addition, activation of FXa in endothelial progenitor cells, endothelial cells, and smooth muscle cells promote cellular senescence by modulating the EGR-1-IGFBP-5-p53 signaling pathway (Sanada et al. 2016). This finding implies that cell senescence, hypercoagulability, and inflammaging may share a common pathway mediated by IGFBP-5 signaling. Intriguingly, some research has emerged to suggest that IGFBP-5- and FXa-positive areas were distributed in the human atherosclerotic plaques (Sanada et al. 2017). Collectively, locally produced coagulation factor Xa in atherosclerotic plaques may promote cellular senescence with SASP and trigger IGFBP-5 levels (Sparkenbaugh et al. 2014). Because aging is a complex mechanisms results from the epigenetic, genetic, and environmental factors, further studies focused on interventions that selectively damage senescent cells, for instance, “senolytic therapies” in the aging host may enhance the therapeutic approach (Roos et al. 2016; Farr et al. 2017; Lehmann et al. 2017; Collins et al. 2018).

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