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Age and Age-related Diseases: Role of Inflammation Triggers and Cytokines

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Author contribution statement

Authors and Contributions

IR conceived and designed the outline of the manuscript.

All authors IR, DG, VMcG, SMcN, DA and OR contributed to the manuscript draft.

All authors contributed to the revising of the manuscript and approved the manuscript prior to submission.

Keywords

Ageing, age-related diseases, Inflamm-aging, redox, Senescence SASP, Autophagy, Inflammasomes, Cytokine dysregulation, Inflammation resolution

Abstract

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Cytokine dysregulation is believed to play a key role in the remodeling of the immune system at older age, with evidence pointing to an inability to fine-control systemic inflammation, which seems to be a marker of unsuccessful aging. This reshaping of cytokine expression pattern, with a progressive tendency toward a pro-inflammatory phenotype has been called 'inflamm-aging'. Despite research there is no clear understanding about the causes of 'inflamm-aging' that underpin most major age-related diseases including atherosclerosis, diabetes, Alzheimer's disease, rheumatoid arthritis, cancer and aging itself.

While inflammation is part of the normal repair response for healing, and essential in keeping us safe from bacterial and viral infections and noxious environmental agents, not all inflammation is good. When inflammation becomes prolonged and persists, it can become damaging and destructive. Several common molecular pathways have been identified that are associated with both aging and low-grade inflammation.

The age-related change in redox balance, the increase in age-related senescent cells and SASP and the decline in effective autophagy that can trigger the inflammasome, suggest that it may be possible to delay age-related diseases and aging itself by suppressing pro-inflammatory molecular mechanisms or improving the timely resolution of inflammation. Conversely there may be learning from molecular or genetic pathways from long-lived cohorts who exemplify good quality aging.

Here we will discuss some of the current ideas and highlight molecular pathways that appear to contribute to the immune imbalance and the cytokine dysregulation, which is associated with 'inflammageing' or parainflammation. Evidence of these findings will be drawn from research in cardiovascular disease and rheumatoid arthritis, two age-related diseases

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1 **Age and Age-related Diseases: Role of Inflammation**
2 **Triggers and Cytokines**

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1 **Abstract 262**

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3 Cytokine dysregulation is believed to play a key role in the remodeling of the immune
4 system at older age, with evidence pointing to an inability to fine-control systemic
5 inflammation, which seems to be a marker of unsuccessful aging. This reshaping of
6 cytokine expression pattern, with a progressive tendency toward a pro-inflammatory
7 phenotype has been called ‘inflamm-aging’. Despite research there is no clear
8 understanding about the causes of ‘inflamm-aging’ that underpin most major age-
9 related diseases including atherosclerosis, diabetes, Alzheimer’s disease, rheumatoid
10 arthritis, cancer and aging itself.

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12 While inflammation is part of the normal repair response for healing, and essential in
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14 not all inflammation is good. When inflammation becomes prolonged and persists, it
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16 been identified that are associated with both aging and low-grade inflammation.

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18 The age-related change in redox balance, the increase in age-related senescent cells
19 and SASP and the decline in effective autophagy that can trigger the inflammasome,
20 suggest that it may be possible to delay age-related diseases and aging itself by
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22 resolution of inflammation. Conversely there may be learning from molecular or
23 genetic pathways from long-lived cohorts who exemplify good quality aging.

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25 Here we will discuss some of the current ideas and highlight molecular pathways that
26 appear to contribute to the immune imbalance and the cytokine dysregulation, which
27 is associated with ‘inflammageing’ or parainflammation. Evidence of these findings
28 will be drawn from research in cardiovascular disease and rheumatoid arthritis, two
29 age-related diseases

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36 **Key words: Aging; Age-related diseases; Inflamm-aging; Redox; Autophagy;**
37 **Senescent SASP; Inflammasome; Pro-inflammatory cytokines, Anti-**
38 **inflammatory cytokines; Inflammation resolution**

1 **1. Introduction**

2 The inflammatory response must be tightly regulated to ensure effective immune
3 protection. It is a dynamic network that is continuously remodelling throughout each
4 person's life as a result of the interaction between our genes, life-styles and
5 environments (1-3). Infections and tissue damage from the external environment and
6 our personal internal response to stress can act as triggers to initiate the inflammatory
7 defense response. While inflammation is part of the normal repair response for
8 healing, and essential in keeping us safe from bacterial and viral infections and
9 noxious environmental agents, not all inflammation is good. When inflammation
10 becomes prolonged and persists, it can become damaging and destructive (4). It is
11 essential that inflammation is tailored to the initiating stress and resolves in a timely
12 and controlled way, to avoid pathology associated with chronicity.

13
14 The cytokine network is a highly complex system of immune molecular messengers,
15 with multiple layers of activation and control mediated through soluble receptors,
16 receptor antagonists, diverse serum mediators as well as gene polymorphisms (5).
17 Proteomic methods measuring cytokine production and expression have demonstrated
18 further layers of complexity and control in cytokine production and expression
19 involving long coding RNAs, siRNAs and miRNAs, which make for challenging
20 interpretation of cytokine production and control in the inflammatory process (6).
21 Many cytokines are able to act in more than one-way or paradoxically at different
22 times, and many act in feedback loops with the ability to auto-control their own
23 production (7). Cytokine expression is also influenced by local cellular
24 microenvironments, suggesting that multiple pathways exist to achieve homeostatic
25 immunologic control and effectiveness, or conversely accentuation of chronic
26 immune activation. However what seems clear is that mirroring other body systems,
27 the homeostatic control, titration and modulation of immune responsiveness becomes
28 more fragile and less tightly focused with increasing age. This loosening of the
29 cytokine balance between the pro-inflammatory and anti-inflammatory control or
30 resolving mechanisms, or inflamm-aging (8,9), is a characteristic feature of both
31 aging and aging-related diseases. This kind of inflammation is similar to that
32 originally described as 'parainflammation' as described by Medzhitov (10).

33
34 Today there is increasing recognition that inflammation is a common molecular
35 pathway that underlies in part, the pathogenesis of diverse human diseases ranging
36 from infection, to immune-mediated disorders, cardiovascular pathology, diabetes,
37 metabolic syndrome, neurodegeneration and cancer, to aging itself (4,11,12).
38 Although there is no exact understanding about the causes of 'inflamm-aging', a
39 common finding seems to involve a dysregulation of the cytokine network and its
40 homeostasis. Several common molecular pathways have been identified that seem to
41 be associated with both aging and low-grade inflammation. Excess oxidative stress
42 and DNA damage trigger the inflammasome, stimulating NF- κ B and the IL-1 β -
43 mediated inflammatory cascade. Autophagy, the cell machinery process that removes
44 damaged proteins and large aggregates, is also slowed up at older age and in age-
45 related disease, causing damaged material to accumulate and reduce cellular
46 efficiency. Senescent cells increase with age and in age-related diseases, and the
47 associated secretome or senescence-associated secretory phenotype (SASP) produces
48 a self-perpetuating intracellular signaling loop and inflammatory cascade involving
49 the NF- κ B, IL-1 α , TGF- β , IL-6 pathway, that participates in the pro-inflammatory
50 milieu. The molecular processes that damp down inflammation include the resolvin

1 family of bioactive molecules, which have been much less evaluated in aging or age-
2 related disease, but are important participants in effective and timely inflammation
3 resolution.

4
5 Here we will discuss some of the current ideas and highlight molecular pathways that
6 appear to contribute to the immune imbalance and the cytokine dysregulation, which
7 is associated with 'inflamm-aging' or parainflammation. Evidence of these findings
8 will be drawn from research in several age-related diseases including cardiovascular
9 and neurodegenerative disease, rheumatoid arthritis and oncological cancers.

10 11 **2. The inflammation pathway to resolution**

12
13 Inflammation is classically induced when innate cells detect infection or tissue injury.
14 The pattern-recognition receptors (PRRs) on immune cells sense 'danger' from
15 protein-associated molecular patterns (PAMPs) associated with pathogens, or from
16 danger-associated molecular patterns (DAMPs) triggered by a wide range of host-
17 derived endogenous stress signals. DAMPs are molecules such as ATP, the cytokine
18 IL-1 α , uric acid and some cytoplasmic and nuclear proteins, which are released from
19 damaged cells during necrosis and contribute to sterile inflammation (Fig 1). There
20 have been suggestions that the extended IL-1 cytokine family (IL-1 α , IL-1 β , IL-18,
21 IL-33, IL-36 α , IL-36 β , and IL-36 γ) might also act as DAMPs and stimulate necrosis-
22 initiated sterile inflammation, as well as amplify inflammation in response to
23 infection-associated tissue injury (13).

24
25 Members of the Toll-Like Receptor (TLR) family are the major pattern-recognition
26 receptors (PRRs). They are expressed on monocytes, macrophages, neutrophils and
27 dendritic cells, and on some lymphocytes and they respond rapidly to the 'danger'
28 response. The cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) pathways of
29 arachidonic acid (AA) metabolism (14,15) produce highly pro-inflammatory lipid
30 mediators responsible for the classical signs of inflammation - redness, heat, pain,
31 swelling and loss of function, with the aim of removing the injurious and noxious
32 stimuli. A third pathway involves the cytochrome 450 pathway of arachidonic acid
33 metabolism and P450 epoxygenases and hydroxylases that produce both
34 vasoconstrictor and vasodilatory effects in blood vessels and other tissues (Fig 2). The
35 reactive biolipid molecules synthesized from arachidonic acid (AA) are; the
36 prostanoids - prostaglandins, (PGs), prostacyclins (PGIs) and thromboxanes (TXs)
37 produced by the action of cyclooxygenase 1 and 2 (COX 1 & 2); the leukotrienes
38 (LTs), hydroxyeicosatetraenoids (HETEs) and lipoxins (LXs) produced by the action
39 of the 5-12- and 15-lipoxygenase (5/1/15-LOX) enzymes and; the P450 epoxygenase
40 generates HETEs and deoxyeicosatrienoids (epoxides) (16). Prostaglandins act to
41 amplify the inflammatory response through enhancing the inflammatory cytokine
42 cascade, upregulating the innate response to DAMPs and PAMPs, activating subsets
43 of T helper cells, recruiting macrophages associated with chronic inflammation and
44 increasing cytokine expression from cytokine inflammatory genes. Additional factors
45 such as histamine, pro-inflammatory cytokines and chemokines amplify the response
46 further and make the vascular endothelium increasingly leaky. The increase in
47 vascular permeability combined with the expression of cellular adhesion molecules
48 (ie selectins and integrins) allows neutrophils, the first responders, to transmigrate
49 across post-capillary venules to the sites of injury or microbial invasion. Together this
50 increases polymorphonuclear (PMN) neutrophil chemotaxis and allows PMNs to

1 transmigrate along chemotactic gradients in order to maximize phagocytosis and
2 killing of pathogens, and deal with the 'danger' signal effectively.

3
4 As the acute inflammatory cascade develops to manage the 'danger' signal, it is
5 essential that a controlled resolution commence, so that immune homeostasis returns
6 in an organized manner. If the inflammatory response does not shut down in a timely
7 way, the inflammation cascade becomes chronic and smoldering. Lipid mediators
8 derived from polyunsaturated fatty acids are now recognised to orchestrate the
9 resolution of inflammation (17). At the peak of inflammation, the eicosanoids that
10 initiated the inflammation undergo a class-switch so that they become the molecules
11 that activate resolution, demonstrable through the clinical signs of-removal of
12 symptoms, relief of pain, restoration of function, regeneration of damaged tissues and
13 return to health. The so called specialized pro-resolving mediators (SPMs) are key to
14 resolving inflammation and include lipoxins derived from the 5-lipoxygenase (5-
15 LOX) arm of the arachidonic acid pathway; the E-group of resolvins derived from
16 dietary-derived eicosapentaenoic acid (EPA); the D-group of resolvins from dietary-
17 derived docosahexaenoic acid (DHA); and protectins (PD), and maresins (MaR) (17-
18 19) (Fig 2). The lipid class-switch starts early in inflammation and is initiated by
19 lipoxins LXA4 and LXB4, and considered to be produced by platelets when they
20 begin to aggregate with PMNs at the sites of inflammation (18).

21
22 After class-switching of the lipid molecules has occurred, specialized pro-resolving
23 mediators are produced. Pro-resolving monocyte-derived macrophages begin to clear
24 PMNs from the site of injury by a process called efferocytosis that removes apoptotic
25 neutrophils, microbes and necrotic debris. As resolution progresses, monocytes and
26 macrophages, change from a pro-inflammatory (M1) to a pro-resolving phenotype
27 (M2) by genetic and epigenetic reprogramming (20-22). Recent investigations suggest
28 that SPMs, particularly the D-series resolvins (resolving D1 and resolving D2) and
29 maresin 1 modulate adaptive immune responses in human peripheral blood
30 lymphocytes. These lipid mediators reduce cytokine production by activated CD8+ T
31 cells and CD4+ T helper I (TH1) and TH 17 cells, but do not modulate T cell
32 inhibitory receptors or reduce their ability to proliferate (23,24). Other reports show
33 an increase in plasma cell differentiation and antibody production that supports the
34 involvement of SPMs in the humoral response during late stages of inflammation and
35 pathogen clearance (25). The anti-inflammatory cytokines IL-10, and IL-37 a member
36 of the IL-1 family, together with TGF- β that is released from monocytes and platelets,
37 are important contributors to damping down the inflammation. The soluble receptors
38 TNFR and IL-1R also limit inflammation in acting as decoy receptors, by binding to
39 and neutralizing their respective cytokines, and inhibiting the biological activity.
40 Additional anti-inflammatory mechanisms include stress hormones, particularly
41 corticosteroids and catecholamines and negative regulators such as microRNAs -
42 MiR-146 and MiR-125 (26).

43
44 The local environment and context also play an important role in the production and
45 function of SPMs, which have both autocrine and paracrine actions. Inflammation
46 resolution is likely to depend on prompt class-switching to pro-resolving lipid
47 mediators, effective apoptosis and efferocytic clearance of inflammatory cells and
48 debris, timely damping down of pro-inflammatory signals and integrated repair of
49 collateral damage. An imbalance between pro-inflammatory and pro-resolving
50 mediators has been linked to a number of chronic inflammatory diseases (27).

1
2 In normal inflammation SPMs do not compromise host immune competence with
3 examples of pro-resolving mediators increasing survival from infections in mouse
4 models (28,29). The common mechanism by which this occurs appears to be through
5 suppression of the NF- κ B activation in a partly PPAR- γ -dependent manner, with
6 associated downstream signaling and alteration in transcriptomics pathways (30,31).
7 Dysregulation of pro-resolving mediators has been associated with diseases of
8 prolonged inflammation in animal models. A maresin mediator (MaR1) has been
9 shown to have potent anti-inflammatory and pro-resolving actions in a model of
10 colitis, and attenuated inflammation in vascular smooth muscle and endothelial cells
11 (32,33). In human studies, the role of SPMs are being explored in chronic
12 inflammatory diseases such as rheumatoid arthritis (34), in atherosclerosis (27), in
13 cancer (35) and in Alzheimer's disease whereas several SPMs promoted neuronal
14 survival and β -amyloid uptake by microglia in 'in vitro' models in Alzheimer's
15 disease (36,37). However little is known about the pro-resolving mediators in age-
16 related diseases and aging itself. Studies are needed assess whether pro-resolving
17 molecules such as E and D-resolvins and maresins decrease or are less effective in
18 damping down inflammation with increasing age and whether they could contribute to
19 the pro-inflammatory phenotype associated with aging. Already synthetic analogues
20 are in process of development and so the design of pharmacological mimetics of
21 naturally occurring pro-resolving mediators and their receptors offers new potential
22 targets for drug design and the opportunity to investigate the underpinning molecular
23 mechanisms of inflammation resolution.

24
25 Could life-style factors play a role in the epidemic of non-communicable and age-
26 related diseases and the associated pro-inflammatory phenotype? Evidence exists that
27 suggests that the Mediterranean diet which includes olive oil and some omega-3
28 lipids, can ameliorate rheumatoid arthritis (38), may give some protection from atrial
29 fibrillation and myocardial infarction (39), and improves diabetic control (40).
30 Research has also demonstrated a protective role of the Mediterranean diet in
31 gene/Mediterranean diet interactions for the risk TT allele of the TCF7L2-rs7903146
32 gene in stroke risk and mortality (41,42). Improving knowledge about how
33 inflammation shuts down in a timely way is crucial to understanding of how chronic
34 inflammation contributes to aging and age-related diseases. Further studies are likely
35 to be needed to advise if dietary modifications with omega-3 lipids or whether
36 synthetic resolving mimetics are part of the answer.

37 38 **3. Triggers of the inflammation pathway**

39 Several common molecular pathways have been identified that seem to be associated
40 with both aging and low-grade inflammation. These pathways trigger the
41 inflammasome, stimulating NF- κ B and the IL-1 β -mediated inflammatory cascade.

42 43 **3.1. Age-related redox imbalance**

44 A redox imbalance has been long been associated with aging and led to the
45 development of the redox stress hypothesis of aging (43). Redox stress is caused by
46 an imbalance between unregulated and overproduced reactive oxidative species
47 (ROS) that are produced secondary to mitochondrial energy production, active
48 immunological phagocytic processes and the prostaglandin pathway through COX
49 enzyme production. While reactive oxygen species (ROS) are important molecules
50 regulating numerous physiological and pathological processes in the cell, there is now

1 clear evidence that overproduction of ROS is involved in the development of a
2 number of diseases such as Alzheimer's disease, rheumatoid and cardiovascular
3 diseases. Increasing evidence supports the notion that low concentrations of ROS or
4 'primary ROS' are involved in well controlled processes (44) where their effect on
5 reactive target molecules can be reversible, suggesting that 'primary' ROS acts as an
6 important intracellular signalling molecule (45). In contrast, the very active 'OH ROS
7 is less effectively controlled and forms the main damaging type of ROS that is able to
8 react with many macromolecules such as lipids, proteins and nucleic acids. This
9 results in DNA oxidation and cell membrane damage, which contributes to the burden
10 of damaged molecules related to aging and age-related diseases.

11 **3.1.1 Mitochondrial ROS**

12 Mitochondria are highly efficient producers of energy but in doing so they produce
13 ROS. It is estimated that about 90% of intracellular ROS is generated in the
14 mitochondria through the mitochondrial transport chain. The chain of electron flow is
15 considered to leak prematurely between complexes I, II and III leading to the
16 formation of damaging oxidants like $O_2^{\cdot-}$. This ROS has been considered to cause
17 damaging mutations in the mitochondrial genes with increasing age (43). With
18 increasing age, mitochondrial function becomes sluggish and this compromises
19 energy production, which in turn further contributes to mitochondrial dysfunction
20 (46). A vicious cycle develops with age-reduced physical activity producing muscles
21 that become weaker, are infiltrated with fat cells, and show less efficient mitochondria
22 energy production (47). Ischaemia and apoptosis can trigger $O_2^{\cdot-}$ and mitochondria
23 themselves can be damaged by ROS production. Mitophagy, the removal of damaged
24 mitochondria is also reduced as age increases (48). A reduced age-related capacity of
25 the body's anti-oxidative defence systems to mop up free radicals also plays an
26 important role in maintaining the inflammatory background of chronic inflammation
27 (49).

28 **3.1.2 The NADPH pathway of ROS**

29
30 One of the other main producers of ROS is the specialised enzyme group of the
31 nicotamide adenine dinucleotide phosphate (NADPH) oxidases of the NOX family-
32 (NOX1, NOX2, NOX3 NOX4, NOX5, DUOX1 and DUOX2). The NOX family or
33 NADPH oxidases' generate $O_2^{\cdot-}$ or H_2O_2 radicals by transferring electrons from
34 cytoplasmic NADPH or the 'NOX' catalytic subunit to molecular oxygen (50). The
35 ROS produced by these enzymes has an essential function in neutrophils and
36 macrophages as a mechanism for effective bacterial killing and host defence (51,52).
37 When the phagocytes sense an endogenous or exogenous danger signal, the NADPH-
38 oxidase unit translocates to fuse with the plasma membrane to form the phagosome.
39 This generates large amounts of highly reactive ROS called the phagocytic burst that
40 is very effective in killing microbes, though phagosomal pH and ion concentration are
41 also likely to contributors.

42
43
44 Although NOX family of isoenzymes was initially associated with the ROS produced
45 in phagocytes, other members of the NOX family are now known to be involved in a
46 wide range of regulatory functions in many tissues and seem likely to play a role in
47 aging and age-related diseases. Studies in the human vascular system suggest that
48 NOX1, NOX2, and NOX5 promote endothelial dysfunction, inflammation, and
49 apoptosis in the vessel walls, whereas NOX4 by contrast is vasoprotective, by
50 increasing nitric oxide bioavailability (53). NOX enzymes therefore appear to play a

1 role in vascular pathology as well as in the maintenance of normal physiological
2 vascular function. Activation of NOX2 and NOX4 occurs in humans with atrial
3 fibrillation and inhibition of NOX by Angiotension Converting Enzyme (ACE)
4 inhibitor drugs or statins has proved helpful in preventing post-operative atrial
5 fibrillation (54).

6 7 **3.1.3 COX pathways of ROS**

8 The bio lipids are highly reactive substances that contribute to both inflammation and
9 healing and their pathways produce and use ROS signalling. The reaction that
10 converts cyclooxygenase-2 (COX-2) to arachidonic acid and into prostaglandin H₂
11 (PGH₂) by a two-stage free radical mechanism (55) involves superoxide and can
12 contribute to cellular oxidative stress as well as signalling. Other enzymes that
13 generate ROS during arachidonic acid metabolism include the arachidonate 12-
14 lipoxygenase (LOX-12 or ALOX12) and arachidonic -5-lipoxygenase (LOX5 or
15 ALOX5), both of which also activate and induce NADPH-oxidases (56).

16
17 While mitochondrial ROS are traditionally seen as the main source of intracellular
18 ROS and therefore major mediators of ROS-induced damage, the relative contribution
19 of mitochondrial and non-mitochondrial sources of ROS to induction of cellular
20 senescence remain unclear. Both mitochondrial ROS and NADPH-produced-ROS
21 appear to be able to cross signal between each other and mitochondria have
22 significant anti-oxidant capacity, which may act as a cellular redox buffer for
23 NADPH-produced-ROS, suggesting there is tight control and integration of ROS
24 signalling within the cell.

25
26 The cellular systems that protect against ROS include the anti-oxidative defense
27 enzymes, (superoxidase dismutase (SOD), glutathione peroxidase (GPx) and catalase
28 (57), oxidant scavengers (vitamin E, vitamin C, carotenoids, uric acid and
29 polyphenols) and mechanisms to repair oxidant damage to lipids, proteins or DNA.
30 Despite these protective mechanisms, uncontrolled ROS can overwhelm the
31 antioxidant capacity of the cell causing mitochondrial dysfunction (49). Increased
32 ROS production from the various cellular sources stimulates intracellular danger-
33 sensing multi-protein platforms called inflammasomes (58-60). Through the
34 inflammasome the ROS activates NF- κ b which sets in motion the transcription of a
35 cascade of pro-inflammatory cytokines - TNF- α , IL-1 β , IL-2 and IL-6, chemokines -
36 IL-8 and RANTES, and adhesion molecules such as ICAM-1, VCAM and E-Selectin,
37 that are central mediators in the inflammatory response.

38 39 **3.2. Autophagy slowing and aging**

40 Approximately a third of all newly synthesised proteins are formed in the
41 endoplasmic reticulum (ER), where they are folded, modified, sorted and transported
42 to sites where they perform specialised roles. Stressors such as low glucose as in
43 fasting, alterations in calcium levels, low oxygen states, viruses, cytokines and
44 nutrient excess or deficiency can trigger the autophagy pathway with the aim of
45 returning normal homeostasis to the cell.

46
47 Autophagy is a cellular process whereby cellular waste such as modified proteins,
48 protein aggregates and damaged organelles are removed from the cell. It is a tightly
49 controlled process that plays a role in growth and development and maintains a
50 balance between the synthesis, degradation and subsequent recycling of cellular

1 products. Autophagy can be considered a protein and organelle quality control
2 mechanism that maintains normal cellular homeostasis.

3
4 Two major pathways degrade cellular proteins. The ubiquitin-proteasome system
5 (UPS) degrades 80-90% of denatured and damaged proteins. In the ATP-dependent
6 ubiquitin-proteasome system, damaged or misfolded proteins are tagged with a small
7 protein called ubiquitin. Three different sets of enzymes -E1, E2, and E3, identify and
8 categorise proteins in order to link ubiquitin or ubiquitin complexes to the damaged
9 proteins. The ubiquitin-protein complexes pass through the proteasome where they
10 are degraded and discharged as free amino acids into the cytoplasm (Fig 3a).

11
12 The other main pathway is the autophagy system that degrades cytosolic components
13 including larger aggregated proteins and cellular organelles such as mitochondria,
14 peroxisomes and infectious organisms (61). This process involves membrane
15 formation, fusion and degradation (Fig 3b). When autophagy is induced a small
16 separate membrane structure called a phagophore arises in the cytoplasm, which
17 gradually expands to form the autophagosome. The outer membrane of the
18 autophagosome fuses with the lysosome and the autophagosome contents are
19 degraded by lysosomal hydrolases (62). Like the proteasome, the macroautophagy
20 system is stimulated by intracellular and extracellular stress-related signals including
21 oxidative stress. Both proteasome and autophagy produce small polypeptides that help
22 maintain a pool of amino acids and control energy balance in starvation, since
23 recycling amino acids is more energy efficient than *de novo* amino acid synthesis.

24
25 In aging and age-related disease there are gradual reductions of cellular repair
26 mechanisms that lead to the accumulation of damaged molecules, proteins, DNA, and
27 lipids leading to loss of efficient cellular function. The cell's capacity for autophagic
28 degradation also declines with age, and this in itself may contribute to the aging
29 process (63). While both major systems for intracellular protein degradation are
30 slowed up with increasing age, a physical reduction of autophagy-related proteins also
31 contributes to the accumulation of misfolded proteins and damaged macromolecules
32 in the cell. Diseases associated with increased oxidative stress such as cardiovascular
33 and Crohn's disease and obesity also slow up cellular clearing and reduce autophagy,
34 further contributing to disease (64-66).

35
36 The lysosome-autophagy system carries out a wide range of non-specific intracellular
37 degradation and cleaning processes, which include managing pathogens, damaged
38 intra-cellular macromolecules and surface receptors (67-69). Lysosomal dysfunction
39 is associated with many age-related pathologies that reduce lifespan, such as
40 Parkinson's and Alzheimer's diseases (70,71). Senescent cells accumulate abnormal
41 protein aggregates in the cytoplasm, which contribute to neurodegenerative disease
42 (72).

43
44 The dysregulation in autophagy has important effects in the innate immune response,
45 in aging and age-related diseases by influencing inflammasome activity, cytokine
46 secretion, antigen presentation and lymphocyte function (73,74). Under normal
47 circumstances the NLRP3 inflammasome fine-tunes the progression of the innate
48 immune response that it has initiated, by upregulating autophagy activity so that the
49 removal of immune mediators is expedited (74). In aging and age-related diseases the

1 autophagy response becomes blunted, the immune mediators remain active and
2 prolong the inflammatory response (75).

3
4 The ubiquitin-proteasome system and autophagy act synergistically and cooperatively
5 to maintain cellular homeostasis (76). Effective autophagic uptake of dysfunctional
6 mitochondria and efficient lysosomal degradation of damaged aggregated proteins
7 and macromolecules are crucial elements in maintaining tissue homeostasis and good
8 health (77). The decline in the autophagy capacity, that impairs cellular housekeeping
9 in ageing, seems an attractive molecular pathway to target to improve the quality of
10 aging.

11
12 Two groups of drugs, the mammalian target of rapamycin (mTOR) inhibitors and
13 AMP-activated protein kinase (AMPK) activators are promising pharmacological
14 agents which stimulate autophagic degradation (78-80). Other drugs such as the
15 diabetic drug metformin and the oncology agent 5-aminimidazole-4 carboxamide
16 ribonucleoside are pharmacological activators of AMPK, which are soon planned for
17 clinical studies in relation to aging (81-83). A number of substances such as
18 curcumin, berberine and quercetin, regularly contained in normal diets, appear able to
19 mimic the action of AMPK and up-regulate autophagy. The action of AMPK has
20 important anti-inflammatory and immunosuppressive effects (83). By up-regulating
21 autophagic activity AMPK promotes effective clearing of DAMPs and by preventing
22 the activation of the inflammasome, it reduces the triggering of the inflammatory
23 cascade. Further evidence of the anti-inflammatory role comes from research with the
24 AMPK agonist A-769662 that mimics AMPK activity (84). This AMPK mimetic has
25 been shown to suppress inflammatory arthritis in mice and reduce IL-6 expression in
26 serum and arthritic joints, suggesting that targeted AMPK activation could be an
27 effective therapeutic strategy for IL-6-dependent inflammatory arthritis (85).

28
29 Non-pharmacological life-style changes also up-regulate autophagy. One of the best
30 researched is the effect of exercise which improves mitochondrial mitogenesis and
31 stimulates mitogeny, so improving the quality of muscle function and exercise
32 performance, with improvement in the quality of aging (86-88). Furthermore in
33 animal model studies, both modulated caloric restriction and exercise increase
34 autophagy, down regulate endotoxin-induced IL-1 β production, improve the aging-
35 related pro-inflammatory profile and reduce disease symptoms (89,90).

36
37 Further understanding of molecular pathways of the signaling networks underpinning
38 autophagy should help identify other novel drug targets. Important research areas
39 include those that could improve the sensitivity of degradation inhibitors useful to
40 improve anticancer treatment, or new drugs to up-regulate autophagy to maintain
41 good cellular housekeeping, with the potential for improving the quality of ageing and
42 the management of age-related degenerative diseases.

43 44 **3.3. Senescent cells**

45 Senescent cells increase with age and are considered important contributors to the
46 pro-inflammatory phenotype (91). The two major hallmarks of cellular senescence are
47 an irreversible arrest of cell proliferation and production of the pro-inflammatory
48 secretome, called the senescence-associated secretory phenotype (SASP). When
49 replicative senescence was first identified in serial cell passage studies (92), telomere
50 attrition was considered to cause the cellular growth arrest that acted as a mechanism

1 to stop damaged or transformed cells from proliferation and transiting to tumour
2 initiation. Today senescence is considered to have much broader role as both a
3 contributor to damage protection and in the control of cellular growth, or as both a
4 'friend and foe' depending on the cellular context. Senescence together with apoptosis
5 is recognized to play an important physiological role in normal embryonic
6 development, in ongoing tissue homeostasis throughout life (93,94), but is
7 increasingly considered to have a role in causing or exacerbating aging and age-
8 related diseases (93,95-97).

9
10 Senescence is a stress response triggered not only by telomere attrition as originally
11 described (92,98), but also by stress insults such as genomic instability, DNA
12 damage, protein misfolding and/or aggregation and ROS. There is also an association
13 between senescent cells and the dysregulated mitochondrial network and associated
14 metabolic dysfunction that is seen with increasing age (99). Through the SASP the
15 senescent cell has an important influence on the extrinsic microenvironment, which
16 suggests a link between senescence and alterations in intracellular and intercellular
17 communications (95).

18
19 Cells that express senescence markers accumulate with age in some tissues in studies
20 in mice and man (100-102). Senescent cells are found in association with age-related
21 diseases such as atherosclerosis, rheumatoid arthritis (RA), neurodegenerative
22 diseases and cancer (103-106). In rheumatoid arthritis (RA) patients T-cells are
23 described as showing a pre-aged phenotype with apparent loss of CD28 expression
24 that reduces T-cell activation and this in association with reduced RA-related NK
25 surveillance, could allow senescent cells and the associated SASP to persist. In cancer
26 SASP factors promote angiogenesis, cell proliferation and cancer invasiveness. Cells
27 attracted by SASP influence the local microenvironment with the potential to promote
28 tumour invasion and cancer progression (107). Senescent cells have been seen in
29 atherosclerotic plaques (103). Recent data from several laboratories has suggested that
30 both aging and age-related neurodegenerative diseases show an increase in SASP-
31 expressing-senescent cells of non-neuronal origin in the brain, which correlated with
32 changes in neurodegeneration (105).

33
34 The SASP consists of a complex combination of growth factors, proteases,
35 chemokines, matrix metalloproteinases and is particularly enriched in pro-
36 inflammatory cytokines, especially IL-6 (108-110). The SASP-secreting cells respond
37 by switching on a self-perpetuating intracellular pro-inflammatory signaling loop,
38 centered around the NF- κ B, TGF- β , IL-1 α , IL-6 pathway (111-113), with suggested
39 mechanisms related to higher basal phosphorylation and altered threshold signaling
40 (114) or alternative splicing (115). Senescent cells influence other cells by paracrine
41 and bye-stander effects (116). There appears to be multi-level control of senescence
42 and the SASP secretome, which includes the tumour suppressor pathways involved in
43 the cell cycle arrest and the NF- κ B and persistent damage response (DAMP) pathway,
44 involved in triggering transcription of the SASP-related factors (117). Several
45 pathways of investigation suggest that senescent primary human CD8+ T cells use
46 anaerobic glycolysis to generate energy for effector functions and that p38 Mitogen-
47 activated protein kinase (p38 MAPK) blockade may reverse senescence via the
48 mammalian target of rapamycin m-TOR (m-TOR)-independent pathway (118). Low
49 doses of glucocorticoid suppress elements of the SASP in patients with rheumatoid
50 arthritis and improve clinical symptoms (119). Senescent cells effectively recruit the

1 immune system to organise their removal, but with increasing age, removal becomes
2 sluggish or otherwise impaired (120,121).

3
4 It can be argued that the increase in senescent cells with aging reflects either an
5 increase in their rate of generation or a decrease in their rate of clearance because the
6 immune response is attenuated or weakened with aging and less capable of clearing
7 senescent cells (122-124). Senescent cells express ligands for cytotoxic immune cells
8 such as natural killer (NK) cells, and have been shown to be able to be specifically
9 eliminated by the immune system (125,126). Through a proteomics analysis of
10 senescent cell chromatin, the NF- κ B pathway appeared to act as a master regulator of
11 the SASP, with NF- κ B suppression causing escape from immune recognition by (NK)
12 cells (127). Other studies show that processes which eliminate senescent cells with
13 p16(Ink4a)-positive markers, delay age-related pathologies in the mouse model of
14 aging though side-effects can be problematical (128,129). Therapies that specifically
15 recognize and trigger the elimination of senescent cells would seem important ways to
16 enhance the immune system in older people. New methods are in the process of being
17 developed to enhance the immune clearance and autophagy of the increased senescent
18 cell burden in aging and age-related disease (130).

19 20 **3.4 Inflammasome NLRP3**

21 The inflammasomes, intra-cellular multiprotein sensors that recognise danger signals,
22 are likely key players in initiating and maintaining the pro-inflammatory phenotype
23 found associated with aging. The Nod-like receptor 3 (NLRP3) is a major
24 inflammasome sensor for intracellular stress molecules called danger-associated
25 molecular patterns (DAMPs), which together with damaged aggregated proteins that
26 are released from destabilised lysosomes and damaged mitochondria contribute to the
27 cellular stress (ROS) and trigger NLRP3 activation (131). Once activated, the NLRP3
28 inflammasome initiates the inflammatory response cascade by stimulating caspase-1
29 (CASP-1) that acts to induce the active precursors of pro-inflammatory cytokines IL-
30 1β , IL- 1α and IL-18, and on-going interaction with NF- κ B (132,133) (Fig 4).
31 Although the baseline activity of NLRP3 is low, the initiation process of the
32 inflammatory cascade requires a complex oligomerisation-priming phase that includes
33 association with NF- κ B and so contributes several layers of regulatory control.

34
35 NLRP3 has also been shown able to activate NF- κ B and induce cytokines in response
36 to sterile signals, such as monosodium urate crystals and aluminum adjuvant,
37 suggesting that NLRP3 could initiate NF- κ B activation to both pathogen-induced and
38 sterile inflammation (134). Conversely NF- κ B, which primes the NLRP3
39 inflammasome for activation also prevents excessive inflammation and restrains
40 NLRP3 activation by enhancing the NF- κ B-p62 mitophagy pathway. By self-limiting
41 the host response the NF- κ B-p62 mitophagy pathway maintains homeostasis which
42 under normal conditions leads to tissue repair (75). It is however unclear if this layer
43 of control of NF- κ B function remains as tightly controlled in aging and age-related
44 disease.

45
46 The NLRP3 inflammasome is a key component of the innate inflammatory response
47 to pathogenic infection and tissue damage (Fig 6). It responds to a wide range of
48 cellular stress and is considered to contribute to the aging process and to age-related
49 diseases (135). Zhou and colleagues identified that mitochondrial ROS was involved
50 in the activation of NLRP3 (58). This study emphasized the important role of

1 mitochondria in maintaining a correct balance between cellular energy production and
2 ROS production and that effective clearance of damaged mitochondria through
3 autophagy was an important regulatory activity. Damaged mitochondria increase with
4 aging and in age-related diseases (136). Mitochondrial dysfunction drives
5 mitochondrial mutagenesis, affecting respiratory chain genes and compromising the
6 efficiency of oxidative phosphorylation (OXPHOS), which may lead to further
7 mtDNA mutations and more cell damage. The subsequent mitochondrial impairment
8 leads to more ROS that further reduces ATP generation and increases the chance of
9 cell death. Mitochondria have been identified as a key source of DAMPs, the so-
10 called mito-DAMPs, which have been considered to play a role in DAMPS-
11 modulated inflammation in diseases such as rheumatoid arthritis (RA), cancer and
12 heart disease (137-140) as well as in the aging process (141). Degraded mt-DNA has
13 been also been reported in neuroinflammation (142). Dysfunctional mitochondria
14 seem able to initiate an auto-feedback loop to increase autophagy so that damaged
15 mitochondria or misfolded proteins are degraded that reduces inflammasome
16 activation and risk of further tissue injury, though this system is less efficient in aging
17 (143).

18
19 Lysosomal destabilization is also associated with NLRP3 activation and can be
20 induced by a number of molecules including cholesterol crystals in macrophages
21 linking atherosclerosis progression with inflammation (144). There is deposition of
22 other harmful intra- and extracellular material in several age-related diseases. The
23 aggregates compromise cellular homeostasis and can provoke the activation of the
24 NLRP3 inflammasome. Research has shown that amyloid fibrils and Alzheimer's
25 amyloid- β can trigger NLRP3 inflammasomes and in that way stimulate
26 inflammation and enhance pathogenesis and association between type 2 diabetes and
27 Alzheimer's disease respectively (145). Palmitate, a saturated fatty acid has been
28 shown to activate NLRP3, whereas oleic acid did not initiate the same inflammatory
29 response (146). The inflammasome has been implicated in the development of the
30 metabolic syndrome through impairment of adipose tissue sensitivity. Evidence
31 showed that obesity triggered NLRP3 activation and that the secreted IL-1 β impaired
32 insulin signaling which promoted insulin resistance in mice (147). Other research has
33 shown that obesity was associated with the activation of the NLRP3 in adipose tissues
34 (148,149).

35
36 A number of intracellular processes seem likely to work together to stimulate and
37 augment the inflammasome pathway and contribute to pro-inflammatory cytokine up-
38 regulation associated with increased age and age-related diseases. Both the redox-
39 sensitive inflammatory pathway and the senescent cell-related-SASP activate the
40 inflammasome through the NF- κ B and IL-1 α cascade, causing persistence of the
41 inflammatory response, that delays resolution and healing (140,127). Similarly
42 reduced autophagy processes allow the accumulation of damaged intracellular
43 proteins and senescent cells that further perpetuate and amplify the pro-inflammatory
44 milieu that is found with increased age and is associated with age-related diseases.

45 46 **4. Pro-inflammatory and anti-inflammatory cytokine dysregulation**

47 48 **4.1. Pro-inflammatory cytokines in aging and age-related disease**

49 Various biomarkers and biochemical indices are used in medicine and age-related
50 diseases as a way of improving diagnosis, beyond the well-recognised clinical signs.

1 Modest increases in concentration of C-reactive protein, a circulating marker of
2 inflammation, have been widely reported to be associated with a large number of age-
3 related conditions and lifestyles felt to be associated with poor health; these
4 conditions represent or reflect minor metabolic stresses. Alongside C-reactive
5 proteins, cytokines have come under investigation as the molecular processes and
6 pathways underpinning inflammation have become better identified. A common
7 finding in aging and age-related diseases is ‘inflamm-aging’, a dysregulation of the
8 cytokine network and its homeostasis. Downstream from NF- κ B signaling, the pro-
9 inflammatory cytokines play a central role in the remodeling of the immune system
10 with age.

11
12 The major pro-inflammatory cytokines such as IL-6, TNF- α and IL-1 α contribute
13 significantly to the phenomenon of inflamm-aging in healthy elderly individuals (8),
14 while also playing a major role in many age-related diseases (11,27,150-153). The
15 key to healthy aging must lie in the ability to maintain a balanced response to these
16 immune messengers and a prompt and integrated return to inflammation resolution
17 and immune homeostasis (17). A summary of the changes that have been described in
18 pro-inflammatory and anti-inflammatory cytokines in aging and some age-related
19 diseases are outlined in this section.

20 21 **4.1.1. Interleukin-1 (IL-1) family**

22 IL-1 α and IL-1 β , known as Interleukin-1 (IL-1), and IL-18 are important cytokine
23 initiators of the stress-induced inflammatory cascade (154). IL-1 β and IL-18 are
24 cleaved to active forms by caspase 1 (Casp-1), whereas IL-1 α is activated by calpain
25 protease. All bind to and activate the IL-1 receptor (IL-1R) that is down regulated by
26 the receptor antagonist IL-1R α , which blocks IL-1 mediated signal transduction.

27
28 Studies in elderly people, including centenarians have reported an age-related rise in
29 the IL-1 receptor antagonist, (IL-1R α), whereas IL-1 β showed no detectable age-
30 related trend. The age-related rise is associated with increased co-morbidity, age-
31 related disease and mortality (155-158).

32
33 Certain IL-1 haplotype-carriers produce increased IL-1 β , and IL-1 gene variations
34 associate with earlier onset or more severe progression of cardiovascular and
35 Alzheimer’s disease, but not with osteoporosis (159-163). In centenarians, no single
36 IL-1 gene polymorphism showed a survival advantage, but in Swedish elderly males
37 an IL-1 gene polymorphism shortened life expectancy (164,165,155). IL-1 gene
38 variants appear to increase the risk of age-related diseases and recombinant drugs,
39 such as IL-1R α -blockers may have a role in the clinical control of inflammation
40 (166).

41 42 **4.1.2. Interleukin-18 (IL-18)**

43 Interleukin (IL)-18, a linked IL-1 pro-inflammatory cytokine, signals in a complex
44 with IL-18 receptors α (R α) and β (R β) chains and induces IFN- γ that is essential for
45 defence against infections (167). IL-18’s multiple pro-inflammatory effects are
46 modulated through IL-18 binding protein (168).

47
48 Higher levels of IL-18 have been found in centenarians, associated with heart failure,
49 ischemic heart disease and type-1 diabetes in patients, and in the Alzheimer’s disease
50 brain (169-174). IL-18 levels associate with physical functioning and with a frailty

1 index in the English Longitudinal Study of Aging, where carriers of IL-18 gene
2 polymorphism that reduced IL-18 levels, showed improved walking speed (175-177).
3 Evidence consistently shows that IL-1 and IL-18 are mediators of inflammation and
4 associated with the aging process (170). Drugs blocking binding between IL-18 and
5 the receptors are currently in development and may be provide benefit in the
6 treatment in diabetes, macular degeneration and autoimmune disease (178).

8 **4.1.3. Interleukin-6 (IL-6)**

9 IL-6 has been long recognised as important in aging and age-related disease and has
10 been called the ‘gerontologist’s cytokine’ (179,180). IL-6 plays a key role in the acute
11 phase response, in the transition from innate to acquired immunity, in metabolic
12 control and in the pathogenesis many chronic diseases (11,150-153,181). It has both
13 pro- and anti-inflammatory activities and modulates the acute inflammatory response
14 by producing IL-1 R α and soluble TNF-receptor p55, (sTNF-R55), that suppress
15 TNF- α and IL-1.

16
17 IL-6 is normally present in low levels in the blood, but is increased in aging and in
18 subjects with markers of frailty and chronic disease, where it tracks with mortality
19 (182-185). IL-6 is a risk factor associated with cardiovascular disease and is
20 associated with sarcopenia and muscle loss (186,187).

21
22 The G allele of IL-6-174C/G polymorphism shows higher IL-6 levels and associates
23 with cognitive decline and mortality in age-related vascular disease, whereas CC
24 allele carriers show decreased Alzheimer’s risk (188-193). In a meta-analysis of
25 longevity in a large cohort of European nonagenarians and centenarians there was
26 longevity benefit for carriers of the lower cytokine producing IL-6 allele, with similar
27 supporting findings for this IL-6 allele in a case control study (194,195). IL-6 or IL-6
28 receptor blockers are already used successfully in the treatment of rheumatoid
29 arthritis, and are proof of concept that damping down IL-6, a product of the NF- κ B
30 pro-inflammatory cascade, can improve clinical symptoms. Studies are in either in
31 progress or planned, to assess the outcome of blocking IL-6 related inflammation in
32 other age-related diseases with the potential for contributing to more successful aging
33 (196,197).

35 **4.1.4 Tumour Necrosis alpha (TNF- α)**

36 Another major player in the immune response is the pro-inflammatory cytokine TNF-
37 α , which increases with age and is associated with age-related disease (198). It is a
38 pro-inflammatory mediator that can be beneficial when it acts locally in the tissues,
39 but can be highly harmful when released systemically.

40 TNF- α has been reported increased in intracellular ageing studies in elderly people, in
41 centenarians and octogenarians, related to atherosclerosis and associated with
42 mortality (199-204). In post-myocardial infarction patients, a rise in TNF- α increased
43 risk of recurrent cardiac events and in renal patients TNF- α receptors predicted
44 cardiovascular disease (205-207). In genetic studies, the A allele of TNF- α 308-G/A
45 gene associated with risk for myocardial infarction, whereas TNF- α polymorphisms
46 and TNF- α itself, have been variably associated with increased Alzheimer’s disease
47 risk (208-212). TNF- α mediates metabolic changes and increased TNF- α was found
48 in type II diabetes mellitus and was associated with lower muscle mass and strength

1 in older groups (213).

2 In studies in nonagenarian/centenarian groups from three European countries, there
3 was no attrition of the TNF- α -308A/G polymorphism in centenarians (214,215,164).
4 With increasing evidence of an association between increases in TNF- α and age-
5 related diseases, research re-purposing anti-inflammatory drugs are under
6 development. Research has demonstrated that TNF- α inhibitors may have possible
7 prophylactic or ameliorating roles in cardiovascular and Alzheimer's disease in
8 animal models (216,217).

9 **4.1.5 Other pro-inflammatory cytokines**

10 Other pro-inflammatory cytokines are increasingly being recognized as dysregulated
11 in association with aging and age-related disease.

12 **IL-2**

13 IL-2 plays a pivotal role in the immune response. It is a growth factor that promotes
14 natural killer cell (NK) activity and the differentiation of naïve T cells into Th1 and
15 Th2 cells (218). Conversely, IL-2, acting via STAT5 pathway negatively regulates IL-
16 17 production (219). Most studies show that lymphocytes in elderly people produce
17 significantly less IL-2, compared to young people (220-222). Intracellular cytokine
18 studies have shown variable results for IL-2, whereas mitogen-induced stimulation of
19 mononuclear from elderly subjects showed significant decreases in IL-2 and IFN γ
20 production (223,224).

21 **The IL-7/IL-7R**

22 The IL-7/IL-7R network is essential at various stages in T-cell development and
23 survival (216). It has an important role in the maintenance of a vigorous health span
24 and higher IL7R gene expression is associated with long life (225-228). Serum IL-7 is
25 increased in some age-related diseases including osteoarthritis and genetic variation in
26 the IL7RA/IL7 pathway increased susceptibility to multiple sclerosis (229,230).
27 Research has suggested that silencing of the IL-7R gene may be an important
28 mechanism underpinning an aging-related loss of binding to NK- κ B (231), linking
29 IL-7R gene to the NF- κ B pathway and inflammation control.

30 **IL-12**, a pro-inflammatory member of the IL-6 family has an active role in the
31 development of cardiovascular diseases such as atherosclerosis, myocardial infarction
32 (MI) and stroke (232). Patients with cardiovascular disease show increased levels of
33 IL-12, 23 and 27 with higher IL-12 predicting poorer long-term outcome after acute
34 MI (233). Other research shows variable results for IL-12 and its receptor antagonist,
35 with increased IL-12 (total) and IL-12p40 in apparently healthy nonagenarians, lower
36 IL-12p70 and IL-23 production in association with frailty and IL-12/23.p40
37 ameliorating Alzheimer's disease in animal models (234-236).

38 **IL-17**

39 Interleukin 17 (IL-17) is a key pro-inflammatory cytokine that belongs to a family of
40 6 cytokine members (A-F). IL-17A (referred to as IL-17) plays a central role in host
41 defense against invading pathogens and is produced by a subset of CD4⁺cells
42 (237,238). Elderly people (age \geq 65) have shown a decreased frequency of IL-17-
43 producing cells in memory subset of CD4⁺ T cells compared to healthy younger
44 people (239). IL-17 enhances production of IL-6, TNF- α , the acute phase reactants,
45 C-reactive protein and serum amyloid A and activates the induction of IL-6, IL-8 and
46 G-CSF in non-immune cells such as fibroblasts and epithelial cells, in part through
47 activation of the NF- κ B transcription factor (240). IL-17 promotes inflammation and
48 is over-expressed in many autoimmune diseases such as rheumatoid arthritis, systemic

1 lupus erythematosus, inflammatory bowel disease and psoriasis and its effects are
2 stabilized by IL-23 (241-244). An IL-17 expressing CD8⁺T subset of cells has also
3 been reported to be involved in psoriatic arthritis and some other autoimmune
4 diseases (245,246).

5 **Interleukin-8 (IL-8)**

6 IL-8 (or CXCL8) is a chemokine secreted by monocyte/macrophages whose key role
7 in the inflammation process is the recruitment and activation of neutrophils. IL-8 has
8 been implicated in a number of inflammatory conditions such as cystic fibrosis,
9 asthma, chronic pulmonary disease, inflammatory bowel disease and some
10 autoimmune diseases, including rheumatoid arthritis and psoriasis.

11 Increased levels of IL-8 have been detected after LPS-stimulation of leucocytes from
12 elderly individuals (247). In one small study of centenarians, IL-8 was proposed as a
13 possible longevity factor (248). A single study of IL-8 polymorphisms found no
14 significant difference in IL-8 -251A/T polymorphisms in nonagenarians compared to
15 young controls (214). IL-8 signalling occurs via the MAPK and PI3K pathways, by
16 binding to the IL-8 receptors-CXCR1/2. Several agents that block IL-8-CXCR1/2
17 signalling have been developed in an attempt to target inflammatory pathways in
18 cancer, asthma, chronic obstructive pulmonary disease, psoriasis and rheumatoid
19 arthritis (249).

21 **4.2. Anti-Inflammatory cytokines in aging and age-related Disease**

23 The anti-inflammatory cytokines play a key role in balancing the immune response,
24 and in preventing the tipping of the steady state of immune homeostasis across into
25 inflamm-aging and a disease-inducing state. Anti-inflammatory cytokines are an
26 important arm of inflammation resolution. They block or modulate the synthesis of
27 IL-1 α , tumor necrosis factor (TNF) and other major pro-inflammatory cytokines and
28 damp down the inflammatory response, so that inflammation resolution can begin.
29 Specific cytokine receptors for IL-1, TNF- α , and IL-18, together with soluble receptor
30 antagonists, chemokines, microRNA, siRNAs, also function as inhibitors for pro-
31 inflammatory cytokines. The anti-inflammatory cytokines and families of soluble
32 receptor antagonists work within a complex network of control of immune regulation.
33 They are critical for balancing the inflammatory outcome and together with pro-
34 resolving lipoxins, are critical to resolving inflammation in an integrated and
35 organized manner.

37 As age increases and in age-related diseases, a chronic inflammatory state
38 predominates, which is not properly contained or resolved and the anti-inflammatory
39 side of the immune system seems to be similarly dysregulated, and unable to damp
40 down the inflammatory episode in a timely effective manner. The following cytokines
41 are the major players in the anti-inflammatory pathway of the control of inflammation
42 and changes in their production and expression have been quite widely reported in
43 aging and age-related disease. Where increases in anti-inflammatory cytokines have
44 been reported, one interpretation would be that increases might reflect the immune
45 system's attempt to suppress the persistent pro-inflammatory response and support a
46 return to immune homeostasis.

48 **4.2.1. Interleukin 10 (IL-10) family**

49 IL-10 is one of the key anti-inflammatory cytokines, which suppresses the actions of
50 IL-6, TNF- α and IL-8 (250,251). Higher IL-10 serum levels and production by both

1 lymphocytes and monocytes have been reported in elderly people (247, 252,157).
2 Conversely an age-and gender-related decline in cellular stimulation studies has been
3 reported (253).

4
5 In age-related disease, IL-10 has been reported to be associated with vascular
6 protection in atherosclerosis and improved endothelial dysfunction (254-256).
7 However, at variance, the authors from the ERA (257) and PROSPER (258) studies,
8 concluded that IL-10 increased cardiovascular risk amongst elderly groups, and
9 suggested that IL-10 blockers merited investigation. In male Sicilian centenarians,
10 male carriers of the high producing GG 1082 allele of the IL-10 promoter
11 polymorphism showed a survival advantage, suggesting that IL-10 anti-inflammatory
12 activities might be a marker for male longevity (215). This result was not replicated in
13 Sardinian, Irish or Finnish nonagenarian/centenarians (259,214,164). It has been
14 argued that an enhanced anti-inflammatory phenotype could be beneficial and
15 contribute to longevity by controlling the pro-inflammatory milieu that predominates
16 in later life and contributes to increased morbidity and mortality (260,9,11).

17 18 **4.2.2. TGF- β**

19 TGF- β , another important anti-inflammatory cytokine limits both the acute phase
20 response, and is involved in tissue repair post-damage or infection (261). Several
21 authors have reported that TGF- β was increased in octogenarians and centenarians
22 (262,150). It is also involved in aging-related disease such as obesity, in vascular wall
23 integrity, in muscle loss and sarcopenia, in osteoarthritis and with frailty in the
24 Newcastle longitudinal study (263-267). In stroke TGF- β signaling was increased in
25 microglia and macrophages suggesting that increased TGF- β likely regulated glial
26 scar formation (268). Reports have linked TGF- β or its polymorphisms with
27 atherosclerosis and Alzheimer's disease (269-271). Other research found TGF- β
28 genotypes associated with longevity in Italian centenarians, a finding not replicated in
29 BELFAST nonagenarians (272,214). Context-specific environmental factors,
30 epigenetic regulation and non-coding RNAs are suggested to play a role in TGF- β 's
31 paradoxical pro-and anti-inflammatory functions (7,273, 274), but important uses
32 have been found for TGF- β in fibrosis management and oncology (275).

33 34 **4.2.3. IL-37**

35 IL-37, formerly an IL-1 cytokine, limits innate inflammation via suppression of pro-
36 inflammatory cytokine production (276). Carriage of an IL-37 haplotype that
37 decreases IL-37 levels contributes to increased inflammation. Research demonstrates
38 that IL-37 reduces TNF- α and IL-1 β cytokine production from human macrophages,
39 is increased in chronic heart failure patients and attenuated the production of
40 inflammatory cytokines in serum or synovial joints in rheumatoid arthritis, suggesting
41 IL-37 may have a role in clinical disease (277-279).

42 43 **Age-related Diseases**

44 **5.1. Cancer**

45 Cancer increases with aging, with one in two people likely to develop malignant
46 tumours in their lifetime. Probable reasons for this age-related increase include
47 exposure to environmental toxins, declining immune surveillance, and increasingly
48 ineffective DNA repair mechanisms. Inflammation is involved at different stages of
49 tumor development, at initiation, promotion, malignant conversion, invasion, and
50 metastasis, has a paracrine by-stander role and is an essential part of the tumour-

1 micro-environment. Inflammation also affects immune surveillance and responses to
2 therapy (280). Thus, malignancy is a major threat to successful aging.

3
4 Whilst inflammatory pathways are vital to promote immune homeostasis, over-
5 activation or dysregulation can be pathological and lead to malignant progression.
6 Prolonged inflammation, either as a result of chronic infections, or reduced
7 homeostasis in the inflammatory response, plays a role through the production of pro-
8 inflammatory cytokines that may be directly or indirectly implicated in the
9 oncogenesis (281,282). More recent investigations have focused on the role of the
10 inflammasome pathway, whose biochemical function is to activate caspase-1, which
11 leads to the activation of the IL-1 β and IL-18 pathways and induction of pyroptosis, a
12 form of cell death. Although inflammasomes have an important role in inhibiting
13 cancer, through the triggering of the programmed-death pathway, they also both
14 initiate and maintain carcinogenesis, dependent on tumour type and the tumour
15 environment (283,284).

16 Bacterial and viral infections are associated with malignancies. For example,
17 *Helicobacter pylori* (*H. pylori*) infection of the gut is associated with both gastric
18 cancer and mucosa-associated-lymphoid-tissue (MALT) lymphoma (285). Epstein
19 Barr virus (EBV) is a causative agent in Hodgkin's Disease (HD) where chronic
20 inflammation is considered a major contributory factor (286), human papilloma virus
21 (HPV) is implicated in most cases of cervical cancer (287), whilst human T-
22 lymphotropic virus 1 (HTLV-1) is a causative agent in adult T-cell leukaemia
23 lymphoma (ATLL) (288). A common factor is the association of infection with
24 oncogenesis, with chronic inflammation a contributory factor.

25
26 In *H. pylori* chronic infection, elevated levels of IL-1 β are detected and recognised as
27 important in the development of gastric carcinoma. Normally gastric acid in the
28 stomach does not permit bacterial survival, but in circumstances of low stomach
29 acidity, *H. pylori* grows vigorously in the mucosa and induces caspase-mediated
30 cleavage of pro-IL-1 β and pro-IL-18 in association with the NLRP3 inflammasome.
31 The overexpression of IL-1 β induces NF- κ B activation and the transcription and
32 expression of IL-6, TNF- α , and IL-10. The proinflammatory cytokine milieu
33 increases the risk for developing both gastric carcinoma and MALT lymphoma (289).
34 Persistently high levels of IL-1 β and IL-18 suppress acid secretion, allow hypoacidity
35 in the stomach, loss of parietal cells, gastric atrophy, metaplasia and eventually gastric
36 cancer. In addition, IL-1 β inhibits gastric acid secretion and carriers of IL-1 β
37 polymorphisms producing higher IL-1 β carry increased gastric cancer risk (290,291)).
38 *H. pylori* infection of gastric mucosa can cause a monoclonal B cell proliferation, with
39 a histological diagnosis of MALT lymphoma. This tumour-like proliferation of gastric
40 mucosal cells and clonal B cells can regress after eradication of the *H. pylori* infection
41 with combined antibiotic therapy and proton pump inhibitor treatment (292).

42
43 Viral infections strongly stimulate inflammatory responses and may lead to malignant
44 transformation of the host cell (293). Although the activation of the inflammasome
45 benefits the clearance of viruses and the regression of cancer, there are several
46 examples of viruses such as EBV and HTLV-1 developing strategies to evade
47 detection, triggering the inflammasome, and high-jacking the inflammatory cascade to
48 induce and amplify the cancer spread. For example, when EBV infects B-
49 lymphocytes and nasopharyngeal cells through its receptor CD21 (294), this leads to a

1 proliferation of infected B cells, followed by an increase in CD8+ T cells that controls
2 the infected cells by lysis. However, where the normal infection-limiting response is
3 'exhausted' or dysregulated, B-cell proliferation continues unabated leading to
4 chromosomal damage, which drives cell proliferation outside normal control
5 mechanisms and may result in an aggressive non-Hodgkin's or Burkitt's Lymphoma
6 (295). NLRP3 activation has been demonstrated in EBV-associated cancerous tissues
7 (296). Furthermore EBV has been shown to be able to overcome the immune
8 response by means of EBV miRNA binding to the 3'untranslated region of NLRP3
9 (297), so preventing effective immune activation and control mechanisms.

10
11 Retro-viruses stimulate inflammatory responses and are associated with malignant
12 transformation of host cells. They reverse transcribe their RNA into the host cell's
13 DNA, leading to dysregulation of cellular proliferation and programmed cell death
14 responses, and elicit a pro-inflammatory response. HTLV-1 causes adult T-cell
15 leukemia by targeting CD4+ T cells that express CD25 (IL-2R α) and FoxP3, similar
16 to Tregs (298,299). The persistent activation of the NF- κ B pathway in HTLV-1-
17 infected T cells and the associated NF- κ B oncoprotein Tax contribute to the
18 oncogenic transformation (300). The resulting hijacking of the NF- κ B pathway,
19 allows uncontrolled upregulation of cellular genes that govern growth-signal
20 transduction, amplification the pro-inflammatory cytokines (IL-2, IL-6, IL-15, TNF,
21 together with increasing expression of proto-oncogenes (c-Myc), and antiapoptotic
22 proteins (bcl-xl) Hiscott Rayet (301,302). Inter-individual susceptibility to HTLV-1
23 infection has been associated with allele carrier status of the NLRP3 gene (303).

24
25 In summary, the interaction of infective agents, host cells, adaptive immune cells,
26 cytokine production and the inflammasome response is complex and incompletely
27 understood. Many cancers arise from sites of infection, chronic irritation and
28 inflammation, which although sometimes reversible in the pre-malignant phase by
29 eradicating the causative virus or bacterium, often treatments are too delayed to
30 prevent the cancer development. There needs to be improved understanding about the
31 roles of inflammation, the inflammatory cells and the paracrine effects that allow
32 tumour cell proliferation, survival and migration. Does the pro-inflammatory
33 environment found in aging enhance and facilitate cancer cell proliferation or does it
34 alternatively represent an up-regulated immune surveillance mechanism to deal with
35 increased damaged and dangerous cancer cells? Improved understanding of the
36 pathways involved should begin to provide insights that could contribute to new anti-
37 cancer and anti-inflammatory therapeutic approaches through manipulation of
38 autophagy for cancer treatment regimes or conversely tagging cancer cells for
39 destruction through proteasome or autophagy up-regulation (304).

40 41 **5.2. Rheumatoid Arthritis**

42 Chronic tissue inflammation has an important role in the aetiology and
43 immunopathogenesis of rheumatoid arthritis (RA) (305), with genetic and
44 environmental factors contributing to a predilection to develop the disease. In the *pre-*
45 *clinical* asymptomatic phase of RA disease, the immune system is characterized by
46 reduced self-tolerance and production of autoantibodies, whereas in the *clinical* phase
47 (306) innate and adaptive immune cells infiltrate the synovial joints and produce
48 symptoms of joint pain and stiffness (307,308). As RA progresses, immune cells and
49 synovial fibroblasts, produce a pro-inflammatory environment in the joint (309,310)
50 leading to joint destruction (305). Cell-specific cytokines include TNF- α , IL-1 and

1 IL-6 from macrophages, IL-6, IL-7 and IL-15 from memory T-cells, IL-1 and IL-17
2 from helper T-cells, and IL-1, IL-6, IL-18, GM-CSF and TGF- β from synovial
3 fibroblasts (306,311). This complex cytokine milieu attracts further immune cells,
4 promotes abnormal angiogenesis and osteoclastogenesis, poorly formed and leaky
5 vasculature and leads to systemic effects (312).

6
7 There is evidence to suggest that activation of the NLRP3-inflammasome contributes
8 to the inflammatory processes in rheumatoid arthritis. Active RA subjects have
9 increased expression of NLRP3 and NLRP3 –mediated IL-18 secretion in whole
10 blood upon stimulation via TLR3 and TLR4 but not TLR2 receptors (313,314).
11 Functional polymorphisms in the genes coding for NLRP3 and its component parts,
12 including CARD8 has been shown to contribute to higher disease activity at diagnosis
13 and for response in the early months of treatment. (315,316).

14
15 Patients with rheumatoid arthritis show premature immune aging and accumulation of
16 CD28⁻ pre-aged effector T cells that associate with disease activation and prognosis
17 (317,318). A novel T-cell subset-CD28⁻ Treg-like cells has been described that
18 produce pro-inflammatory cytokines, mirroring the SASP associated with senescent
19 cells (319). Rheumatoid arthritis patients who show CD28⁻ senescent Treg-like cells
20 in blood seem to demonstrate earlier and more severe osteoporosis.(320).

21
22 Limiting inflammation before damage occurs is central to successful RA management
23 and the use of specific monoclonal antibodies has been a key therapeutic strategy. The
24 central roles of TNF and IL-6 in RA have been corroborated by clinical trials of
25 biologic drugs, which can specifically target and neutralize these cytokines. Evidence
26 from RA clinical subgroups stratified by responses to specific biologic drugs strongly
27 suggest that for a particular individual, inflammation is coordinated by a predominant
28 cytokine pathway, such as TNF or IL-6 (321).

29
30 Anti-TNF biologics such as adalimumab, etanercept and infliximab reduce
31 inflammation, pain, neovascularisation, lymphocyte infiltration and increase
32 macrophage apoptosis (321-324). Anti-IL-6R biologics such as tocilizumab and anti-
33 IL-6 such as sirukumab, strongly reduce disease activity and erosive progression
34 (325,326). Evidence suggests that the predominant cell cytokines seen in synovial
35 histopathology may act as prognostic biomarkers for stratification of RA patients
36 (327-329).

37
38 Studies of TNF and IL-6 gene polymorphisms further support their role in RA risk
39 and severity. SNPs in IL-6 and IL-6R genes associate with increased RA risk and
40 joint damage (330-332) and the TNF 308G gene polymorphism with RA disease
41 severity and poor response to anti-TNF treatment (333-337). In the elderly person
42 with RA, there is difficulty in distinguishing whether chronic inflammation or genetic
43 ‘predisposition’ initiates disease or if late-onset RA is hastened by the pro-
44 inflammatory phenotype associated with aging. Tumor necrosis factor α (TNF- α)
45 inhibitors used as disease-modifying agents in RA improve not only the clinical
46 symptoms of rheumatoid arthritis but decrease the associated vascular risk (338),
47 suggesting that a stratified biologic approach may be of use to therapeutically dampen
48 chronic systemic inflammation related to aging and other age-related diseases.

49

1 Like other age-related diseases and aging itself, there is evidence for dysregulation in
2 both the autophagy-lysosomal and the ubiquitin-proteasomal systems in rheumatoid
3 arthritis (339). Autophagy seems to be activated in RA in a TNF α -dependent manner
4 and regulates osteoclast differentiation and bone resorption, emphasising a central
5 role for autophagy in joint destruction (340). Gene and allele frequency population
6 differences seem also to contribute to the how effectively cellular autophagy
7 processes work within the cell in removing damaged proteins and other necrotic
8 cellular debris. Polymorphisms of the ubiquitin E3 ligase gene that directly affects of
9 autophagy have also been identified and have been associated with the aetiology and
10 response to drug treatment in RA (341,342). Both are likely important contributors to
11 the action and effectiveness of disease modifying and monoclonal biological drugs
12 used in RA treatment. The role of the NLRP3 inflammasome may give opportunities
13 for developing other disease modifying drugs by targeting upstream triggers of the
14 NLRP3 pathway.

15 16 **5.3. Atherosclerosis**

17 Atherosclerosis is recognized as a chronic inflammatory condition (343) and
18 atherosclerotic plaques show cellular senescence (344,345). Cytokines are involved in
19 all stages of the pathogenesis of atherosclerosis, having both pro- or anti-atherogenic
20 effects (346,347). In response to increased low-density lipoprotein (LDL),
21 hypertension and subsequent shear stress, cytokines modulate endothelial cell
22 permeability and recruit monocytes and T-lymphocytes (348,349). The continuous
23 monocyte recruitment, foam cell and fatty streak formation eventually result in
24 unstable plaque development, thrombosis and a cardiac event (349,350).

25
26 Chronic unresolved inflammation is a key feature in atherosclerosis and the levels of
27 SPMs, particularly resolvin D1 (RvD1), and the ratio of SPMs to pro-inflammatory
28 leukotriene B₄ (LTB₄), are significantly decreased in the vulnerable plaque regions
29 (27). Vulnerable atherosclerotic plaques are recognized as having distinct features;
30 increased inflammation; oxidative stress; areas of necrosis overlain by a thin
31 protective layer of collagen (fibrous cap). In advanced atherosclerotic plaques,
32 macrophages have more abundant nuclear 5-lipoxygenase (5- LOX), which is
33 suggested to lead to conversion of arachidonic acid to proinflammatory leukotrienes,
34 with the potential to contribute to plaque rupture (27).

35
36 The NLRP3 inflammasome, a central regulator of inflammation (58), is activated by
37 cholesterol crystals and oxidized LDL (351,352) that drives the IL-1 β inflammation
38 pathway. Recent research targeting IL-1 β inflammation in atherosclerosis using
39 cannakinumab, a therapeutic monoclonal antibody, has shown up to fifteen percent
40 lower rates of recurrent cardiovascular events, which was independent of lipid
41 lowering (353). As well as playing a major role in chronic inflammation, NLRP3 is
42 also upregulated during endothelial cell senescence (354) via ROS, and is negatively
43 regulated by autophagy (355,356). The NLRP3 inflammasome therefore appears to
44 warrant further investigation as a potential target for inflamm-aging related to
45 atherosclerosis given that such mechanisms are now of well known importance in
46 atherosclerosis (357).

47
48 The gut microbiome has been implicated in age-related inflammation (358) with
49 numerous studies reporting bacterial organisms in arterial plaque (359-361).
50 Emerging research reports bacterial DNA in blood associated to a personal microbiota

1 fingerprint as a predictor of cardiovascular events and stool microbiome as a signature
2 of cardiovascular disease (362,363). Similarly bacterial DNA has been noted in cell-
3 free plasma in cardiovascular and chronic renal disease patients (364,365). Altered gut
4 microbiota composition or dysbiosis is also seen in elderly people, and is associated
5 with inflammatory markers (358). Aging leads to changes in intestinal permeability in
6 gut bacterial milieu (366) and the increased circulatory bacterial DNA observed
7 associated with atherosclerosis support further investigation of the microbiome as a
8 contributory factor to age-related inflammation and atherosclerosis.

9 10 **5.4. Neuroinflammation and neurodegenerative disease**

11 Inflammation has been well established as a major component of neurodegenerative
12 disorders, but it has never been clear if this was a direct cause of the disease or a
13 consequence of the progressive degenerative process that was occurring (367,368).
14 The central role of cytokines in regulating the immune response has been implicated
15 in neurodegeneration, but over the last decade, there has been a revolution in our
16 understanding of how cytokines contribute to the aetiology of the leading
17 neurodegenerative disorders, including Alzheimer's (AD) and Parkinson's disease
18 (PD).

19
20 In AD, central events seem to include the inflammasome, the NF- κ B pathway and
21 activation of microglia by a variety of factors including beta amyloid and pro-
22 inflammatory cytokines (174). Microglia, the primary components of the CNS innate
23 immune system (369), produce cytokines and monitor the integrity of CNS. Together
24 with astrocytes, microglia are the primary effectors of neuroinflammation and express
25 PRRs that allow early recognition of PAMPs and DAMPs. When the NLRP3
26 inflammasome is activated, the inflammation cascade begins with caspase-1 that
27 facilitates the processing of IL-1 β and IL-18. These proinflammatory cytokines drive
28 the inflammatory cascade through downstream signalling pathways and lead to
29 neuronal damage and death (370). The activated microglia release proinflammatory
30 cytokines such as IL-1 β , IL-6, TNF- α and IL-18, that contributes to neuronal death
31 and dysfunction.

32
33 There is interest in the role of sphingolipid metabolites such as ceramide and
34 sphingosine-1-phosphate that regulate a diverse range of cellular processes that are
35 important in immunity, inflammation and inflammatory diseases (371). Growing
36 evidence suggests that ceramide may play a critical role in NLRP3 inflammasome
37 assembly in neuroinflammation. Research has shown that microglia treated with
38 sodium palmitate (PA) induce *de novo* ceramide synthesis, triggering the expression
39 of NLRP3 inflammasome assembly and resulting in release of IL-1 β (372), linking
40 neuroinflammation with dietary lipids. Recent insights into the molecular mechanisms
41 of action of sphingolipid metabolites suggest roles in altering membrane composition,
42 with effects on cellular interactions and signaling pathways with potential causal
43 relationships to neuroinflammatory disease.

44
45 Dysregulated autophagy has been considered to play a role in neurodegenerative
46 diseases, particularly AD, and is felt to be a key regulator of A β abnormal protein
47 generation and clearance (373). In AD the maturation of autophagolysosomes (i.e.,
48 autophagosomes that have undergone fusion with lysosomes) and their clearance are
49 hindered. Evidence suggests that A β peptides are released from neurons in an
50 autophagy-dependent manner and that the accumulation of intracellular A β plaques is

1 toxic to brain cells leading to AD pathology (374). Furthermore lysosomal and
2 autophagocytic dysfunction has been associated with both Alzheimer's and
3 Parkinson's diseases (72,71). Senescent cells too, accumulate abnormal protein
4 aggregates in the cytoplasm that contribute to neurodegenerative disease (72).
5 Cellular senescence has been reported in the aging brain with an increase in SASP-
6 expressing senescent cells of non-neurological origin that are likely to contribute to
7 the pro-inflammatory background (105,375).

8
9 In AD and PD the application of genome-wide association studies (GWAS) have
10 demonstrated a number of key genes, relating to immunity, including the Human
11 Leukocyte Antigen (HLA) complex on chromosome 6 that regulates the immune and
12 inflammatory response (376,377). In the most recent Parkinson's disease GWAS a
13 locus containing the IL-1R2 gene was identified as significantly associated with
14 disease risk and awaits further investigation (376). There is some evidence that
15 carriage of certain pro-inflammatory cytokine gene alleles may confer increased
16 Alzheimer's disease risk. Single studies have reported that carriers of the A allele of
17 the TNF- α 308 G/A gene were variably associated with increased risk of Alzheimer's
18 disease (209-212) and that carriage the higher IL-6 producing allele of IL-6 (174G/C)
19 may confer increased risk (188,192,193). Animal studies have provided some clearer
20 understanding of the role of TNF- α in Alzheimer's disease with evidence of disease
21 modulation with the use of anti-TNF agents (217). Three studies, published in 2013,
22 confirmed a role for the immune response in AD identifying the microglia-related
23 gene TREM2 as harboring an intermediate effect size variant in risk of AD that has
24 also been implicated in other related neurodegenerative diseases (378-380). A recent
25 study of rare variants has also implicated a role for microglial-mediated innate
26 immunity in AD (381).

27
28 A better understanding of the molecular pathways involved in the use of established
29 drugs such as non-steroidal anti-inflammatory or statin drugs in risk and progression
30 of neurological disorders may provide further opportunities to treat earlier or prevent
31 disease onset (382-384). It has been considered that down-regulation of the type and
32 magnitude of the pro-inflammatory immune response in neurodegeneration might be
33 a key to earlier and more successful targeting of these pathways. However results, to
34 date, have been disappointing and anti-TNF-a therapies and targeted treatment of
35 TNF-a levels that are elevated in cerebrospinal fluid and in patients' serum, have
36 produced, at best, modest results (385). Multiple sclerosis patients have benefited
37 from treatment with fingolimod (FTY720) that has been reported to attenuate
38 neuroinflammation, by regulating the activation and neuroprotective effects of
39 microglia, by modulating the sphingosine-1-phosphate receptor (S1P receptor) (386).
40 Given the success of FTY720 for treatment of multiple sclerosis, it is hoped that next-
41 generation S1PR1 modulators will find wider therapeutic uses in other inflammatory
42 disorders. Fingolimod is now under a phase 2 clinical trials for acute stroke and phase
43 4 for neurodegeneration (387).

44 45 **6. Future Considerations**

46 Aging is heterogeneous amongst people and highly variable between different organs
47 and tissues. Our genes, our lifestyles and our response to stress are infinitely
48 individual and variable, so that the immunobiography of each life tells a different
49 story of how each will respond to the internal and external environmental stressors (1-
50 3, 388). But evidence is accumulating that the aging process may be malleable.

1
2 Because aging is the major risk factor for age-related diseases, understanding how to
3 age better and maintaining the health of older people and societies is highly important
4 personally and for societies and governments. Knowledge about the underlying
5 molecular pathways and the genetic and life-style processes associated with age-
6 related disease and aging itself is increasing. Evidence from centenarian and
7 nonagenarian studies suggests that these oldest members of populations have had the
8 ability to delay aging and age-related disease (389,390). Other studies suggest that
9 centenarians may demonstrate optimized cardiovascular risk factors (391,392), or
10 have either intuitively or through social example, adopted lifestyles which have
11 interacted with their genes to facilitate a successful aging phenotype (3,393,394).
12

13 Population studies across the world show that the age-specific incidence of
14 cardiovascular disease, stroke and dementia is decreasing (395-399). This suggests
15 that better blood pressure and diabetic control and statin use may directly or indirectly
16 link into, and down-regulate molecular pathways associated with inflammation (400-
17 403). Research into how carriage of certain gene alleles, such as TCF7L2 or IL-6 can
18 increase inflammation or stroke risk respectively, and can be ameliorated by
19 following a Mediterranean-type diet (42, 404,405), or how gene splicing and features
20 of senescence may be modulated by resveratrol in food (406), herald research into
21 how gene, diet and life-styles can interact, with positive or negative effects on the
22 immune system and health. Increased knowledge is emerging as to how epigenetic
23 modulation can affect cytokine genes with reports linking cytokine epigenetic change
24 to neuroinflammation (407-409). Obesity, smoking and malnutrition have been shown
25 to have next generational epigenetic effects, and seem likely to contribute to the
26 predilection of offspring developing age-related disease or conversely the longevity
27 phenotype (410-413).
28

29 Other strategies should be adopted which link with public health messages and
30 encourage people to adopt behavioural changes in life-styles. Modifications should
31 include: changes in diets to include more omega-3 containing foods or fruits and
32 vegetables as in the Mediterranean diet (414-417); engagement in regular moderated
33 exercise routines (418-421); continued engagement with social connections and
34 intellectual activities in daily lives (422-424); or best of all a combination of life-style
35 factors (3,425,426), all of which have been shown to reduce the inflammatory profile
36 and improve the quality of aging. Although the role of diet on human health and
37 connections through nutrition, inflammation and cancer are not as linear as those
38 between tobacco, smoking and lung cancer, obesity is linked to chronic inflammation
39 through several mechanisms including the dysregulation of autophagy, whereas
40 fasting has anti-inflammatory effects, similar to the effect of exercise (427-430), and
41 may down-regulate inflammatory biomarkers (431-433). There is therefore
42 considerable interest in the role of the intestinal microbiota and health and the so-
43 called immune-relevant microbiome (358) 327), with important correlations between
44 inflammation and neurodegenerative disease, (434-436), bacterial β -hydroxybutyrate
45 metabolites (427), and the role of vagal stimulation (428).
46

47 Increasing evidence shows that many signalling pathways are activated in a stress-
48 type-dependent fashion, and all appear to converge with nuclear factor (NF)- κ B
49 signalling, which is a central controller of the immune response, and inflammatory
50 cascade (439-443). With increasing age immune homeostasis loosens, NF- κ B

1 signalling becomes less tightly controlled or is more readily triggered, cytokine
2 dysregulation occurs and a pro-inflammatory phenotype predominates that underpins
3 most major age-related diseases from atherosclerosis to cancer, and aging itself
4 (Figure 5). Understanding how different factors trigger the NF- κ B cascade is an
5 important pathway of research (440). In animal models, miRNA-based regulatory
6 networks involving miR -155 and miR-146a, finely regulate NF- κ B activity, with
7 miR-146a down-regulating and miR-155 upregulating NF- κ B expression (441). There
8 is an important temporal separation of miR -155 and miR-146a cellular expression
9 that allows finely controlled NF- κ B signalling and enables a precise macrophage
10 inflammatory response, which merits further research.

11
12 Therapeutic opportunities may arise through better understanding of the molecular
13 mechanisms that induce senescent cells and SASP in the cellular environments of
14 chronic disease or whether senescent cells can be removed by up-regulating
15 autophagy and using sophisticated tagging mechanisms (442). There will be increased
16 opportunities to use the knowledge gained from clinical studies in auto-immune
17 disease, about the roles and actions of monoclonal antibodies in modulating
18 inflammation, which may be able to be utilized in treatments for other age-related
19 diseases involving inflammation (443). The formulations of new and more specific
20 drugs are likely to become available as the modes of action of kinases such as AMPK
21 and m-TOR which control the senescence and inflammation pathways, become better
22 understood (444-446). Old drugs such as metformin, still used in diabetes control, are
23 being repurposed and have been shown to have exciting new uses through their ability
24 to modify epigenetic gene expression. Clinical studies are underway to assess any
25 modulating effect of metformin in aging and age-related diseases (445). The use of
26 histone deacetylating drugs is likely to increase as the clinical use of deacetylation
27 and methylation agents is evaluated in cancer with improved knowledge of their
28 effects and safety criteria (447). The current interest in diet and modified diets will
29 encourage further studies assessing how nutraceuticals modify gene expression, for
30 example, through the regulation of intracellular receptors that bind the promoters of
31 certain genes, and may help design more specific drugs to modify metabolism and
32 benefit health (448).

33
34 Turning research to focus on improved understanding of the mechanisms of
35 inflammation resolution in aging and age-related disease, should also be prioritised
36 since it is an under researched area. Developing synthetic resolvins for use in
37 inflammation resolution may have advantages over the use of single biological anti-
38 inflammatory blockers in auto-immune disease clinical management, since cytokine
39 networks are highly interactive and complex (449), with many auto-regulatory
40 feedback loops. All these molecular pathways are, or have the potential for being
41 developed as drug targets towards clinical interventions useful in damping down and
42 modulating inflammation (450,451) and may have a role in delaying the onset or
43 treatment of age-related diseases.

44
45 Evidence from on-going global studies of the oldest members of our societies such as
46 centenarians and nonagenarians (452-463) suggests that it may be possible to delay
47 age-related diseases and that aging may be a potentially modifiable risk factor (464).
48 Further investigation has shown that centenarians and super-centenarians also have an
49 enhanced pro-inflammatory background (465-467), which at first seems surprising,
50 given their long lives. However, studies have demonstrated that the pro-inflammatory

1 background is accompanied and perhaps modulated, by an enhanced anti-
2 inflammatory status in some centenarians. Some have argued that an enhanced anti-
3 inflammatory phenotype could be beneficial as a contributor to longevity by
4 effectively controlling the pro-inflammatory background (9,11,260). Others suggest
5 that some inflammation is good, in the same way as hormetic stress triggers systems,
6 and upgrades them but does not overwhelm them (468). Regular exposure to pro-
7 inflammatory stressors could train the immune system to up-regulate and fine-tune its
8 cellular processes, so that it responds better and provides better outcomes, when faced
9 with real life-threatening pathogenic threats.

10
11 GWAS have proved a powerful methodology to assess the influence of common
12 variation in AD and PD disease susceptibility, but by their nature have reflected low
13 effect size variants that likely have a cumulative effect on risk (469). As Next-
14 Generation sequencing technology becomes more cost-effective, the ability to identify
15 variants that are less common (<1% minor allele frequency) will become more
16 achievable. These unbiased approaches should aid the identification of key players in
17 the inflamm-aging pathway and will play a critical role in the development of
18 therapeutic intervention strategies in neurodegenerative and age-related diseases.

19
20 There is the increasing opportunity to link large global datasets with the technologies
21 of genomics, transcriptomics and proteomics through bioinformatics and artificial
22 intelligence methods to unlock the physiological, genetic and molecular pathways that
23 underpin the pro-inflammatory aging-phenotype. Using systems biology methods has
24 the potential to lead to the generation of novel therapeutic approaches for old diseases
25 and modern health challenges. Improving knowledge about how to delay or modify
26 the pro-inflammatory ageing-phenotype, the hallmark of ageing and age-related
27 disease, will give hope of a better quality aging and the longevity dividend for all.

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1 **Conflict of Interest Statement.**

2 The authors declare that the research was conducted in the absence of any commercial
3 or financial relationships that could be construed as a potential conflict of interest.

4
5 **Authors and Contributions**

6 IR conceived and designed the outline of the manuscript.

7 All authors IR, DG, VMcG, SMcN, DA and OR contributed to the manuscript draft.

8 All authors contributed to the drafting and revising of the manuscript and approved
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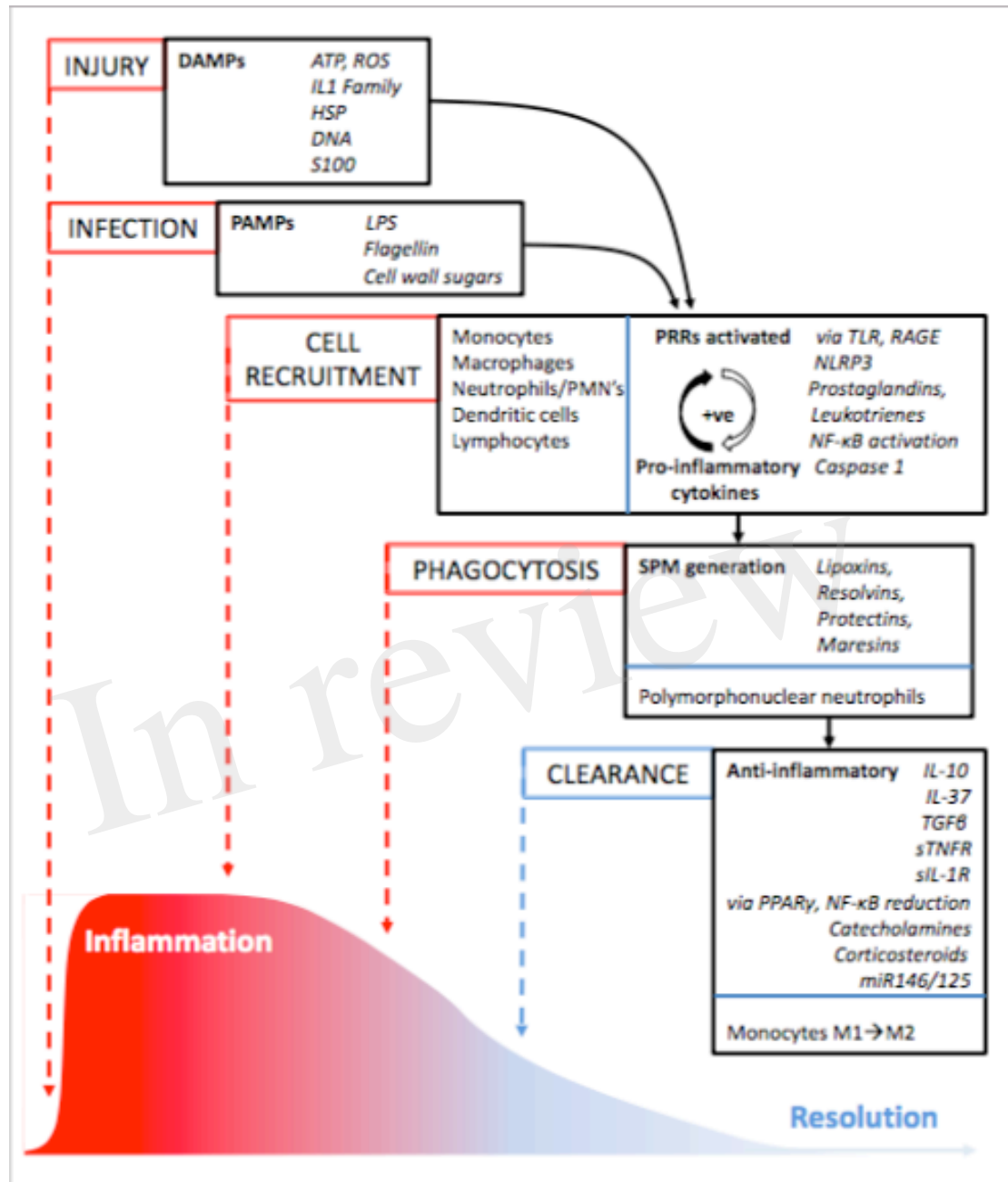
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Figure 1 Inflammation Pathway to Resolution

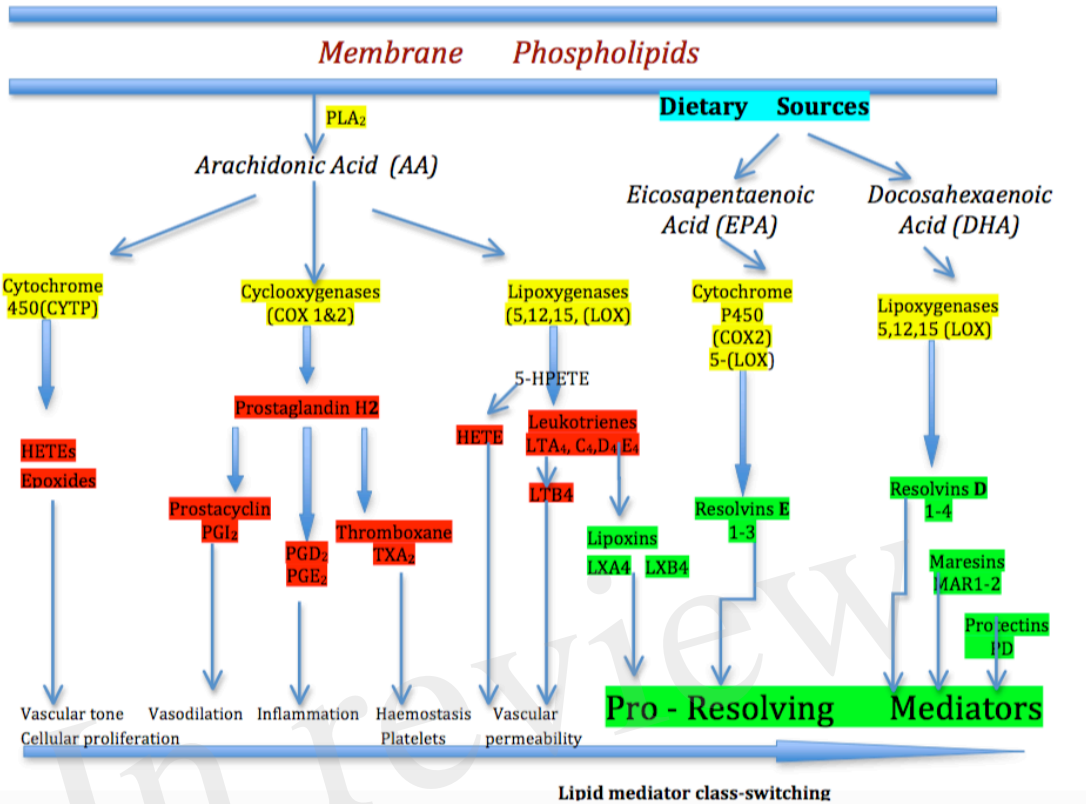


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An illustration of the sequence of key processes (in capitalised text), cells and molecules involved in reaction to injury or infection, and how the inflammatory episode is resolved over time (from left to right). Cells from the innate and adaptive immune system that are involved in cell recruitment, phagocytosis and clearance processes are highlighted in blue text; key molecules are in italic text.

1 **Figure 2 The Arachidonic Acid Pathway of Inflammation**
 2 **Mediators**

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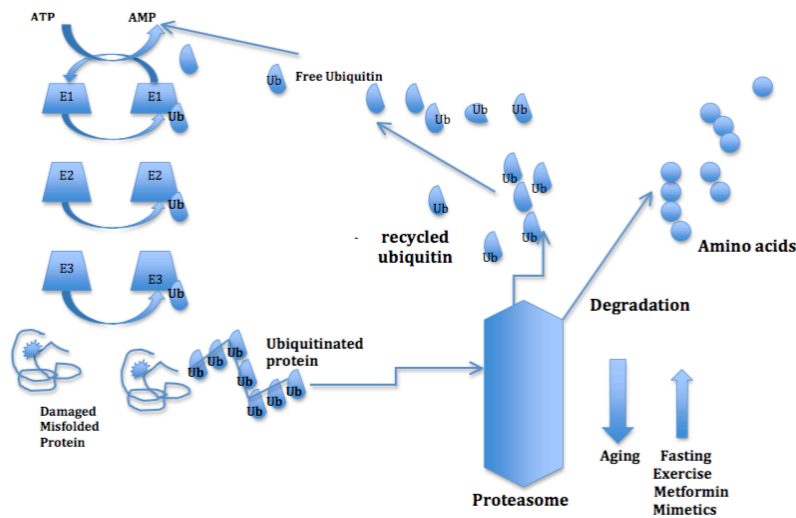
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In the simplified pathway for the eicosanoid metabolic pathway, arachidonic acid (AA) is released from membrane stores by phospholipase 2 (PLA₂). Arachidonic acid is metabolised to biological mediators by three enzymatic pathways: cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYTP). Each pathway contains enzyme-specific steps that result in a wide variety of bioactive compounds that drive the pro-inflammatory (prostaglandins) response. After lipid mediator class switching at the height of inflammation the pro-resolving mediators-lipoxins begin to drive inflammation resolution. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) derived from dietary sources produce the E-series of resolvins and D-series of resolvins, maresins and protectins respectively, which are important pro-resolving mediators in progressing the resolution of inflammation.

1 **Figure 3a The Ubiquitin Proteasome Pathway of Protein**
 2 **Degradation**

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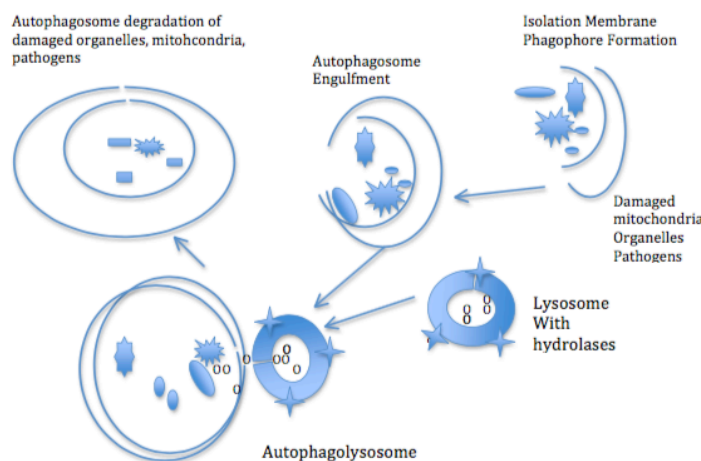
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5 Three different sets of enzymes -E1, E2, and E3, identify and categorise proteins in
 6 order to link ubiquitin (ub) or ubiquitin complexes to the damaged proteins. The
 7 ubiquitin-protein complexes pass through the proteasome where they are degraded
 8 and discharged as free amino acids into the cytoplasm.

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10 **Figure 3b The Autophagy Pathway of Degradation of Damaged**
 11 **Organelles and Pathogens**

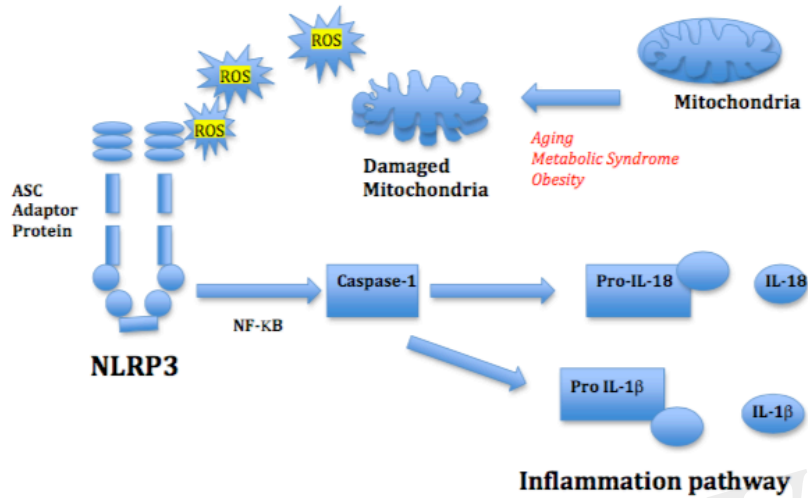
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14 The autophagy system degrades larger aggregated proteins and cellular organelles
 15 such as mitochondria, peroxisomes and infectious organisms. The process involves
 16 membrane formation, fusion and degradation. A small separate membrane called a
 17 phagophore forms and then forms the autophagosome that fuses with the lysosome.
 18 The autophagosome contents are degraded by lysosomal hydrolases.

1 **Figure 4 Mitochondrial ROS and NLRP3 Activation of**
 2 **Inflammation Pathway**
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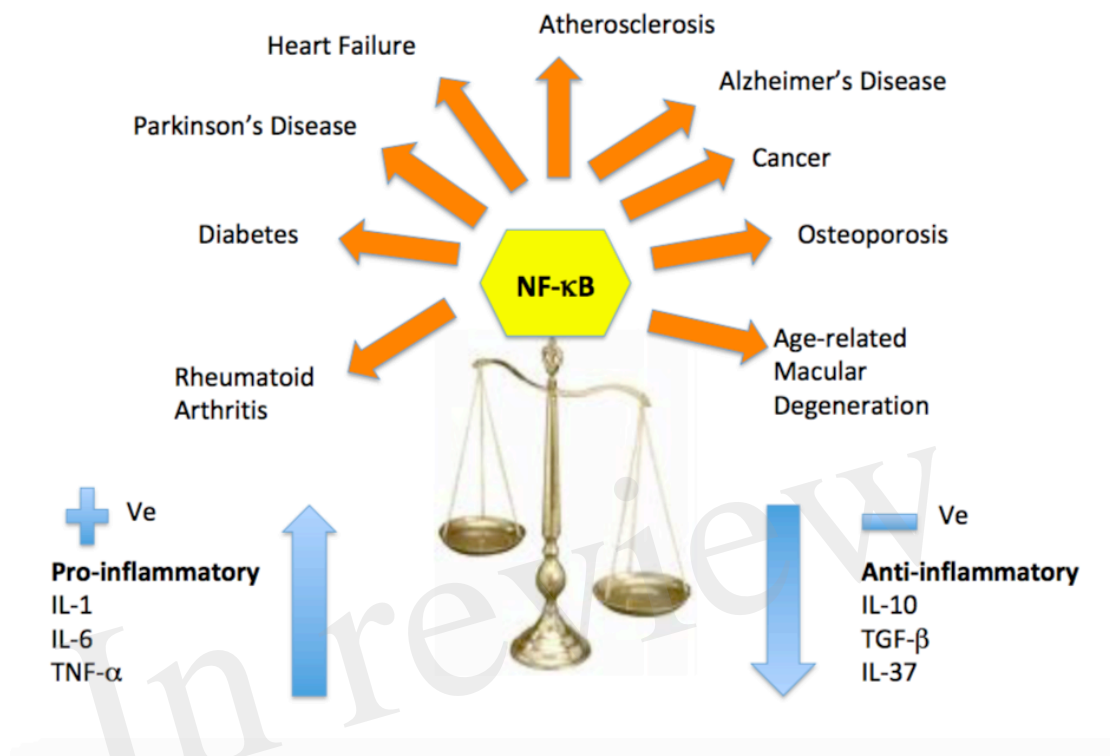


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 5 Mitochondrial reactive oxygen species (ROS) from damaged mitochondria triggers
 6 the inflammasome NLRP3, stimulating NF-κB and the IL-1β-and IL-18 mediated
 7 inflammatory cascade. The adapter protein ASC mediates innate signaling by
 8 bridging the interaction between the damage recognition receptor (DAMP) and the
 9 NF-κB caspase-1-inflammasome complex.

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1 **Figure 5 Cytokine Dysregulation and NF-κB Inflammation**
2 **Pathway**

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This reshaping of cytokine expression pattern, with a progressive tendency toward a pro-inflammatory phenotype has been called 'inflamm-aging' and is found associated with age-related diseases. Several molecular pathways have been identified that trigger the inflammasome and stimulate the NF-κB and the IL-1β-mediated inflammatory cascade of cytokines.