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Chronic Inflammation - Inflammaging – in the Ageing Cochlea: A Novel Target for Future Presbycusis Therapy

Nathan Watson^{a,c,d}, Bo Ding^{b,c}, Xiaoxia Zhu^{b,d}, and Robert D. Frisina^{b,c,d,*}

^aDept. Biomedical Engineering, Fitzpatrick Center (FCIEMAS), 101 Science Drive, Campus Box 90281, Duke University, Durham, NC 27708-0281, USA

^bDept. Communication Sciences & Disorders, 4202 E. Fowler Avenue, PCD1017 University of South Florida, Tampa, FL 33620-8200, USA

^cGlobal Center for Hearing & Speech Res., 3802 Spectrum Blvd., BPB Suite 210, University of South Florida Res. Park, Tampa, FL 33612, USA

^dDept. Chemical & Biomedical Engineering, 4202 E Fowler Avenue, ENB 118 University of South Florida, Tampa, FL 33620, USA

Abstract

Chronic, low-grade inflammation, or inflammaging, is a crucial contributor to various age-related pathologies and natural processes in aging tissue, including the nervous system. Over the past two decades, much effort has been done to understand the mechanisms of inflammaging in disease models such as type II diabetes, cardiovascular disease, Alzheimer's disease, Parkinson's disease, and others. However, despite being the most prevalent neurodegenerative disorder, the number one communication disorder, and one of the top three chronic medical conditions of our aged population; little research has been conducted on the potential role of inflammation in age-related hearing loss (ARHL). Recently, it has been suggested that there is an inflammatory presence in the cochlea, perhaps involving diffusion processes of the blood-brain barrier as it relates to the inner ear. Recent research has found correlations between hearing loss and markers such as C-reactive protein, IL-6, and TNF- α indicating inflammatory status in human case-cohort studies. However, there have been very few reports of *in vivo* research investigating the role of chronic inflammation's in hearing loss in the aging cochlea. Future research directed at better understanding the mechanisms of inflammation in the cochlea as well as the natural changes acquired with aging may provide a better understanding of how this process can accelerate presbycusis. Animal model experimentation and pre-clinical studies designed to recognize and characterize cochlear inflammatory mechanisms may suggest novel treatment strategies for preventing or treating ARHL. In this review, we seek to summarize key research in chronic

*Corresponding Author: Dr. Robert D. Frisina, Professor, Director & Chair, Global Center for Hearing & Speech Research, 3802 Spectrum Blvd., BPB Suite 210, University of South Florida Res. Park, Tampa, FL 33612, USA, Phone: 813-974-4013, Fax: 813-905-9840, rfrisina@usf.edu, Web: www.gchsr.usf.edu.

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inflammation, discuss its implications for possible roles in ARHL, and finally suggest directions for future investigations.

Keywords

Age-related hearing loss; presbycusis; chronic inflammation; inflammaging; aging cochlea; aging inner ear

1. Introduction

Age-related hearing loss (ARHL) or presbycusis is one of the most prevalent conditions among elderly individuals. Currently, about 10 percent of the world's population is affected by ARHL which correlates to about 30 million people in the US alone. Consequently, these individuals generally have trouble communicating with family members and co-workers, have declines in quality of life, and can suffer from depression, especially when their hearing impairment is accompanied by tinnitus- ringing of the ears (Dalton et al, 2003). Current research suggests that presbycusis is a multifactorial condition with multiple pathways and underlying conditions contributing to the biological mechanisms (Gates, Mills, 2005). Unlike other medical disorders with similar prevalence, ARHL lacks any biomedical treatment or preventative measures that materially reduce risk. Because of the dynamic nature of the condition, the full mechanisms of its actions are still being investigated.

In recent years, inflammation has been a key area of interest in biomedical research investigations of age-related conditions. As tissue ages, the body experiences a phenomenon known as “chronic inflammation.” Chronic inflammation also referred to as “inflammaging” is a mild form of inflammation that worsens with age. This inflammaging process is the phenomenon of immunosenescence, including the normal fluctuations resulting from an aging immune system (Gruver et al, 2007). This age-dependent immunosenescence process ultimately results in the body becoming increasingly worse at controlling or down-regulating the production of pro-inflammatory proteins during and after immune responses (Capri et al, 2006). Consequently, a progressively higher inflammatory state is observed in many aging tissues (Verschuur et al, 2014; Fulop et al, 2016). However, the potential pathways of inflammation and its effect on ARHL have received little attention in the fields of hearing research and auditory neuroscience.

Despite the paucity of research in sensory systems such as hearing, there is still intriguing evidence of inflammaging in other disease models of aging which can impact sensory processing in the aged. Conditions such as cardiovascular disease (Osiecki, 2004), type II diabetes (Grant, Dixit, 2013), as well as Alzheimer's disease (Blasko et al, 2004) show signs of chronic inflammation, and the available evidence often links these diseases to hearing loss. So, due to the similar age-dependence of these conditions, chronic inflammation is a likely candidate in the aging cochlea.

Related to this, acute inflammation and early-phase inflammatory responses have been implicated in noise-induced hearing loss models (Fujioka et al, 2006). These parallels in other disease models suggest the likeliness of inflammation being involved in ARHL.

2. Chronic Inflammation or Inflammaging

Chronic inflammation is now understood to be a ubiquitous characteristic of aging tissue. Stemming from natural ageing processes of the immune system, the majority of tissues slowly acquire an increased inflammatory state with aging. The pathway of chronic inflammation is not fully understood, however several possible mechanisms have been proposed (Franceschi, Campisi, 2014). Due to the buildup of pro-inflammatory proteins, inflammaging is likely to be a result of an acquired high “inflammatory state” (Verschuur et al, 2014). Since the overall goal of an inflammatory reaction is to clear the body of a particular cause of cell injury, optimal rates are beneficial. Causes of cell injury can be pathogens, toxins, or even physical injuries. Inflammation can initiate a series of events that ultimately leads to healing of the damaged tissue (Sarkar, Fisher, 2006). Unfortunately, chronic inflammation may follow acute inflammation. The acute immune responses call for up-regulation of various leukocytes, which should then be down-regulated after the completion of the process (Woods et al, 2012). However, in some chronic situations, such as aging, the body becomes increasingly worse at down regulating pro-inflammatory proteins, which often results in a slow but continuous buildup over time. This buildup of reactive molecules and cells designed to target pathogens, eventually damages the body’s own tissue structure (Chung et al, 2002). Another source of inflammaging could be the accumulation of cell debris resulting from insufficient elimination of cell waste. This “self-debris” can simulate pathogenic behavior and call for an innate immune response (Franceschi, Campisi, 2014). These various acute inflammatory responses over a duration of time eventually contribute to chronic cell damage. To summarize, acute inflammation falls under the category of short-term inflammatory processes that last a few hours or even a few days. Chronic inflammation is characterized to be a much longer and low-grade acquisition of inflammatory agents in tissue and in some cases, is not a sequel to acute inflammation but can even be an independent response. Although certainly related, acute inflammation and inflammaging can have seemingly opposing effects on the body.

Most age-related conditions involving inflammatory processes consist of similar proteins and molecular mechanisms (Michaud et al, 2013). Experimentally, similar biomarkers apply for determining inflammatory status across various pathologies. Improved knowledge of the key inflammatory biomarkers will pave the way for future biomedical interventions involving drugs or other agents that can modulate the activity of the key biomarkers and their pathways. Table 1 below summarizes some of the most commonly investigated factors.

The cytosolic part of the IL-1 receptor family member contains the Toll-IL-1-receptor domain. This domain is involved in the functional response of the IL-1 family, a fundamental part of innate immunity (Dinarello, 2011). More than any other cytokine family, the IL-1 family of ligands and receptors is primarily associated with acute and chronic inflammation and is among the first genes activated with any stimulation to a tissue that requires an immune response. This family is at the head of the cascade of steps involved

in inflammation (Kornman et al, 2006). However, among the cytokine protein family, interleukin-6 (IL-6) is another common inflammation marker. IL-6 is a pro-inflammatory cytokine that has been proven to be linked to age-related tissue. Stimuli inducing inflammatory actions call for phosphorylation and ubiquitination processes, which in turn degrade inhibitory proteins known as IKBs (Maggio et al, 2006). This degradation allows transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) to regulate the production of various pro-inflammatory proteins including IL-6 (Lawrence, 2009). IL-6 in conjunction with other indicators has been used in a wide variety of inflammaging studies to assess the presence and extent of inflammatory processes (Fujioka et al, 2006; Dandona et al, 2004; Duncan et al, 2003; Kubaszek et al, 2003; Pradhan et al, 2001; Verschuur et al, 2006).

Another cytokine that has received considerable interest is tumor necrosis factor- α (TNF- α). This cytokine is a central circulating factor that proliferates under pro-inflammatory conditions. The overall signal transduction mechanisms that induce TNF- α expression are relatively unknown. There is some evidence, however, that NF- κ B regulates its expression levels (Bradley, 2008). After the production of TNF- α , vascular endothelium cells begin displaying various adhesion molecules that call for the binding of different leukocytes, thus promoting pro-inflammatory behavior (Bradley, 2008). Investigations have demonstrated that elevated TNF- α tissue and serum levels correlate to the severity of inflammation present (Popa et al, 2007). The cytokines interleukin-6 (IL-6), IL-1, and TNF- α are elevated in most, if not all, inflammatory states, so therefore have been recognized as targets of therapeutic intervention (Scheller et al, 2011).

Subsequently, the TGF- β family of cytokines and receptors have been shown to participate in the pathways of chronic inflammation in ageing tissue (Monteleone et al, 2008). TGF- β possesses two functional domains - both critical for innate immunity. TGF- β proliferates under a typical immune response and assists in regulating cell regeneration, angiogenesis, and recruitment of other pro-inflammatory proteins. It is well known that proper regulation promotes healthy inflammatory homeostasis *in vivo* (Marek et al, 2002). Current literature overwhelmingly acknowledges that insufficient regulation of TGF- β synthesis contributes to various chronic inflammatory pathologies. Considerable work has documented how deficiencies in signaling contribute to chronic inflammatory conditions such as inflammatory bowel disease (Hahm et al, 2001; Kanazawa et al, 2001). Studies focused on inhibiting TGF- β signaling using either IL-15 or Smad-7 demonstrate increased inflammatory character and overexpressed inflammatory bowel disease (Benahmed et al, 2007; Monteleone et al, 2001).

Moreover, inflammaging has been investigated in a variety of disease models, some of which have been linked to hearing loss. Of these, considerable research has been done on type II or adult onset diabetes. Diabetes was first investigated as an inflammatory condition because obesity (a major precursor of type II diabetes) has a well-known inflammatory presence (Dandona et al, 2004). Duncan *et al.* performed a pioneering investigation on the role of inflammation in type II diabetes. This group used a case-cohort study to observe a significant correlation between overall calculated “inflammatory score” and development of type II diabetes. This group’s inflammation score was based off the presence of interleukin-6

(IL-6), C-reactive protein (CRP), sialic acid, orosomucoid, white blood cells and fibrinogen levels, all strong indicators of inflammatory status. Paying particular attention to interleukin-6, the study concluded that low-grade inflammation predicts type II diabetes in non-smoking individuals (Duncan et al, 2003). Furthermore, Kubaszek and his colleagues explored cytokine levels and their association with the conversion from impaired glucose tolerance (IGT) to type II diabetes. His group concluded that the -308A allele of the TNF- α cytokine gene was coupled with an almost two times higher likelihood for type II diabetes. Pro-inflammatory cytokine expression is also directly associated with a greater risk for type 2 diabetes (Kubaszek et al, 2003). Supplementary studies before and after these investigations have additionally supported these findings (Pradhan et al, 2001; Schmidt et al, 1999; Barzilay et al, 2001; Han et al, 2002). Currently, it is accepted that a chronic, low-grade inflammatory process is in the overall mechanism for the progression of type 2 diabetes. Interestingly, Frisina and colleagues demonstrated that type II diabetics have worse hearing based upon a number of measures of audition including pure-tone audiograms, otoacoustic emissions, temporal processing, and speech perception in the presence of background noise (Frisina et al., 2006). Similar studies in animal models also show that both type I and type II diabetes can result in poorer hearing when compared to age-matched controls without diabetes (e.g., Vasilyeva et al., 2009).

Additionally, extensive research has been conducted on chronic inflammation's role in cardiovascular disease. Over a decade ago, Ridker *et al.* performed an innovative study that associated a low-grade inflammation processes as a method of determining potential risk of cardiovascular disease among women (Ridker et al, 2000). Various further investigations have added this line of research (Koenig et al, 1999; Osiecki, 2004; Bermudez et al, 2002; Pearson et al, 2003; Blake, Ridker, 2002). Table 2 summarizes additional disease possessing inflammaging components and their corresponding literature.

3. Inflammation in the Cochlea

A likely causal effect between chronic inflammation and hearing loss has been seen in inner ear disorders induced by chronic systemic autoimmune disease, such as polyarthritis nodosa, Cogan's syndrome, systemic lupus erythematosus, and others (Harris, Ryan, 1995; Hughes et al, 1993). Chronic activation of inflammatory cytokines such as IL-1 α , IL-2, TNF- α and NF- κ B, essential in the initiation, modulation and amplification of the immune response, can infiltrate cells of the inner ear, such as those in the endolymphatic sac (Satoh et al, 2003; Satoh et al, 2006). Corticosteroids, which are anti-inflammatory, historically have been used to treat autoimmune sensorineural hearing loss, acutely in cases of sudden hearing loss, and somewhat effectively (Trune et al, 2006). Taken as a whole, the previously discussed literature suggests that it is likely that inflammaging is present in the auditory system contributing to ARHL. However, the role of the immune system in cochlear aging, has changed over time, and much is still unknown. An historical view was that the cochlea was immune-privileged, in some ways similar to the blood-brain barrier (Harris, 1983). This was believed because the cochlea contains a tightly regulated microcirculation environment and lacks any type of lymphatic drainage (Okano, 2014). Specifically, the stria vascularis cells in the cochlear lateral wall possess a network of tight-junctions meticulously connected to prevent the intrastrial region from coming into contact with the blood flow. These junctions

make up one of the most effective blood-tissue barriers in the body. This separation of tissue and blood in the inner ear is known as the “blood-labyrinth” barrier or the “fluid-blood” barrier (Juhn et al, 2001). However, this immune-privileged status of cochlear immunology changed when Rask-Andersen and colleagues discovered that lymphocytes and macrophages are able to infiltrate the endolymphatic sac in guinea pigs (Rask-Andersen, Stahle, 1979). This group provided the first strong evidence of direct immune responses in the auditory system.

So, since the introduction of this new idea, follow-up studies have substantiated direct immune effects in the inner ear. For example, there is evidence that the lateral wall of the cochlea is now a common site of inflammation (Fujioka et al, 2014). The “fluid-blood” barrier in stria vascularis cells is known to be permeable due to regulation provided by cells known as perivascular-resident macrophage-like melanocytes (PVM/Ms). Research has suggested that PVM/Ms have the capability to regulate the permeability of the intrastrial fluid-blood barrier (Zhang et al, 2012). It has been found that stria vascularis cells, regulated by PVM/Ms, are the site for the release of pro-inflammatory cytokines through this tight-junction barrier (Zhang et al, 2013). PVM/M cells are essential to penetrability of the fluid-blood barrier as well as regulator of inflammation in the auditory system. Due to this release in the stria vascularis, the spiral ligament and the entirety or the lateral wall are common sites to observe inflammation as well.

A potential application of these types of discoveries is for patients coping with acute acoustic traumas (AAT), such as soldiers suffering from gunshot noise exposure. Clinically, steroid based regimens have been used to treat AAT patients as a means to prevent or attenuate noise-induced hearing loss, (Salihoglu et al, 2015). A particular study on AAT in gunshot noise exposure in soldiers revealed that 69% of the subjects showed some type of hearing improvement after receiving a steroid based therapeutic (Psillas et al, 2008). The consequences of such steroid treatment may perhaps be attributed to a suppression of excessive cochlear inflammation (Fujioka et al, 2006). It has also been shown that cytokine release, including IL-6 is actually suppressed by steroid treatment in regions of the cochlea such as the lateral wall (Maeda et al, 2005). While the mechanisms of such action are still unknown, inflammation-based explanations are quite plausible. Indeed, there is much promise for future investigations studying therapeutics that target cytokines such as IL-6 for preventing different types of hearing loss, including ARHL.

4. Chronic Inflammation in Age-Related Hearing Loss

Chronic inflammation that may begin in a slow, insidious, and even unnoticed manner, which is compatible with the temporal progression of presbycusis. The previous discussion of the role of inflammaging in many diverse age-related diseases suggest that inflammaging is an essential component in the physiology of ageing. This extensive research has demonstrated that low-grade inflammation processes have critical roles in the causation of age-related diseases including ARHL. Interactions between presbycusis, and inflammatory pathways have scarcely been examined. Only a few groups have explored the role of inflammation in the auditory system and most have endorsed a human-based cross sectional analysis approach, so animal model investigations are rare.

Most notable of the human studies was conducted by Verschuur *et al.* (2012). This group examined relationships between hearing thresholds and key serum biomarkers of low-grade inflammation (Verschuur et al, 2012). They utilized findings from the British birth cohort study known as the Hertfordshire Ageing Study. They analyzed quantitative relations between the average hearing thresholds of elderly individuals and their IL-6 and CRP levels, white blood cell counts, as well as neutrophil counts. These data, all precise indications of inflammation, indicated a gradual *increase* in systemic inflammation as aging persisted as well as a *decrease* in hearing thresholds. Verschuur and colleagues concluded that inflammation is a component of the mechanisms underlying presbycusis. In order to eliminate potential sample bias, this same group conducted a similar investigation on a different population data set and concluded many of the same basic findings (Verschuur et al, 2014).

The ASPREE-HEARING study is the only other group currently investigating inflammation in ARHL. This group is studying the potential therapeutic benefits of low-dose aspirin, a weak anti-inflammatory agent, on ARHL. The aim of the investigation is to determine whether this basic therapy will lessen the progression of the disease in elderly individuals. This large Australian-based clinical trial is targeting 1262 individuals age 70 years old or older but is still currently in progress. Results are not expected to be finalized until 2018 (Lowthian et al, 2016). The ASPREE-HEARING trial provides large potential for an incredibly inexpensive yet feasible treatment option for preventing or reducing ARHL.

While ARHL research has not explicitly focused on cochlear inflammation with aging, there have been such studies in noise-induced hearing loss (NIHL) models. NIHL is a very prevalent condition and in some ways related to ARHL. Though NIHL is not in the family of age-related diseases, it likely possesses some similar mechanisms, but on more of an acute timeline (Wong, Ryan, 2015). Several studies have focused on the mechanisms; for example, a study conducted by Fujioka *et al.* (2006). This group examined pro-inflammatory cytokine biomarkers in the cochlea following noise-induced damage to the cochlea. In particular, they were interested in TNF- α , IL-1 β and IL-6. Upon experimentation, they concluded that the non-sensory areas of the cochlea, in particular the lateral wall are common and key areas of inflammation after noise-induced trauma. Specifically, IL-6 cytokine expression in the lateral wall of the cochlea was observed at the highest levels 3 and 6 hours after noise exposure. They concluded that the non-sensory areas of the cochlea, in particular the lateral wall are key areas of inflammation after noise overexposures (Fujioka et al, 2006). Additionally, blockage of the cytokine IL-6 pathway has been shown to improve hearing after noise exposure, and be a potential avenue for future therapies for various kinds of hearing loss (Wakabayashi et al, 2010).

These pioneering investigations sparked clear understanding that there is not only an immune presence in the cochlea but an acute inflammatory presence in response to stressors such as loud noise. Given some similarities between ARHL and NIHL, identifying a link between inflammation and presbycusis provides a range of new implications when considering clinical translational interventions. Some of these include blocking inflammatory pathways during and after noise overexposure, and possibly particular nutritional and mineral supplements (Pae et al, 2012). Moreover, it is consistent with the fact

that certain lifestyle choices can lead to hearing loss, such as weight gain and smoking (Kumar et al, 2013). Specifically, smoking is a known contributor to higher levels of chronic inflammation in different tissues including the cardiovascular system, which may be the underlying link in its role in presbycusis (Verschuur et al, 2014).

5. Summary, Conclusions and Future Work

Over the past decade, considerable evidence has accumulated that chronic inflammatory processes are critical mechanisms underlying age-related pathologies. Some of these have included a more extensive look at the role of acute inflammation in noise-induced hearing loss models as well as an investigation of chronic, age-linked diseases that may be related to hearing loss. It is likely that these varying diseases have similar inflammatory mechanisms which apply to ARHL, i.e., our supporting hypothesis is that the chronic nature of inflammation plays a role in mechanisms of ARHL. To date, several human-based cohort investigations present evidence of the role of systemic inflammation in ARHL. Promising results suggest that inflammation is a key area of future research. However, there is still little known about inflammation in the ageing cochlea or parts of the brain used for hearing – central auditory system.

This review of the inflammaging literature suggests a clear direction for future projects, such as investigating chronic cochlear inflammation in animal models. The overarching aim is to the presence and roles of pro-inflammatory molecules and pathways, such as those summarized in Table 1, in the ageing cochlea. By targeting the molecular pathways of chronic inflammation processes in the auditory system, we will be able to better understand possible roles in presbycusis. Based upon research of other disease models, particular attention will be given to both the sensory and non-sensory areas of the cochlea. For instance, various research efforts have pointed to the lateral wall, the stria vascularis and the spiral ligament areas, as being critical areas of inflammation (Hirose, Liberman, 2003). Further understanding of the nature of pro-inflammatory molecules in the cochlea and auditory brain, as well as potential non-sensory areas of interest will allow for development of novel therapeutic interventions for ARHL.

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Highlights

- Chronic inflammation is a crucial contributor to various age-related conditions.
- Studies are needed to understand the molecular pathways of cochlear inflammation.
- Cochlear inflammation is a promising pathway to better understanding presbycusis.

Figure 1. Cytokines, chemokines and their pathways

Cytokine signaling proceeds through cell membranes via oligomers of single-pass, type I transmembrane receptors, with distinct extracellular domains for ligand binding, and intracellular domains for signal transduction. 1) IL-1 β activates IL-1R associated kinases (IRAKs) and ultimately leads to the phosphorylation of I κ B α via TRAF6 and IKK. The phosphorylated I κ B α is subsequently ubiquitinated for degradation by the proteasome. The phosphorylated p65/p50 heterodimer translocates to the nucleus, where it binds to response elements in NF- κ B-dependent genes and leads to the induction of pro-inflammatory gene expression. 2) IL-6 signal is initiated by cytokine binding of the FIII domains of the IL-6R chains which ultimately activates signal transduction via the gp130 proteins. Signal transduction leads to STAT3 phosphorylation and dimerization. Phosphorylated STAT3 dimers translocate to the nucleus and bind to the IFN γ activation site (GAS) in responsive genes. This leads to the transcription of pro-inflammatory genes, p65 and p50, and intracellular adhesion molecules. 3) Signals via TNF- α are followed by mitogen-activated protein kinase (MAPK, TRAF-2 and MEKK1)) cascades, leading to transcription factor activation. JNK activates the AP1 heterodimer. In addition, the TNF- α complex I signal leads to IKK activation, which results in the phosphorylation and degradation of I κ B α by the ubiquitin–proteasome system. Downstream, the NF- κ B heterodimer of p65/p50 is

activated by IL-1 β , and p65/p60 can then migrate to the nucleus, bind to response elements and induce the expression of pro-inflammatory genes. Importantly, the outcome of the Complex I signal pathways favor proinflammatory cytokine expression. **4)** IL-8 exists as monomers in the plasma but local concentrations in tissue favors dimer formation. Binding of IL-8 to the chemokine receptors leads to activation of the heterotrimeric G-proteins (G α , β , γ). The G α subunit in particular activates the membrane-bound adenylate cyclase, which generates cyclic AMP (cAMP), which can activate protein kinase A (PKA). Alternatively, the G $\beta\gamma$ heterodimer can dissociate from the G α subunit and stimulate phospholipase β (PLC β) activity, which cleaves phospholipids to produce inositol 3,4,5-triphosphate and diacylglycerol (DAG). DAG activates PKC, which then induces MAPK (MEK 1–2) activation. Of note, anti-inflammatory antagonists such as aspirin can inhibit all these cytokine signals.

Table 1**Examples of Primary Chronic Inflammation Biomarkers**

Biomarker	Abbrev.	Description	Literature Citations
Interleukin-6	IL-6	A pro-inflammatory cytokine with an inflammaging component central to various aging mechanisms.	Fujioka et al, 2006 (rats, cochlea tissue); Dandona et al, 2004 (human, plasma); Duncan et al, 2003 (human, plasma); Kubaszek et al, 2003 (human, plasma); Pradhan et al, 2001 (human, plasma); Verschuur et al, 2012 (human, serum)
Tumor necrosis factor- α	TNF- α	A central circulating factor essential to the systemic inflammatory mechanism. Thought to stimulate pro-inflammatory behavior by promoting compilation of various leukocytes.	Fujioka et al, 2006 (rats, cochlea tissue); Dandona et al, 2004 (human, plasma); Kubaszek et al, 2003 (humans, plasma); Koziorowski et al, 2012 (humans, plasma)
Interleukin-1 β	IL-1 β	A member of the IL-1 family of cytokine proteins. IL-1 β is essential to pro-inflammation cellular function as well as regulating cell proliferation and differentiation.	Ren, Torres, 2009 (review); Fujioka et al, 2006 (rats, cochlea); Larsen et al, 2009 (human, plasma)
Nuclear factor kappa-light- chain-enhancer of activated B cells	NF- κ B	A transcription factor that stimulates the production of many pro- inflammatory cytokines including IL-6 and TNF- α .	Bollrath et al, 2009 (review); Kempe et al, 2005 (human, HMEC-1 cells); Greten et al, 2007 (mouse, plasma)
Signal transducer and activator of transcription 3	STAT3	Like NF- κ B, STAT3 is a transcription factor that positively mediates the production of various pro-inflammatory cytokines.	Bollrath et al, 2009 (Review); Phesse et al, 2009(mouse, mucosal membrane); Grivennikov et al, 2009 (mice, distal colon); Yu et al, 2009 (Review)
C-reactive protein	CRP	CRP belongs to a group of proteins known as acute phase reactants whose concentrations increase in response to inflammation. C-reactive protein (CRP) is one of the most commonly investigated inflammatory markers in cardiovascular research.	Nesto, 2004 (review); Duncan et al, 2003 (human, plasma); Pradhan et al, 2001 (human, plasma); Barzilay et al, 2001 (human, plasma); Verschuur et al, 2012 (human, serum); Han et al, 2002 (human, plasma)

Table 2

Summary of Chronic Inflammation Literature in Various Disease Models Pertinent to Aging

Disease Model	Basic Findings	Disease Model Literature
Type II Diabetes	Overall inflammatory scores calculated by total levels of pro-inflammatory markers such as IL-6, CRP, and TNF- α provide a novel prediction of likeliness to acquire type II diabetes later in life.	Dandona et al, 2004 (human, plasma); Duncan et al, 2003 (human, plasma); Kubaszek et al, 2003 (human, plasma); Pradhan et al, 2001 (human, plasma); Schmidt et al, 1999 (human, whole blood); Barzilay et al, 2001 (human, plasma); Han et al, 2002 (human, whole blood); Larsen et al, 2009 (human, whole blood)
Cardiovascular Disease	Pro-inflammatory markers, specifically CRP, play a critical role in the long term development of cardiovascular disease and the complications that comes with it.	Ridker et al, 2000 (human, plasma); Koenig et al, 1999 (human, serum); Bermudez et al, 2002 (human, whole blood); Blake, Ridker, 2002 (human, plasma)
Alzheimer's Disease	Age-related conditions associated with Alzheimer's Disease suggest that chronic neuro-inflammatory mechanisms as well as innate immunity specifically in the microglial cells and astrocytes play a critical role in the course of the disease.	Blasko et al, 2004 (human, brain tissue); Walker et al, 2009 (human, brain tissue); Heppner et al, 2015 (Review); McGeer et al, 2003 (Review)
Frailty Syndrome	Frailty among elderly individuals has been shown to worsen with an increased chronic inflammatory state. In particular, white blood cell counts as well as CRP and IL-6 levels provide an effective mechanism of measuring or predicting frailty.	Baylis et al, 2013 (human, serum); Leng et al, 2007 (human, serum); Walston et al, 2002 (human, whole blood)
Parkinson's Disease	Pro-inflammatory markers such as IL-1 β , IL-6, and TNF- α are higher in both the brain and blood serum in Parkinson's patients when compared to a healthy group.	Koziorowski et al, 2012 (human, whole blood); Mogi et al, 1994 (humans, dopaminergic, striatal regions of brain); Walker et al, 2009 (humans, brain tissue)