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Review

Chronic inflammation – inflammaging – in the ageing cochlea: A novel target for future presbycusis therapy

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

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 and 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

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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 and 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-depended nature 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 and 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 and 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 and 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 (Fig. 1).

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, 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-κB) 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., 2012).

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-κB 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 overwhelming 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