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Molecular and Cellular Mechanisms of Loss of Residual Hearing After Cochlear Implantation

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Objectives: We describe the various molecular and cellular pathways that lead to early and delayed loss of residual hearing after cochlear implantation.

Methods: We performed a systematic review using the Medline database with the key words cochlear implant, residual hearing, inflammation, apoptosis, and necrosis.

Results: The mechanisms underlying the loss of residual hearing after cochlear implantation are multiple. Early hearing loss may be provoked by the surgical access to the inner ear spaces and by trauma caused by insertion of the electrode array. After the initial trauma, an acute inflammatory response promotes elevated levels of cytokines and reactive oxygen species, which in turn promote sensory cell loss by apoptosis, necrosis, and necrosis-like programmed cell death. Treatments that counteract such an inflammatory reaction, production of reactive oxygen species, and apoptosis are effective at preventing hair cell degeneration. However, delayed hearing loss appears to be a consequence of chronic inflammation with development of fibrotic tissue. The mechanisms that lead to fibrosis are poorly understood, and standard anti-inflammatory drugs are insufficient for preventing its development.

Conclusions: Cochlear implantation is followed by an inflammatory response involving several pathways that lead to either short-term or long-term sensory hair cell degeneration. Future studies should focus on revealing the precise molecular mechanisms induced by cochlear implantation to allow the discovery of new targets for the effective prevention and treatment of loss of residual hearing.

Key Words: apoptosis, cochlear implantation, fibrosis, necrosis, residual hearing.

INTRODUCTION

Cochlear implantation is a state-of-the-art technique that has become the standard procedure for restoring auditory perception to profoundly deaf people. The exponential growth of cochlear implant research and development over the past few decades is the consequence of the remarkable postoperative speech perception outcomes of patients with implants. Thus, indications for cochlear implantation have progressively extended to include people who had residual hearing but who had benefited very little from conventional hearing aids, through the development of electroacoustic stimulation.

Electroacoustic cochlear stimulation relies on simultaneous stimulation using a cochlear implant coupled with a hearing aid.[1-4] The middle- and high-frequency sounds are coded by the electrical signal delivered through the electrode array inserted in the cochlea, whereas the low-frequency sounds are amplified by the hearing aid and delivered through the ear canal just as with conventional hearing aids. This type of hybrid stimulation requires not only significant preoperative residual hearing in the low frequencies, but also the preservation of this residual hearing after cochlear implantation.

The follow-up of patients with implants reveals distinct possible outcomes regarding residual hearing after cochlear implantation.[5] Although residual hearing is preserved in a significant number of cases, postoperative hearing loss may occur within the few days following surgery or later, up to several weeks or months after surgery, in these patients. Differences in the time courses of postoperative hearing loss after cochlear implant surgery strongly indicate that distinct cellular and molecular mechanisms are involved in these processes. This review will describe the molecular and cellular events triggered by cochlear implantation and depict the therapeutic pathways that can be used to prevent this hearing loss.

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TRAUMA ASSOCIATED WITH COCHLEAR IMPLANTATION

A first obvious explanation for an early loss of residual hearing after cochlear implantation is the trauma suffered during the electrode array insertion. The electrode array may be inserted through the round window of the cochlea or through a cochleostomy of the basal turn of the scala tympani. Whatever the insertion site chosen, the aim is to perform an atraumatic insertion of the electrode array into the scala tympani. The round window would seem to provide an easy access to the basal turn of the scala tympani; however, anatomically, nontraumatic deep insertion of the electrode array can be difficult by the round window approach.[6] Indeed, by this route, the curvature of the cochlea cannot always be respected by the array, and the friction of the electrode array can cause tearing of the lateral wall or malpositioning of the array into the scala media or the scala vestibuli.[7] On the other hand, basal turn cochleostomy requires drilling through the promontory, and the acoustic pressure delivered by the drilling bur may reach 130 dB and provoke acoustic trauma.[8] Moreover, the drilling site chosen for the cochleostomy is critical. It must be anteroinferior, in order to avoid opening the scala media or the scala vestibuli. Whatever the technique chosen — round window approach or basal turn cochleostomy — a thorough preoperative assessment and good surgical practice are required to avoid accidental destruction of the organ of Corti or a fracture of the spiral osseous lamina or the modiolus containing the spiral ganglion neurons and fibers. Other surgical events may also alter cochlear functioning during or after surgery, among which contamination of the perilymph with blood seems to play a modest but significant role.[9,10]

In addition to surgical considerations, specific designs of electrode arrays have been proposed to reduce the insertion trauma. Shorter arrays may be used to reduce the risk of tearing or malpositioning when the array cannot bend and conform to the curvature of the cochlea.[11,12] However, in case of loss of residual hearing secondary to surgery or to the natural evolution of the disease, shorter arrays may not be able to reach the middle turn of the cochlea and stimulate the middle and low hearing frequencies. For this reason, longer but more malleable electrode arrays are under development. Owing to the fact that mechanical damage to cochlear structures is also related to the diameter of the array (sometimes larger than the scala tympani itself in the middle and the upper turns of the cochlea), the dimensions of the longer arrays decrease from base to tip in order to limit such trauma.

Despite appropriate surgical techniques and electrode array design, the preservation of functional residual hearing with electroacoustic stimulation is achieved in only 44% to 84% of cases.[5,13-17] In the other cases, the residual hearing either is completely lost or is insufficient to benefit from hearing aids. Therefore, a better understanding of and control over the cellular and molecular mechanisms that lead to postoperative hearing loss is greatly needed.

MOLECULAR PATHWAYS INVOLVED IN HEARING LOSS AFTER COCHLEAR IMPLANTATION

Clinical and experimental data from animal models suggest that early and delayed hearing loss following cochlear implantation is the consequence of the activation of independent pathways. Electrode insertion–induced hearing loss results from direct trauma (mechanical damage due to electrode array insertion or acoustic trauma due to drilling of the cochleostomy) that leads to a direct activation of cell death pathways. Conversely, delayed hearing loss may result from inflammatory processes that promote fibrosis development and the indirect activation of cell death pathways.

Early Hearing Loss. The exact pathophysiologic mechanisms that result in early postoperative hearing loss are largely unknown. It has been proposed that early hearing loss may be associated with cochlear cell death through apoptosis, necrosis, and necrosis-like cell death pathways.[18,19] Apoptosis is a well-documented active programmed cell death in which the activation of caspases, a family of cell suicide cysteine proteases, plays a central role[20,21] (Fig 1). Morphologically, apoptosis is defined by cytoskeleton collapse, cell shrinkage, membrane blebbing, chromatin condensation, and DNA fragmentation.[22,23] A progressive increase in apoptotic hair cell death has been observed in traumatized cochleas 12, 24, and 36 hours after electrode insertion.[19] Necrosis is considered to be a passive cellular event and may be induced by mechanical damage or by exposure to certain toxic organisms, agents, or chemicals. Necrosis is characterized by cellular edema and disruption of the plasma membrane, which leads to the release of cellular components and thus to an acute inflammatory tissue response.[24] Necrosis-like programmed cell death (nonlysosomal vesiculate or cytoplasmic) is a caspase-independent mode of cell death with necrotic morphology that appears to be regulated by intrinsic cellular programs.[25-28] Necrosis or necrosis-like cochlear cell death may also occur after electrode insertion trauma.[29]

Generation of reactive oxygen species and other free radicals is one of the mechanisms by which acute trauma causes the apoptosis of cochlear sen-

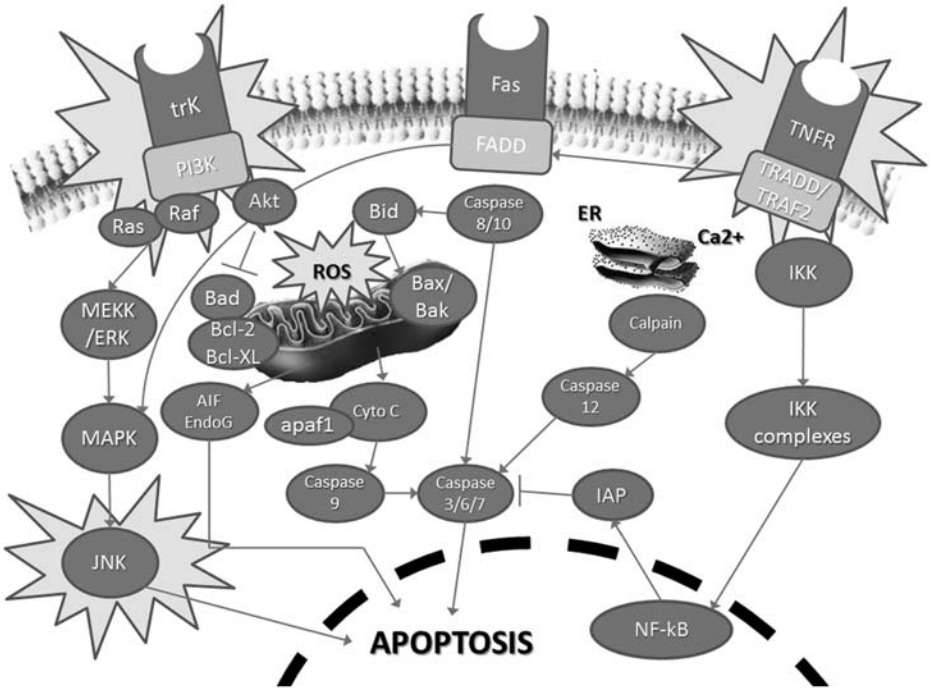

Fig 1. Apoptotic pathways activated during hair cell loss. Apoptosis is induced either directly by extracellular signals or after activation of intrinsic pathway. Extrinsic pathways involve tyrosine kinase receptor activating MAPK/ERK/JNK pathway or CD95 (Fas) activating caspase 8/10 and their respective subsequent cascade. Extrinsic pathways also regulate intrinsic pathways involving mitochondria and endoplasmic reticulum. Release of cytochrome C by mitochondria is under control of pro-apoptotic (Bak, Bax) or anti-apoptotic (Bcl-2, Bcl-XL) proteins that are themselves regulated by proteins such as Bad or Bid, both of which play pro-apoptotic role. In cytoplasm, cytochrome C combines with Apaf-1 and activates caspases. After ROS exposure, mitochondria may also release other pro-apoptotic factors such as AIF or EndoG. On other hand, intrinsic pathways also involve endoplasmic reticulum. Increase in $Ca2^{+}$ promotes calpain activation and caspase 12 cleavage. Role of IKK is more complex; in certain conditions, activation of IKK releases NF-κB that causes its nuclear translocation. NF-κB promotes IAP production and protects against apoptosis. After cochlear implantation, regulation of ROS production, TNF activation, and JNK pathway results in significant protection against residual hearing loss (light stars). AIF — apoptosis-inducing factor; Akt — protein kinase B; Apaf1 (apaf1) — apoptotic protease activating factor 1; Bad — bcl-2 associated death; Bak — Bcl-2 homologous antagonist/killer; Bax — Bcl-2–associated X protein; Bcl-2 — B-cell lymphoma 2; Bcl-XL — B-cell lymphoma extra-large; Bid — BH3 interacting-domain death agonist; Cyto C — cytochrome C; EndoG — endonuclease G; ER — endoplasmic reticulum; ERK — extracellular signal regulated kinase; FADD — Fas-associated protein with death domain; Fas — CD95; IAP — inhibitor of apoptosis; IKK — IκB kinase; JNK — Jun N-terminal kinase; MAPK — mitogen activated protein kinase; MEKK — mitogen activated protein kinase kinase; NF-κB (NF-kB) — nuclear factor kappa light chain enhancer of activated B cells; PI3K — phosphatidyl inositol 3 kinase; ROS — reactive oxygen species; TNFR — tumor necrosis factor receptor; TRADD — tumor necrosis factor receptor type 1–associated death domain protein; TRAF2 — tumor necrosis factor receptor–associated factor 2; trK — tyrosine kinase receptor.

sory cells (Fig 1). Several reports have placed the reactive oxygen species pathway at the core of electrode-induced cochlear damage.[19,30] Although it has only been postulated that free radical formation causes cochlear cell damage following electrode insertion, this hypothesis has strong support from the results of experiments that demonstrate that treatment with antioxidant precursor *N*-acetyl cysteine prevents hearing loss in a guinea pig model of cochlear implantation.[31]

Delayed Hearing Loss. Besides the early events following cochlear implantation, fibrotic proliferation of tissues within the cochlea may occur and provoke the progressive delayed loss of residual hearing.[32,33] As in tissues besides the cochlea, fibrosis is believed to be a consequence of chronic inflammation, excessive extracellular matrix secretion, and fibroblast proliferation[34-36] (Fig 2). Such fibrotic tissue around the electrode array is a common feature following cochlear implantation both in humans and in animal models. This fibrosis is deleterious to cochlear implantation for several reasons. First, fibrosis increases electrode impedance, decreases the electrical dynamic range for stimulation, and reduces battery life.[37] Second, fibrosis may impair sound transmission to the cochlear apex and reduce the possibility of using residual hearing.[38] Finally, it disrupts the architecture of the organ of Corti and provokes subsequent hair cell and neuronal loss, further compromising the maintenance of residual hearing.[39]

The development of cochlear fibrosis can be as-

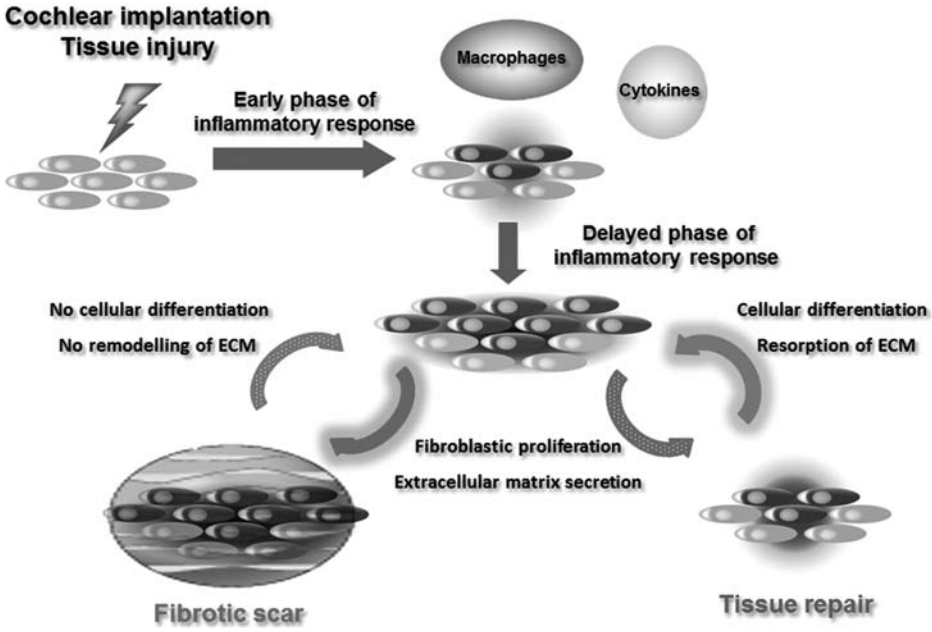

Fig 2. Fibrotic scar formation after cochlear implantation. Acute inflammatory reaction is triggered by insertion trauma that induces recruitment of inflammatory cells such as macrophages or lymphocytes to site, thus promoting elimination of cellular debris and secretion of cytokines and growth factors. This phase is followed by chronic inflammatory response involving fibrocyte proliferation and extracellular matrix (ECM) secretion. Tissue repair can be achieved if ECM secretion is tightly regulated and excess is removed, and also if fibrotic proliferation stops and newly formed cells differentiate into tissue-specific phenotype. If ECM secretion and cell proliferation are left uncontrolled, tissue repair leads to formation of fibrotic scar.

sessed in humans and in animals through monitoring the changes in residual hearing and in electrode impedance over time. Residual hearing has been shown to progressively decline alongside a progressive increase in electrode impedance after cochlear implantation in animal models.[40] Similar observations have been made in humans after cochlear implantation.[9]

The precise mechanisms of cochlear fibrosis following cochlear implantation are not known, although fibrosis is known to be a general repair mechanism controlled by several cytokines such as tumor necrosis factor (TNF) α, transforming growth factor β, platelet-derived growth factor, fibroblast growth factor, interleukin (IL) 1, IL-13, and tissue inhibitor of metalloproteases.[32,41-45] These factors, secreted by inflammatory cells recruited at the site of the lesion, stimulate angiogenesis, the elimination of cellular debris, the proliferation of mesenchymal cells, and extracellular matrix secretion (Fig 2).

Secretion of TNF-α and IL-1β is frequently observed after cochlear ischemia, acoustic trauma, or presbycusis,[46] and also in diseases that lead to cochlear fibrosis, such as keyhole limpet hemocyanin–induced labyrinthitis or streptococcal labyrinthitis.[47-51] Tumor necrosis factor α has a dual role. On one hand, TNF-α can promote apoptosis through caspase, JNK (Jun N-terminal kinase), and mitochondrial pathways after activation of FADD (Fas-associated protein with death domain).[52] On the other hand, TNF-α secretion may inhibit apoptosis through activation of NFκB (nuclear factor κ light chain enhancer of activated B cells) and IAP (inhibitor of apoptosis; Fig 1). In cochlear cells, IL-1β promotes reactive oxygen species formation and apoptosis without activation of JNK or ERK (extracellular signal regulated kinase) pathways.[51,53-57] Despite the fact that no evidence yet exists of the secretion of TNF-α, IL-1β, or other proinflammatory cytokines during cochlear implantation, evaluating their implication in fibrosis development may offer new therapeutic tools.

PHARMACOLOGIC STRATEGIES

Early Hearing Loss. Several targets have been identified to reduce the early loss of residual hearing. In guinea pigs, Eastwood et al[31] demonstrated that the antioxidative drug *N*-acetyl cysteine can prevent high-frequency hearing loss after cochlear implantation. Interestingly, the authors reported no effect in the middle- and low-frequency regions, probably because these regions were far from the insertion site and were therefore less exposed to production of reactive oxygen species. Another explanation could be that *N*-acetyl cysteine was applied on the round window with a pledget and may not have reached the apex of the cochlea. Vivero et al[58] performed intracochlear perfusion of dexamethasone using an osmotic pump into cochlear-implanted guinea pigs and found that they displayed less hearing loss than did implanted animals perfused with artificial perilymph. Furthermore, morphological analysis showed a better protection of hair cells with dexamethasone. Similarly, Ye et al[59] found that extracochlear or intracochlear injection of the corticosteroid triamcinolone in implanted guinea pigs allowed a better recovery of initial threshold shifts in treated animals, with an effect lasting for 4 weeks. A dose-dependent benefit of dexametha-

sone on high-frequency hearing preservation was also noted when this drug was applied on the round window with a carboxymethylcellulose–hyaluronic acid pledget.[36,60]

The mechanisms of action of corticosteroids have been extensively studied. Corticosteroids bind to their receptor and activate annexin-1 production by target cells. The annexin-1 inhibits phospholipase A2 and cyclooxygenases and reduces the production of numerous inflammatory molecules such as prostaglandins and leukotrienes. The corticosteroids inhibit secretion of IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, and interferon γ, and thereby the proliferation and secretion of T- and B-cells.[61] In cochlear implantation, one would therefore expect corticosteroids to act by reducing the inflammatory response and thus protecting the sensory cells from necrotic or apoptotic death. Apoptosis can be triggered by the activation of numerous pathways involving cytochrome C release, NF-κB activation, PI3K (phosphatidyl inositol 3 kinase) and Akt1 (protein kinase B1) activation, or MAPK (mitogen activated protein kinase) and JNK activation[62,63] (Fig 1). It has been shown in vitro that dexamethasone prevents TNF-α–induced apoptosis through the activation of NF-κB and PI3K/Akt signaling.[29] These signaling pathways could be the targets of corticosteroids during cochlear implantation; however, the involvement of TNF-α secretion has never been demonstrated. Conversely, the involvement of the MAPK/JNK pathway in the apoptosis of hair cells after cochlear implantation was shown by Eshraghi et al.[64] Application of the JNK inhibitor D-JNKI in implanted guinea pigs prevented hair cell loss after cochlear implantation, with a protection similar to that observed after noise trauma or cisplatin ototoxicity.[65,66] In a mouse model of pressure trauma caused by cochlear implantation, Do et al[30] showed the involvement of caspases 3, 5, and 6 in hearing loss — but not caspases 2, 8, and 9.

Delayed Hearing Loss. In contrast with the early phase following cochlear implantation, the efficacy of corticosteroids in preventing impedance changes for long-term residual hearing is largely debated, especially in humans.[37,67,68] Experimental data from animals show that antioxidative treatments do not prevent fibrosis, and can even increase it with osteoneogenesis.[31]

Several studies have used streptococcal or keyhole limpet hemocyanin–induced labyrinthitis as a cochlear fibrosis model to test drugs aimed at preventing fibrosis and hearing loss. In rats, transtympanic or systemic administration of corticosteroids[69] did not prevent hearing loss after streptococcal induced labyrinthitis. However, transtympanic glucocorticoid injection did increase the number of surviving neurons in this model. On the other hand, Yang et al[70] found no effect of dexamethasone, cyclosporine, prednisolone acetate, fluorouracil, or FK506 on hearing preservation in animals immunized against keyhole limpet hemocyanin. Huang et al[71] demonstrated that triamcinolone, dexamethasone, and sodium hyaluronate were unable to prevent the fibrosis and long-term elevation of impedance observed in implanted cats and guinea pigs. Similarly, Braun et al[72] showed that a single intracochlear dose of dexamethasone or triamcinolone was unable to prevent cochlear fibrosis 3 months after cochlear implantation in guinea pigs. However, corticosteroids allowed a temporary reduction in threshold shifts in implanted ears, with no correlation between the amount of fibrotic proliferation and residual hearing. These discrepancies could be due to the differential expression of inflammatory factors during infectious and immunogenic labyrinthitis versus cochlear implantation.

CONCLUSIONS

Preserving residual auditory function for electroacoustic stimulation is challenging. Despite much progress in surgical techniques and electrode design, the preservation of useful residual hearing is achieved in only half of operated cases. Recent evidence shows that the detection and control of the early molecular events that lead to hair cell and neuron loss can lead to improved hearing in implanted animals. However, sustained hearing preservation relies on sufficient understanding of the chronic inflammatory processes that stimulate fibrosis development and delayed loss of sensory cells. Efforts should now be focused on identifying the molecular pathways involved and the therapeutic targets able to reduce both immediate and delayed hearing loss after cochlear implantation.

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