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Intracochlear Tissue Responses after Cochlear Implantation: Review Article

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ABSTRACT

Background: Cochlear implants are biocompatible and have low complication rates. However, there is an inflammatory response after electrode implantation into the cochlea. The tissue response to CI is divided into two phases: Immediate or acute and delayed. The acute response is because of trauma throughout electrode insertion, potentially damaging the osseous spiral lamina, lateral wall, stria vascularis, basilar membrane, or disrupting cochlear fluids.

Objective: This review article threw the light on Intracochlear tissue response after cochlear implantation.

Methods: We searched Google Scholar, Science Direct, PubMed and other online databases for Intracochlear Tissue Responses and Cochlear Implantation. The authors also reviewed references from pertinent literature, however only the most recent or comprehensive studies from 2006 to 2022 were included. Documents in languages other than English were disqualified due to lack of translation-related sources. Papers such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations that were not part of larger scientific studies were excluded.

Conclusion: The protracted phase of the inflammatory reaction arises from the host-mediated FBR (Foreign body response) in the cochlea, initiated by the rapid adsorption of plasma proteins onto the surface of biomaterial, leading to the provisional matrix formation rich in pro-inflammatory cytokines & developmental factors. In an animal study, interlukine-6, interlukine-1β, NOS2, and TNF-α significantly enhanced in the first day after cochleostomy and sustained for three days. The acute stage of the response incorporates the invasion of neutrophils and mast cells, subsequently evolving into a chronic inflammatory reaction.

Keywords: Intracochlear Tissue Responses, Cochlear Implantation, pro-inflammatory cytokines.

INTRODUCTION

Cochlear implants are deemed biocompatible with minimal rates of complications. Nonetheless, a reaction to inflammation happens following the electrode array insertion into cochlea. This inflammatory reaction includes the development of a densely structured fibrous sheath wrapping the track of electrode, which may extend to incorporate granulomas, neo-ossification, or loose areolar fibrotic tissue [1]. Numerous histopathologic investigations of the temporal bone in cochlear implant recipients corroborate this inflammatory response. **Seyyedi & Nadol** [2] documented a chronic inflammatory response characterized by fibrosis, inflammatory cells, as well as neo-ossification in each temporal bone analyzed from cases with CIs across their entire lives.

Benatti & Castiglione [3] similarly investigated the intensity & site of the inflammatory reaction within the cochlea of twenty-eight temporal bones. Every electrode in the investigation was wrapped in a fibrous sheath. Multiple investigations indicate that the fibrotic reaction is greatest significant in the turn of basal of the cochlea, adjacent to the location of insertion of electrode, & diminishes in seriousness with more space from the location of cochleostomy.

Several animal studies have proven a comparable reaction including fibrosis of intracochlear and neo-ossification after cochlear implants with maximum severity at the basal turn and decreases gradually along the course of electrode to its tip [4].

The tissue reaction to CI is categorized into two phases: acute (immediate) & delayed. The immediate response is due to damage from electrode insertion, which disrupts the normal structure of cochlea. Insertion trauma could involve injury to the lateral wall, osseous spiral lamina fracture, disruption of intracochlear endosteum, translocation of electrode into scala vestibuli, dislocation of basilar membrane, impairment of the stria vascularis, and disruption of cochlear fluids [1].

The protracted aspect of reaction to inflammation is ascribed to reaction of host-mediated foreign body inside cochlea. The foreign body reaction happens in reaction to almost all biomaterials. The process initiates with the rapid plasma proteins adsorption of (such as fibrinogen, albumin) onto the biomaterial surface, leading to the establishment of a provisional matrix abundant in pro-inflammatory cytokines & developmental factors. **Lyu *et al.*** [5] conducted an animal investigation revealing that interlukine-6, TNF-α, interlukine-1β, & NOS_2 levels dramatically elevated on the first day post-cochleostomy & remained elevated for three days. The acute phase of the response is distinguished by the infiltration of mast cells & neutrophils. This leads to a chronic inflammatory response, as macrophages/monocytes & lymphocytes move to the injury area of tissue in reply to chemokines, particularly TNF-α. Upon adhering to the surface of biomaterial, macrophages amalgamate to become foreign body giant cells (FBGCs). Foreign body giant cells & macrophages secrete degradation mediators such as

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enzymes, ROS, & acids. In reaction to activation of macrophage, fibroblasts relocate to the location of implant, increase, then synthesize extracellular matrix (ECM) proteins, such as collagen. Fibroblasts & macrophages participate in granulation tissue development. The presence of a foreign substance leads to dysregulated fibroblast proliferation & extracellular matrix deposition, culminating in an irreversible fibrotic reaction that advances to creation of a fibrous capsule encasing implant [6].

The foreign-body reactions may result in the deterioration of CI biomaterials. Cochlear implants consist of platinum-iridium (90/10) electrode arrays implanted in a polydimethylsiloxane referred as PDMS medium. Both particles of platinum & silicone were observed outside the cell & inside the cell within macrophages in sections of temporal bone of recipients of cochlear implant. It is assumed that these biomaterials receive phagocytosis to eliminate the debris. In the cochlea, an intensified foreign body response frequently advances to encompass neo-ossification [7].

Cochlear implantation and death of auditory hair cell:

Auditory hair cells have cell death via necrosis & apoptosis. Apoptosis is a systematic kind of programmed cell death marked by membrane blebbing, cellular shrinkage, mitochondrial swelling, disruption as well as loss of stereocilia, reduction of chromatin condensation, & cuticular plates in the nucleus, preceding the junctional complexes disruption & the extrusion of auditory hair cells. The cell subsequently divides into many fragments known as apoptotic bodies, which are eliminated through phagocytosis. Throughout necrotic death of cells, cell volume expands, organelles undergo swelling, & the ruptures of plasma membrane. Intracellular contents flood into the extracellular space, resulting in following-lytic fragmentation of DNA [8].

Molecular mechanisms of inner ear trauma:

Following electrode implantation, an acute inflammatory response is initiated to repair the injured region. Mast cells & monocytes secrete vasoactive amines, including serotonin & histamine, which promote local vasodilation & enhance capillary permeability. The stria vascularis & spiral ligament synthesize & secrete inflammatory moderators, involving chemokines, cytokines, proteolytic enzymes, & adhesion molecules [9].

TNF-α is referred to tumor necrosis factor alpha is the predominant & most extensively researched pro-inflammatory cytokine. It facilitates migration of leukocyte via the spiral modiolar vein & its tributaries. It additionally promotes the expression of various chemokines, cytokines, & adhesion molecules, including interleukins (IL) interleukins -1β, interleukins -6, MIP-2 (Macrophage inflammatory protein-2), MCP-1 (Monocyte chemoattractant protein-1), VCAM-1 (Vascular cell adhesion molecule-1) & VEGF (Vascular endothelial growth factor). These inflammatory moderators can also facilitate the adhesion & migration of cells of inflammation, including basophils, neutrophils, lymphocytes, macrophages, monocytes, eosinophils, & natural killer cells. Tumor necrosis factor alpha can attach to TNFR1 (tumor necrosis factor receptor 1) on the auditory hair cells surface, triggering a signaling cascade that may result in death of cell by necrosis and apoptosis [10, 11]. TNF-α triggers NF-κB (nuclear factor kappa B) signaling to inhibit cell death by upregulating the pro-survival genes BCL-2 & B-cell lymphoma-extra-large in auditory hair cells. NF-κB is a factor of transcription that mediates proliferation, inflammation of cell & apoptosis. Upon initiation, NF-κB translocate to nucleus of the afflicted cell & initiates the transcription of many pro-survival genes & pro-inflammatory [12].

Apoptosis:

Apoptosis can transpire via 2 distinctive signaling cascades, known as the extrinsic (death of receptor, DR) & intrinsic (mortality of mitochondria) pathways. These 2 channels have connections & can intertwine. Both pathways finish in the execution phase, during which the activation of execution caspases (primarily caspase-3, along with caspases-6 and -7) initiates the apoptosis process. Caspase-3 activates endonuclease CAD (Caspase-Activated DNAse) with other endonucleases that start DNA fragmentation and chromatin condensation [13].

Intrinsic (Mitochondrial) pathway:

Stress signals involving damage of mitochondrial DNA (mtDNA), oxidative stress, heat shock, growth factor deprivation, hypoxia, initiate a disturbance between pro-& anti-apoptotic proteins of Bcl-2 (B-cell lymphoma protein -2) family. Mitochondrial membrane permeability increases, and multiple pores open to release 2 groups of pro-apoptotic proteins into cytoplasm. The 1st group comprises **cyt *c*** (cytochrome *c*), **HtrA2/Omi** (mammalian homolog of bacterial high temperature requirement protein A2), &. **Smac/DIABLO** (2nd mitochondrial activator of caspases/direct inhibitors of apoptosis proteins binding protein with low PI). These proteins initiate caspase-dependent mitochondrial pathway as follows. **[12, 13] :** Cyt c interacts with and activates Apaf-1 is referred to apoptotic protease-activating factor-1) & procaspase-9, resulting in formation of an "apoptosome," which then activates Caspase-9. Smac/DIABLO & HtrA2/Omi facilitate apoptosis by suppressing action of IAPs (inhibitors of apoptosis proteins). The 2nd category of pro-apoptotic proteins, including AIF is referred to Apoptosis Inducing Factor, Endo G is referred to endonuclease G, & CAD, are liberated from mitochondria throughout apoptosis & are associated with caspase-independent apoptosis. They translocate to the nucleus, resulting in DNA damage & the cleavage of nuclear chromatin [10].

Extrinsic (Death receptor) pathway:

The extrinsic routes that trigger apoptosis require transmembrane fatality receptors from the tumor necrosis factor receptor superfamily. They comprise tumor necrosis factor receptor 1, Fas-R (Fas receptor), & TRAIL-R1/R2 (TNF-related apoptosis-inducing ligand receptors one & two). Attachment of a death ligand to its corresponding cell membrane receptor, followed by the recruitment of adaptor cytoplasmic molecules via the receptor death domain (DD). The most recognized & researched death ligands comprise FasL is referred to Fas ligand, TRAIL, & tumor necrosis factor alpha.

The interaction of FasL with Fas receptors resulting in recruitment of the adaptor protein Fas-associated death domain referred as FADD the receptor's intracellular surface, facilitating the assembly of the DISC is referred to death-inducing signaling complex. FADD subsequently engages with initiator procaspases-8 or -10 via their respective death effector domains, resulting in their auto-activation. This compound initiates execution caspase-3 or -7. This is the identical process that occurs in TRAIL-mediated apoptosis [15].

The interaction of tumor necrosis factor with tumor necrosis factor-receptor-1 facilitates the recruitment of the TNFR1 -related adaptor protein with a death domain (TRADD) to its cytoplasmic region. This complex can facilitate either survival of cells or death of cells, contingent upon the accompanying components it interacts with. The assembly of complex one at plasma membrane, comprising tumor necrosis factor receptor1, TRAF2, and RIP (Receptor-interacting protein), results in the swift activation of NF-κB & MAPKs (mitogen-activated protein kinases), hence facilitating inflammation & the survival of hair cells. After receptor endocytosis, complex II is established, wherein TRADD recruits Fas-associated death domain & procaspase-8 or -10. Complex II induces apoptosis solely when complex one-mediated nuclear factor kappa B activation is insufficient to generate adequate anti-apoptotic signaling through the activation of effector caspase-3 [16].

Necrosis:

Necrosis is a regulated and planned form of cellular mortality. It is the outcome of extensive crosstalk among numerous biochemical as well as molecular events at various cellular levels, rather than a single well-described signaling cascade. It is signified by cytoplasmic edema, permanent damage to the plasma membrane, and disintegration of organelles [17].

Necroptosis, a distinctly defined kind of controlled necrosis, is a cell death mechanism dependent on receptor-interacting protein (RIP) kinases, exhibiting the morphological characteristics of necrosis. TNF-α can elicit necroptosis via a caspase-independent mechanism when caspase inhibitors are present. The binding of tumor necrosis factor alpha to TNF-R1 results in creation of complex one, subsequently leading to fast activation of NF-κB & MAPKs. If complex one fails to prompt adequate production of antiapoptotic proteins, caspase-8 is stimulated, hence triggering programmed cell death. Caspase-8 functions as an initiator of apoptosis caused by death receptors and serves as an inhibitor of necroptosis. The inhibition of caspase-8 cleavage alters cell death to necrosis, mediated by RIP kinase 3 & mixed lineage kinase [18]. The MLKL (mixed lineage kinase domain-like pseudokinase) is principal mediator of necroptosis. Upon onset of necroptosis, MLKL, in conjunction with RIP1 & RIP3, assembles into a necrosome that translocates to the plasma membrane to promote cellular mortality [19].

Poly-(ADP-ribose) polymerase-1 (PARP-1) is responsible for death of cell that happens by specific pathophysiological processes. These processes include ischemia-reperfusion, inflammation, damage caused by reactive oxygen species, & glutamate excitotoxicity. Several agents, including hydrogen peroxide & the DNA-alkylating chemical MNNG is referred to N-Methyl-N′-nitro-N-nitrosoguanidine, which have the ability to directly or indirectly impact mitochondria, are also responsible for the death of cells that are mediated by polymerase-1. The depletion of NAD+ & the reduction of mitochondrial ATP synthesis are both the results of the stimulation of polymerase-1, which catalyzes the hydrolysis of Nicotinamide adenine dinucleotide+ into nicotinamide & poly-adenosine diphosphate ribose. This results in the depletion of cellular energy & the death of cells that are not dependent on caspase [20].

Mitogen-activated protein kinases (MAPK) signaling pathway:

MAPK are protein kinases that control critical cellular functions including stress responses, proliferation, apoptosis, & immunological defense. The stimulation of mitogen-activated protein kinases cascade happens through a chain of sequential phosphorylations. A mitogen-activated protein kinases module consists of a mitogen-activated protein kinases-3 that stimulates a mitogen-stimulated protein kinases-2, which subsequently activates a mitogen-activated protein kinases, enabling the mitogen-activated protein kinases to phosphorylate target substrates. The primary substrates include ERK1/2 referred to extracellular signal-regulated protein kinases 1 & 2, c-Jun N-terminal kinases (JNK one, two, & three), & p38 kinases. Growth factors primarily initiate extracellular signal-regulated protein kinases 1 & 2 activation, but p38 & JNK performances are boosted by numerous chemical & physical stresses, involving hypoxia, oxidative stress, & cytokines like TNF-α [21].

ERK1/2 signaling is involved with cell proliferation & survival, enhancing nuclear factor kappa B function, whereas TNF-α stimulation of p38 & c-Jun N-terminal

kinases signaling cascades facilitates downstream processes correlated with death of cell. P38 and active JNK inhibit Bcl-2, facilitating pro-apoptotic Bcl-2 family members activation, including Bax & Bak are essential for cytochrome c release. JNK can translocate to the phosphorylate c-Jun & nucleus alongside various transcription causes, including p53, therefore enhancing the expression of pro-apoptotic genes (e.g., FasL, TNFa, Bax) & inhibiting the anti-apoptotic genes transcription like B-cell lymphoma protein -2 & B-cell lymphoma-extra-large [12]. Pro-apoptotic members of the Bcl-2 family facilitate Ca^{2+} release from the endoplasmic reticulum, resulting in a substantial and/or sustained influx of Ca^{2+} into mitochondria. This process can activate the MPTP (membrane permeability transition pore) complex, leading to mitochondrial swelling as well as disruption of the outer mitochondrial membrane, ultimately causing the release of pro-apoptotic factors into the cytosol as well as initiating apoptosis. The effect of pore opening seems to be contingent upon the concentration of Ca^{2+} elevated levels favor necrosis, whereas lower concentrations encourage apoptosis [15].

Oxidative stress:

Reactive oxygen species (ROS) are oxygen-containing free radicals. They are generated throughout numerous pathological & physiological occurrences. Mitochondria serve as the 1ry source of intracellular ROS, while external reactive oxygen species are generated by neutrophils & macrophages. Electrons commonly dissociate along electron transport chain (ETC), predominantly at complex one. The interaction of the rogue electron with molecular oxygen generates an oxygen radical, which is typically transformed into ROS like hydrogen peroxide, superoxide, nitric oxide, & hydroxyl radicals. Endogenous enzymes, including glutathione peroxidase, superoxide dismutase, NADP dehydrogenase, glutathione reductase & catalase, mitigate oxidative stress by neutralizing free radicals & regulating cellular redox balance. Excessive generation & accumulation of reactive oxygen species beyond the buffering ability results in heightened oxidative stress, leading to cellular apoptosis. Reactive oxygen species can stimulate ATSK-1, also known as apoptotic signal-regulating kinase, a MAPKKK that phosphorylates & activates mediators of the c-Jun N-terminal kinases & p38 pathways involved in intrinsic programmed cell death. Reactive oxygen species may also facilitate c-Jun N-terminal kinases-mediated apoptosis by inducing oxidation & inhibiting MAPK phosphatases (MAPKP), which typically attenuate JNK activity. Reactive oxygen species activate tumor suppressor protein p53, which transcriptionally mediates apoptosis by down-regulating prosurvival proteins like B-cell lymphoma protein-2 & B-cell lymphoma-extra-large, while upregulating pro-apoptotic proteins like FasL, TNF-α, & Bax. ROS also enhance & modulate the effects of TNF-α in a positive feedback loop [22].

Role of Excitotoxicity on SGN cells:

Excitotoxicity is a multifaceted phenomenon initiated by the over stimulation of glutamate receptors, leading to degenerative neuronal cell death. Type I spiral ganglion neurons are stimulated by glutamate, therefore excessive levels of this excitatory neurotransmitter from inner hair cells may result in the degeneration of SGN. Excitotoxicity is believed to be a crucial factor in noise-induced hearing loss and the degradation of hair cells. Excessive glutamate release following noise overstimulation or hair cell injury results in the glutamate receptors overactivation on the postsynaptic membrane of spiral ganglion neurons. This overactivation results in an inflow of cations, including sodium and calcium. Subsequently, Cl^- ions & water molecules traverse the plasma membrane passively, resulting in edema & potentially demise of the spiral ganglion neurons. Furthermore, elevated influx of calcium into mitochondria activates the MPTP complex, resulting in the breakdown of the outer mitochondrial membrane & initiating mitochondrial death of cells [23].

Protective mechanisms against intracochlear trauma:

The binding of Tumor necrosis factor-alpha to TNF-R1 activates MAPKs & NF-κB, particularly ERK 1/2, hence enhancing cell proliferation & survival. NF-κB is crucial for the survival & proliferation of hair cells. The nuclear factor kappa B signaling pathway inhibits cell death by upregulating the pro-survival genes BCL-2 & B-cell lymphoma-extra-large in auditory hair cells as well as suppressing c-Jun N-terminal Kinase (JNK) activity within the MAPK cascade. NF-κB may function to suppress ROS accumulation by upregulating antioxidants like superoxide dismutase [24]. ERK 1/2 are constituents of the MAPK family, whose signaling is associated with cell proliferation & survival. It facilitates proliferation by modulating the transcription of growth factors & essential cell cycle-associated proteins [25].

Raised concentrations of transforming growth factor β1 (TGF-β1) facilitate curing of wound through a response of fibroproliferative distinguished by excessive collagen deposition & extracellular matrix accumulation, leading to tissue of fibrous scar surrounding the electrode of cochlear implant. The scar tissue could impact structures of apical crucial for small-incidence residual hearing, while also elevating impedance & influencing cochlear implant effectiveness. This form of healing of wound involves angiogenesis, inflammation, fibroblast migration & proliferation, & connective tissue remodeling, resulting in scarring. [22].

Factors affecting intracochlear trauma during CI:

Throughout cochlear implantation, the hair cells are subjected to several trauma-related stimuli. These stimuli

may encompass: Vibrational as well as acoustic trauma from drilling near the cochlea, direct injury to auditory hair cells due to mechanical trauma from the electrode array affecting the membrane of apical basilar membrane as well as sensory cells, dislocation of bone & blood elements into the scala tympani throughout operation and stria vascularis as well as trauma to the spiral ligament, which are crucial for maintaining the endocochlear potential. In addition, insertion of inadvertent of electrode array throughout the membrane of basilar into the media of scala or vestibuli of scala, leading to mixing of perilymph as well as endolymph as well as subsequent alterations of the endocochlear potential, inflammatory responses from bacterial infections of the cochlea as well as foreign body reactions [26].

Mechanical trauma from Electrode Array insertion (EIT):

Arrays of cochlear implant electrode have been planned with attributes that facilitate protection of intra-cochlear structures throughout both insertion and explanation [27]. Three types of electrodes are available: Straight lateral wall electrode arrays. Pre-curved modiolar-hugging electrode arrays. Midscale (MS) electrode arrays, situated centrally within the ST, are typically classified as modiolar-hugging type electrodes. A certain level of trauma is anticipated with all presently available electrode configurations. The mechanical trauma inflicted on fragile intracochlear structures during the electrode array insertion into the scala tympani could induce inflammation & oxidative stress, which may disseminate into cochlear tissues, resulting in the necrosis and apoptosis of auditory hair cells. Furthermore, the translocation of the electrode from the scala tympani (ST) to the scala vestibuli (SV), injuring the scala media (SM), would cause a conflation of perilymph (ST) with endolymph (SM), leading to a reduction of endocochlear potential and perhaps resulting in the loss of residual hearing before operation. [22] Numerous investigations indicated that pre-curved metal hydride electrode arrays received greatest frequency of translocation from scala tympani to the scala vestibuli, posing a greater risk of trauma compared to other electrode types. The reason for this is the existence of a stylet wire that straightens pre-curved electrode prior to full implantation. During insertion, the rigidity of the electrode tip, because of the presence of the stylet, may result in the electrode penetrating the ligament of spiral near the conclusion of straight segment of the cochlea basal turn (about 180º of insertion depth), which may go unnoticed by physician. Furthermore, MH electrodes possess a predefined shape that might match to the coiling patterns of distinct cochlear geometries [28].

The insertion of electrode into the cochlea requires the application of significant strain to the intra-cochlear structures, estimated to range from forty to 120 mN; such minimal force is typically imperceptible throughout the operation. Applying more force and push will cause the electrode to buckle at the first contact point with the LW of the basal turn, which adds more mechanical trauma especially when using stiffer LW or MH electrodes. So very slow insertion speed is required [29].

Acoustic & Vibratory Trauma from drilling:

Aggressive penetration of the bony cochleostomy or the overhang of round window niche can generate acoustic trauma to organ of Corti and hair cells, also iatrogenic injury of the ossicular chain can generate similar trauma. **Pau *et al.*** [30] estimated that drilling the cochlear promontory produces more than 100 dB sound pressure level (SPL), this SPL can increase to 130 dB when cochlear endostium is violated or touched by the burr [30]. Acoustic trauma may cause edema and inflammation of stria vascularis, impairing cochlear blood flow, leading to hypoxia & damage to auditory hair cells, which subsequently results in the generation of reactive oxygen species by the marginal cells of the stria vascularis. The lateral wall components of the cochlea produce cytokines (likeIL-1β &TNFα) that promote leukocyte migration into cochlea through the spiral modiolar vein & activate the extrinsic pathway of apoptosis. Apoptosis of outer hair cells due to noise exposure may transpire via the cytochrome c release from stress-damaged mitochondria, then initiation of caspase-3 [12]. Noise trauma may lead to the overstimulation of the inner hair cells, causing a substantial release of glutamate in type one fibers of auditory nerve. This glutamate excitotoxicity induces postsynaptic calcium & influx of sodium ion, leading to the edema & rupture of the dendrite terminals of the SGNs. [22].

Intracochlear bone blood & dust:

The introduction of bone dust & minute bony fragments into the ST throughout cochlear implantation can facilitate intracochlear osteoneogenesis. The existence of intrascalar blood may result in low-frequency hearing loss as well as auditory hair cells apoptosis in the apical turn, mediated by the release of cytokines like TNF-alpha, interleukin-1b, and interlukine-6 in response to byproducts of blood, & production of ROS from byproducts of hemoglobin, including Fe^{2+} [22].

Ethical considerations: All the procedures of the research were permitted by the ethics committee of Faculty of Medicine, Otolaryngology Department, Suez Canal University. Administrative consents required have been taken. The objective of this research was to conduct research on humans in accordance with the Declaration of Helsinki, the ethical norm established by the World Medical Association.

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REFERENCES

1. **Foggia M, Quevedo R, Hansen M (2019):** ntracochlear fibrosis and the foreign body response to cochlear implant biomaterials. Laryngoscope Investig Otolaryngol., 4 (6): 678-683.
2. **Seyyedi M, Nadol J (2014):** Intracochlear inflammatory response to cochlear implant electrodes in humans. Otol Neurotol., 35 (9): 1545-51.
3. **Benatti A, Castiglione A, Trevisi P *et al.* (2013):** Endocochlear inflammation in cochlear implant users: case report and literature review. Int J Pediatr Otorhinolaryngol., 77 (6): 885-93.
4. **O'Leary S, Monksfield P, Kel G *et al.* (2013):** Relations between cochlear histopathology and hearing loss in experimental cochlear implantation. Hear Res., 298: 27-35. doi: 10.1016/j.heares.2013.01.012.
5. **Lyu A, Kim D, Lee S *et al.* (2018):** Effects of dexamethasone on intracochlear inflammation and residual hearing after cochleostomy: A comparison of administration routes. PLoS One, 13 (3): e0195230. doi: 10.1371/journal.pone.0195230.
6. **Sheikh Z, Brooks P, Barzilay O *et al.* (2015):** Macrophages, Foreign Body Giant Cells and Their Response to Implantable Biomaterials. Materials (Basel), 8 (9): 5671-5701.
7. **O'Malley J, Burgess B, Galler D, Nadol J (2017):** Foreign Body Response to Silicone in Cochlear Implant Electrodes in the Human. Otol Neurotol., 38 (7): 970-977.
8. **Dinh C, Goncalves S, Bas E *et al.* (2015):** Molecular regulation of auditory hair cell death and approaches to protect sensory receptor cells and/or stimulate repair following acoustic trauma. Front Cell Neurosci., 9: 96. doi: 10.3389/fncel.2015.00096.
9. **Bas E, Gupta C, Van De Water T (2012):** A novel organ of corti explant model for the study of cochlear implantation trauma. Anat Rec (Hoboken), 295 (11): 1944-56.
10. **Cavalcante G, Schaan A, Cabral G *et al.* (2019):** A Cell's Fate: An Overview of the Molecular Biology and Genetics of Apoptosis. Int J Mol Sci., 20 (17): 4133. doi: 10.3390/ijms20174133.
11. **Fiers W, Beyaert R, Declercq W, Vandenabeele P (1999):** More than one way to die: apoptosis, necrosis and reactive oxygen damage. Oncogene, 18 (54): 7719-30.
12. **Dinh CT, Bas E, Chan S *et al.* (2011):** Dexamethasone treatment of tumor necrosis factor-alpha challenged organ of Corti explants activates nuclear factor kappa B signaling that induces changes in gene expression that favor hair cell survival. Neuroscience, 188: 157-67. doi: 10.1016/j.neuroscience.2011.04.061.
13. **Elmore S (2007):** Apoptosis: a review of programmed cell death. Toxicol Pathol., 35 (4): 495-516.
14. **Idriss H, Naismith J (2000):** TNF alpha and the TNF receptor superfamily: structure-function relationship(s). Microsc Res Tech., 50 (3): 184-95.
15. **Redza-Dutordoir M, Averill-Bates D (2016):** Activation of apoptosis signalling pathways by reactive oxygen species. Biochim Biophys Acta., 1863 (12): 2977-2992.
16. **Zhang D, Lin J, Han J (2010):** Receptor-interacting protein (RIP) kinase family. Cell Mol Immunol., 7 (4): 243-9.
17. **Festjens N, Vanden Berghe T, Vandenabeele P (2006):** Necrosis, a well-orchestrated form of cell demise: signalling cascades, important mediators and concomitant immune response. Biochim Biophys Acta., 1757 (9-10): 1371-87.
18. **Li X, Li F, Zhang X *et al.* (2022)**: Caspase-8 auto-cleavage regulates programmed cell death and collaborates with RIPK3/MLKL to prevent lymphopenia. Cell Death Differ., 29 (8): 1500-1512.
19. **Li L, Tong A, Zhang Q *et al.* (2021):** The molecular mechanisms of MLKL-dependent and MLKL-independent necrosis. J Mol Cell Biol., 13 (1): 3-14.
20. **van-Wijk S, Hageman G (2005):** Poly(ADP-ribose) polymerase-1 mediated caspase-independent cell death after ischemia/reperfusion. Free Radic Biol Med., 39 (1): 81-90.
21. **Soares-Silva M, Diniz F, Gomes G, Bahia D (2016):** The Mitogen-Activated Protein Kinase (MAPK) Pathway: Role in Immune Evasion by Trypanosomatids. Front Microbiol., 7: 183. doi: 10.3389/fmicb.2016.00183.
22. **Bas E, Dinh C, Garnham C *et al.* (2012)**: Conservation of hearing and protection of hair cells in cochlear implant patients' with residual hearing. Anat Rec (Hoboken), 295 (11): 1909-27.
23. **Zhang L, Chen S, Sun Y (2022):** Mechanism and Prevention of Spiral Ganglion Neuron Degeneration in the Cochlea. Front Cell Neurosci., 15: 814891. doi: 10.3389/fncel.2021.814891.
24. **Papa S, Bubici C, Zazzeroni F *et al.* (2006):** The NF-kappaB-mediated control of the JNK cascade in the antagonism of programmed cell death in health and disease. Cell Death Differ., 13 (5): 712-29.
25. **Kong T, Liu M, Ji B *et al.* (2019):** Role of the Extracellular Signal-Regulated Kinase 1/2 Signaling Pathway in Ischemia-Reperfusion Injury. Front Physiol., 10: 1038. doi: 10.3389/fphys.2019.01038.
26. **Friedland D, Runge-Samuelson C (2009):** Soft cochlear implantation: rationale for the surgical approach. Trends Amplif., 13 (2): 124-38.
27. **Cosetti M, Roland J (2010):** Cochlear implant electrode insertion. Operative Techniques in Otolaryngology-Head and Neck Surgery, 21 (4): 223-232.
28. **Dhanasingh A, Jolly C (2017):** An overview of cochlear implant electrode array designs. Hear Res., 356: 93-103. doi: 10.1016/j.heares.2017.10.005.
29. **Kratchman L, Schuster D, Dietrich M, Labadie R (2016)**: Force Perception Thresholds in Cochlear Implantation Surgery. Audiol Neurootol., 21 (4): 244-249.
30. **Pau H, Just T, Bornitz M *et al.* (2007):** Noise exposure of the inner ear during drilling a cochleostomy for cochlear implantation. Laryngoscope, 117 (3): 535-40.