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Hair Cell Regeneration: Factors and Possible Accelerators

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Abstract

Cell regeneration is a procedure of re-development of certain dam-aged organ from its respective tissue. Cochlear is the hearing part of inner ear situated in the temporal bone. It directly interacts with middle ear through oval window and round window. Sensory cells also known as Hair cells have a cuticular plate with stereocilia bathing in the endolymph surrounding it. These are mainly of two types of Inner Hair Cells (IHC) and Outer Hair Cells (OHC). The final no. of hail cells are produced during 10 week of foetal ges- tation above this stage the cell are only loosed. Stereocilia plays an important role in electro-mechanical transduction. Myosin plays role in hearing process. During the development of mouse inner ear, cell cycle inhibitor plays an im- portant role. Rb helps in triggering the cell cycle exit. Various factors affect the hair cells like age, genetic factors, surrounding environment etc.

Keywords:

Hair cell; Cochlea; Hearing loss; Organ of corti; Rb gene; Proliferation; Hedgehog pathway

Introduction

Cell regeneration is a science in which the procedure of reestablishment, reclamation and development that makes genome, cells and biological system. In human's regrowth of damage organ parts from remaining tissue is known as regeneration 120. The study of human aging process through the study of regeneration is called regenerative medicine.Organ of Corti mainly is composed of sensory cells which are also known as Hair cells, nerve fibres that connects them and supporting structures. The function of Organ of Corti and the sound wave is transmitted by perilymph which gives rise to the vibration of basilar membrane. This passive signal mobilizes the basilar membrane from high sound to low sound of the cochlea. The Stereocilia of OHC bends when basilar membrane rises which leads to depolarization [1].

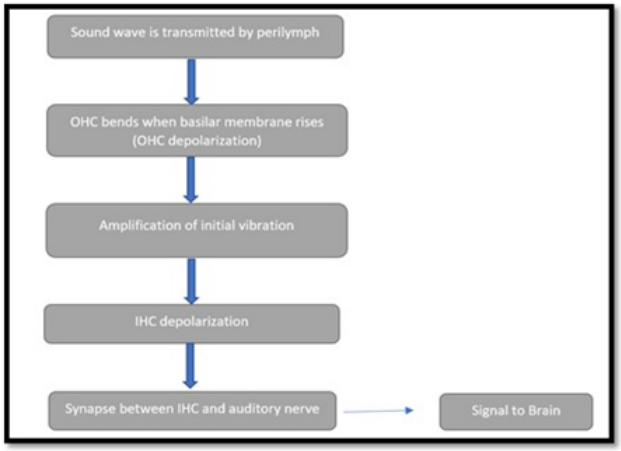

Figure 1: Transmission of sound wave to the brain.

Materials and Methods

Transduction channel opening

OHC contract due to close link between OHC, basilar membrane and reticular membrane which creates energy to amplify the initial vibration. IHC is depolarized due to direct contact with Hensen stripe. The synapse between IHC and auditory nerve, transmit signal to brain [2].

Cochlear, vestibular, sensory cells are known as hair cells. In Mammals, inner ear lacks the capacity to regenerate hair cells, therefore the sensory cells required for hearing and balance . Their main role is converting mechanical energy into electrical signals. Due to the short distance between the receptor and the target neuron, auditory hair cells, photoreceptors and taste receptors do not generate action potentials, but instead transmit their response signals through passive currents.

Mechanotransduction helps in detection of movement in their environment. In human cochlea there are 3,500 inner human cochlea (1 row) and 12,000 outer human cochlea (3 row). The inner human cochlea are sensory receptors and gives rise to 95%of the fibres of the auditory nerve that connects to the brain.

Efferent exons that arise from brain plays role in termination on the outer human cochlea. The receptor cells of the inner ear, have specialized cilia and microvilli detect endolymph movement. The deviation of the static cilia produces a receptor potential, which is transmitted to the sensory neurons connected to the hair cells. These are sensitive to cell aging, environment, genetic makeup, acoustic trauma which may lead to permanent hearing loss [3].

The origination of cells of inner ear are from otic placode and nearby mesenchymal tissues. Whereas few numbers of cells originate

elsewhere in organism and enter the inner ear later during development. It is assumed that more the cells are specialized the more it become incapable of replication like supporting cells of hair cells and neurons. In the adult mammalian inner ear all the cells are capable of assuming the phenotype of hair cell are post mitotic. Therefore, when the cochlea is damaged Organ of Corti cannot produce its replacement. Stereocilia plays an important role in electro-mechanical transduction [4].

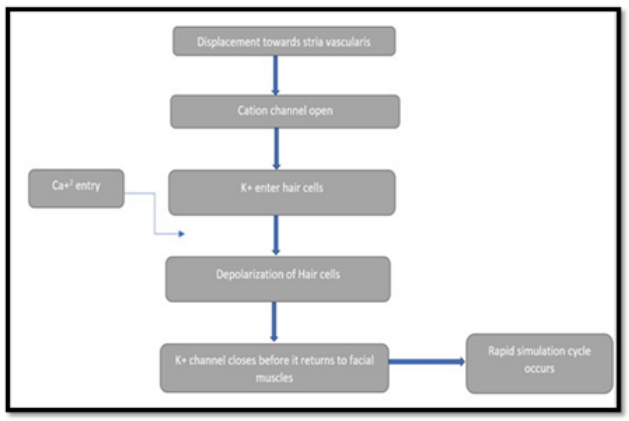

Figure 2: Transduction channel opening.

Results

Transduction channel adaptation

Myosin plays an important role in the growth and development of neurons and special cells such as the sensory hair cells of the cochlea and vestibular organs. Myosin is mainly composed of N-terminal conserved motor domain (head), light chain binding region (neck) and class specific C- terminal region domain (tail).

Various forms of Myosin are found localized in different part of stereocilia regulating in hearing process. Two types of Myosin I plays a role in hearing process i.e., MYO1A and MYO1C which are expressed in inner ear.

The most major Myosin is myosin II, which forms thick filaments of smooth muscle and skeletal muscle, but also exists in non-muscle cells. Myosin II heavy chains form dimers, which can interact with other myosin II dimers to form bipolar filaments. In tissue culture, many cells contain clusters of actin microfilament tension fibres. Myosin II has a characteristic sarcomeric distribution, but the tension fibres are not obvious in in situ neurons and glial cells. However, thick bipolar filaments assembled from myosin II dimers can separate from nervous tissue.

Although brain myosin II was one of the first non-muscular myosin's described, little is known about the function of myosin II in neurons.

Many cellular contraction events in non-neuronal cells, such as contraction loops in mitosis, involve myosin II. Protein myosin I has a single small heavy chain, does not form filaments, but has a homologous ATPase domain that inactivates actin,

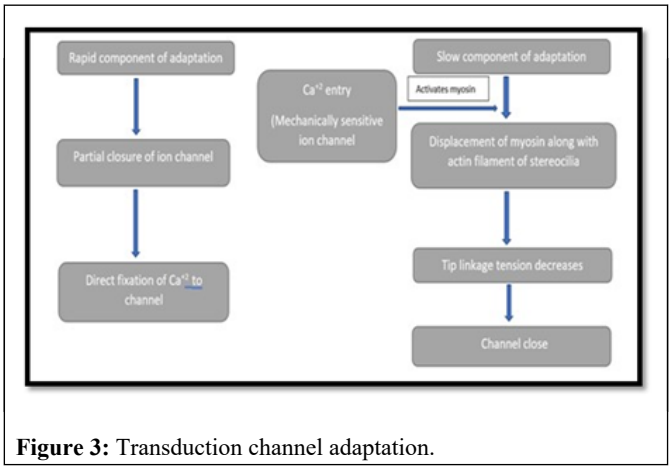

Figure 3: Transduction channel adaptation.

It has been purified from nerve and neuroendocrine tissues. Some myosin I motors can directly interact with the membrane surface to produce the movement of plasma membrane components or intracellular organelles. There are at least three myosin 1 genes in mammals, and there are many forms in the brain. For example, myosin I c is found in the static cilia of vestibular and cochlear hair cells and plays a key role in mechanical transduction [5].

Discussion

Cell cycle

The cell cycle is a complex process involving many regulatory proteins that guide the cell through a specific sequence of events, ultimately mitosis and the production of two daughter cells. At the centre of this process is Cyclin-Dependent Kinases (CDK), which are complexed with cyclin proteins. These proteins regulate cell processes at various stages of the cell cycle, which in turn are regulated by many proteins, including p53, p21, p16, and cdc25. The downstream targets of the cyclin-cdk complex include pRb and E2F.Cellular replication is divided into intervals which occur in each stage of cycle. The phases of cell cycle are G1, S, G2 and M. In G1 phase or GAP phase the size ofof the cell increases. In S phase or Synthesis phase replication of DNA occurs. In G2 or GAP2 phase the cell prepares to divide. In M or Mitosis phase the cell divides and segregates the duplicated chromosomes into the two daughter cells. The G1, S, and G2 stages form the interface, which explains the time between cell divisions. In the Prophase stage, the nuclear envelope of dissolves and the chromosomes begin to condense; in the metaphase, the fusion chromosomes are arranged along the cell axis to prepare for the separation of daughter cells; in the Anaphase stage, aligned chromosomes begin to separate; they continue to separate in the Telophase stage, and completes this Process and move to the opposite end of the cell. At the end of the telophase, daughter cell nuclei reassemble and undergo cytokinesis, dividing cytoplasm between daughter cells. After the M phase, the daughter cells re-enter G1, where they can initiate another round of cell division or exit the cell cycle to a resting or G0 state. According to the stimulus and inhibition information the cell receives, it "decides" whether it should enter the cell cycle and divide [6].

Checkpoints help determine that cell cycle events occurred in the correct order, providing a first look at the molecular pathways that prevent DNA-damaged cells from replicating [7]. During embryonic development, the cell cycle machinery is regulated to control organ

and tissue morphogenesis through controlled cell proliferation within certain cell lineages [8]. Some cell types, upon exiting the cell cycle and entering a quiescent state [9]. Can upon the right stimuli emerge from G0 to re-enter G1 and begin the process of cell division again in order to renew or regenerate specific tissues. Whereas, many cells, such as neurons and hair cells, become terminally postmitotic, in which case they never re-enter the cell cycle and if stimulated to do so will frequently undergo cell death [10].

Hair cell development

During development of mouse inner ear, cell cycle inhibitor plays an important role in developing well organized mature cochlea [11]. Mouse cochlea develop from otic placodewith the cochlear duct. It first starts appearing at approximately E11.5 and elongates until approximately Hair cells and the other supporting cells share the same prosensory proginetor cells as determined by many signalling pathways like Notch, Sox2, BMP4 and FGF. Rb plays an important role in triggering cell cycle exit, maintain the postmitotic state of hair cells, survival of postnatal hair cells and directly participates in differentiation as a transcription activator [12].

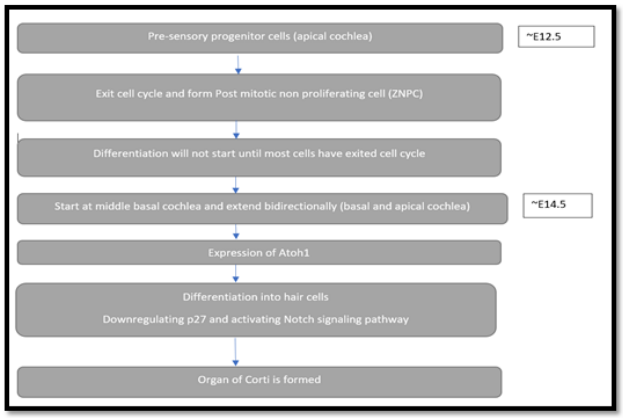

Figure 4: Development of hair cells.

To regenerate mammalian cochlear hair cells, three steps were hypothesized based on non-mammalian model:

The first and the most important step is unblocking inhibition of cell cycle re-entry in post mitotic, quiescent supporting cells [13].

- Hair cells release signal in response to the damage
- Supporting cells respond and re-enter cell cycle
- Dividing supporting cell triggered to trans diffusion into functional hair cells

The association between hair cell development and the cell cycle has been studied using a range of techniques, including the incorporation of thymidine and BrdU, the production of cell cycle-related proteins, and the mutation of cell cycle-controlling genes. The outcomes of these investigations have not always been consistent. The processes of cochlear morphogenesis may be to blame for some of this discrepancy. The insertion of cells from the basal end of the epithelium causes elongation of the cochlear duct, resulting in early birth dates for apical hair cells. Hair cell differentiation, on the other hand, appears to progress from the base to the apex, resulting with basal turn hair cells maturing molecularly and morphologically earlier [14].

Conclusions

Role of Rb

Rb stands for Retinoblastoma which is a tumor suppressor gene [15]. The main role of Rb gene is negative control of cell cycle and tumor progression. Rb protein (pRb) plays an important role in G1 checkpoint, blocking S phase entry and cell growth [16]. Rb gene is functionally inactive in human neoplasm either by direct mutation/deletion or indirectly through altered expression of upstream regulators [17]. pRb plays role in promoting terminal differentiation by inducing both cell cycle exit and tissue specific gene expression [18].

Underphosphorylated pRb interact with E2f of transcription factor and supress transcriptional activities whereas phosphorylated pRb (by CDK) prevent pRb from binding with E2F and hence promotes transcriptional activities from G to S phase of cell cycle [19].

The Hedgehog pathway is a signaling pathway that plays a major role in the early stages of inner ear development, including the proliferation of progenitor cells and their subsequent cell fate determination and differentiation. Most vertebrate species have three Hedgehog genes [20].

- Sonic Hedgehog (Shh)
- Indian Hedgehog (Ihh)
- Desert Hedgehog (Dhh)

The transmembrane protein Patched (Ptc) acts as a ligand for hedgehog protein. The presence of Ptc activity into the hedgehog is inhibited, leading to the de-inhibition of another transmembrane protein Smoothened (Smo), which initiates the signal cascade. This leads to the activation of the glioma-related oncogene Gli transcription factor (in vertebrates) and the expression of hedgehog target genes [21].

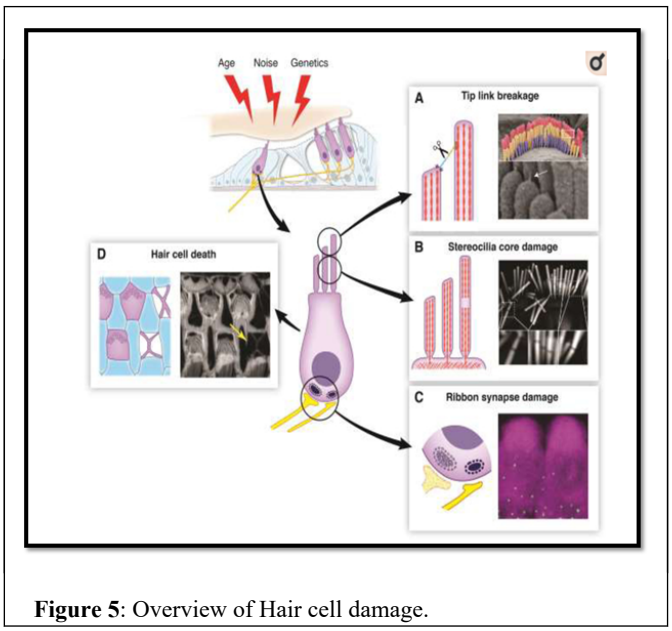

Figure 5: Overview of Hair cell damage.

Many research have shown that Hedgehog signaling plays important and complicated roles during the development of the inner ear, and inactivation of Hedgehog signaling leads to the mis-regulation

of proliferation and differentiation in the mammalian cochlea during development [22].

Factors affecting hair cells

Hair cell death can be caused by a variety of factors, such as

- Chronic exposure to noisy environments,
- Acute exposure to deafening factors such as explosions
- Chemical drugs.
- Age
- Environmental factors
- Genetic factors

Mechanosensitive organelle is present at the apical surface of hair cells, known as the hair bundle, is deflected in response to these auditory and vestibular stimuli. The hair bundle is composed of actin-based protrusions called stereocilia arranged into a staircase-like array.

Possible treatments

Two pathways have been targeted to develop hair cell regeneration therapies. Studies of hair cell regeneration centre on three approaches:

- Generation of hair cells from intrinsic stem cells.
- Generation of hair cells from existing cochlear supporting cells.
- Induction of cellular replication followed by maturation of both hair cells and support cells.

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