Cochlear anatomy, function and pathology IV

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Aims and objectives of these lectures

• Focus (4) on cochlear pathology:
  – Presbyacusis
  – Ototoxicity
  – Noise trauma
  – Genetic hearing loss
  – Molecular mechanisms of cell loss
  – Regeneration and repair
Age-related hearing loss - presbyacausis

• Hearing loss is a commonly encountered progressive impairment in the elderly
• 30 percent of people aged 65
• 50 percent of people aged 75
• It can profoundly affect physical, psychosocial and cognitive function
• Other factors contribute to the hearing handicap experienced by older persons
  - difficulty in understanding speech in noisy situations
  - difficulty in supplementing hearing with visual information
  - the slowing of cognitive and psychological processes
Age-related hearing loss - presbyacusis

- Defines four types of age-related cochlear pathology
  - strial
  - sensory
  - neural
  - cochlear conductive
Diagnostic features of presbyacusis

- Human audiograms have been modelled according to animal data
- Different patterns reflect different pathologies
- Pathologies and types can be mixed

Sensorineural hearing loss

- The main cause is loss of hair cells, often followed by loss of ganglion cells.
- Hair cell loss is greatest amongst the outer hair cells which appear more vulnerable than inner hair cells.
- It also begins with high frequency (basal) hair cells and progresses apically with time.
- Ganglion cell loss can occur independently.
The major losses affect outer hair cells

- Outer hair cells are more susceptible to damage than inner hair cells
- This means frequency selectivity and thresholds are impaired, even if hearing is not completely lost
The aged human organ of Corti

Image courtesy of Prof Mike Gleeson
Typical pattern of age-related hearing loss
Patterns of hair cell loss reflect high frequency hearing loss

- Mouse model evaluated at 10, 15 and 20 weeks old
- Hair cell counts conducted
- Outer hair cells from the base most affected
- IHCs less affected
- Replicates a typical human pattern
Patterns of hair cell loss reflect high frequency hearing loss
Metabolic (strial) hearing loss

- Defined initially as atrophy of the *stria vascularis*
- Now thought to be a complicated mixture of strial and spiral ligament degeneration resulting in endolymphatic potential reduction and failure of homeostasis
- Evidence from some animal models suggests fibrocyte degeneration is a factor perhaps stimulated/caused by generation of reactive oxygen species (ROS)
Lateral wall degeneration can cause hearing loss

- In CD/1 mice fibrocyte loss and strial thinning occur.
- Fibrocytes show signs of degeneration first.
- Later hair cells and spiral ganglion become damaged, significant fibrocyte loss has occurred and the *striata vascularis* has shrunk.
Evidence of early fibrocyte degeneration in CD/1

- Types II, III and IV are affected between weeks 3 and 20
- Other cell types and structures are less affected
- Hair cell losses also occur
- What happens first?

[Graph showing comparison of mean number of fibrocytes and structures counted between 3 weeks and 20 weeks, with some categories marked with an asterisk.]
• Ultrastructural studies reveal significant damage in all fibrocyte types at 3 weeks
• By contrast, organ of Corti appears normal
Changes in EP and $K^+$ in CD/1 mice and CBA mice with age
Ototoxic drugs

• These are drugs usually given to treat other, life threatening conditions
• This can include:
  – Septicaemia (e.g. aminoglycoside antibiotics)
  – Cancer (e.g. carboplatin)
• Often they cause hair cell damage and loss
Aminoglycoside antibiotics

- Kanamycin causes hair cell loss and damage to hair bundles
Noise damage

• Noise damage is produced by excessively loud sounds entering the inner ear
• Prolonged exposure to 85 dB noise
• High impulse noise (e.g. a shotgun firing off near your ear)
• Music devices played too loud into your ear
Type of noise damage

- Noise damage affects the delicate sensory hairs of the hair cells
- Noise (and also some drugs) can cause swelling of the afferent nerve endings onto the inner hair cells probably through glutamate excitotoxicity
- In animals swelling can be prevented by glutamate antagonists
- Higher levels of noise cause mechanical damage to the organ of Corti
Noise damaged organ of Corti

Significant loss of hair cells and mechanical disruption to the stereocilia
Swelling of nerve terminals

- Excitotoxicity
- Can be caused by
  - Noise
  - Ototoxic drugs
- Can be prevented by glutamate receptor antagonists (e.g. DNQX)


Furness and Hackney, unpublished
Mechanisms of cochlear cell loss programmed vs non-programmed

- Apoptosis vs necrosis
- Necroptosis
- Reactive oxygen species can trigger intrinsic apoptosis
- Also evidence of extrinsic apoptosis in the cochlea
- Balance between different forms of cell death changes

Mechanisms of cochlear cell loss

- Programmed vs non-programmed
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Apoptotic hair cells

- Normal and apoptotic IHCs after kanamycin (above)
- Normal and apoptotic immature OHCS (left) in diminuendo (a mouse model of deafness dn/dn)
Genetic hearing loss

• Defects in many genes have been implicated in hearing loss

• Some of the commonest include:
  – gap junction proteins (connexins) \textit{GJB2} is \textit{DFNB1}
  – Transmembrane channel proteins \textit{TMC1}
  – Cadherins, \textit{PCDH15} (Usher syndrome), (Usher syndrome, age related hearing loss) \textit{CDH23}
Distribution of connexins 26 and 31

From: Jagger and Forge, 2015, Cell and Tissue Research 360, 633-644
# Link proteins in Usher syndrome

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<th>Type</th>
<th>Freq</th>
<th>Gene locus</th>
<th>Gene</th>
<th>Protein</th>
<th>Function</th>
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<td>USH1B</td>
<td>39–55%</td>
<td>11q13.5</td>
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<td>Myosin VI A</td>
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<td>USH1D</td>
<td>19–35%</td>
<td>10q21-q22</td>
<td>CDH23</td>
<td>Cadherin 23</td>
<td>Cell adhesion</td>
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<td>USH1E</td>
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<td>21q21</td>
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<td>USH1G</td>
<td>7%</td>
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<td>USH2A</td>
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<td>1q41</td>
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<td>Usherin</td>
<td>Transmembrane linkage</td>
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<td>15%</td>
<td>5q14.3-q21.1</td>
<td>GPR98</td>
<td>VLGR1b</td>
<td>Very large GPCR</td>
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<td>9q32-q34</td>
<td>DFN B31</td>
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<tr>
<td>USH3A</td>
<td>100%</td>
<td>3q21-q25</td>
<td>CLRN1</td>
<td>Clarin-1</td>
<td>Synaptic shaping</td>
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Source – Wikipedia (accessed January 2013)
Mouse orthologs of Usher I syndrome

- Mutations in waltzer and ames waltzer mice occur in two genes: *Cdh23* and *Pcdh15* respectively
- These can serve as a model of Usher type I
- Mutations in these genes affect the structure and function of the stereocilia and the tip links

Mouse orthologs of Usher I syndrome

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- These mutations serve as a model of Usher type I syndrome.
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The affected genes

- This is a representation of Pcdh15 (upper) and Cdh23 (lower)
av3J, a null mutation of Pcdh15
av3J, a null mutation of *Pcdh15*

- The hair bundle is disturbed
- The tip links are almost completely eliminated
- The transducer currents are reversed in polarity
- The channel is present but not operated correctly
Artificial treatments for hearing loss

• Hearing aid:
  – Boosts sound (amplifies) entering the ear at a range of frequencies
  – Does not restore the elegant frequency selectivity of the cochlea (the cochlear amplifier)
Cochlear implant

• The cochlear implant is an array of electrodes pushed into the cochlea
• Can restore a good range of frequencies and a degree of frequency selectivity
  – 22 electrodes
  – Stimulates surviving cochlear nerve fibres/ganglion cells
Cochlear implants require intact spiral ganglion neurones

http://www.healthyhearing.com/content/articles/Technology/Cochlear-implants/30632-How-cochlear-implants-work
Natural repair in the cochlea

• If hair cells go missing they are not naturally replaced
• However, swollen nerve terminals may return to normal (Functional significance of dendritic swelling after loud sounds in the guinea pig cochlea. Robertson D. Hear Res. 1983 Mar;9(3):263-78.)
• This underlies a type of hearing loss called temporary threshold shift (TTS - hearing ‘gets better’)
• More typically hearing loss is permanent (permanent threshold shift - PTS)
Natural repair in the cochlea

• In the lateral wall, fibrocytes have some natural repair/regeneration, but insufficient to prevent age-related degeneration
Possible treatments

• Hair-cell and nerve fibre loss is permanent and regeneration cannot yet be stimulated
• When degeneration is progressive, neurones could be “rescued” by some growth factors
• Possible genetic controls are being identified and tried
• When sufficient nerve fibres survive, a cochlear implant can be used
• The commonest treatment is a hearing aid or a cochlear implant
MATH1 AKA ATOH1

- Transfection with MATH1 into the damaged adult cochlea switches on certain genes that appear to make new hair cells.

Notch inhibition

- New hair cells can be induced after noise induced loss by inhibiting Notch signalling
- Notch inhibition increases the expression ATOH1 (similar to previous study)
- Hair cells are recruited by transdifferentiation from supporting cells
- Hair cell regeneration is partial but coincides with some recovery of hearing.

Other forms of gene therapy – Cx26

• Replacement of defective GJB2 with wild type, or knockdown of mutated gene
  – Lizuka: adeno-associated viral (AAV) to replace the gene in a knockout mouse
  – drives expression of exogenous Gjb2 \textit{in vivo}.
  – Exogenous Gjb2 significantly improved the auditory responses and development of cochlear structure.

Other forms of gene therapy – Tmc1

• Replacement of defective gene with wild type, or knockdown of mutated gene
  – Holt et al use adeno-associated viral (AAV) serotype AAV2/1 together with the chicken beta-actin (Cba) promoter in Beethoven mice (point mutation in Tmc1)
  – drive expression of exogenous Tmc1 or Tmc2 in inner hair cells \textit{in vivo}.
  – Exogenous Tmc1 was capable of restoring sensory transduction, partial auditory brainstem responses, and acoustic startle reflexes in otherwise deaf mice.

Summary

• Four major causes of hearing loss: age, noise, ototoxic drugs, genetic
• Four different types, two main ones being metabolic and sensorineural
• Each has their specific features
• Artificial aids are primary means of therapy
• Gene therapy is rapidly being developed as a possible treatment