Juntendo, 11 November 2016 - **A collaboration, including researchers from Juntendo University, demonstrate differentiation from stem cells into specialised cells thought to be the most important therapeutic target for the treatment of hereditary deafness.**

One in a thousand children suffers deafness or hearing loss, and hearing is the most common sense to be affected by congenital disease. Deafness at birth is often caused by mutations in a specific gene known as Gap Junction Beta 2 (*GJB2*), which codes for the protein connexin 26. In some populations mutations of this gene are responsible for as many as half the instances of congenital hearing loss. Now, Kazusaku Kamiya and the co-authors of his recent report demonstrate a means of producing supplies of these cells on demand for use in therapeutic studies.

“Human cochlear cells are not readily accessible for biopsy or direct drug administration because of anatomical limitations,” state the researchers in their report. “Therefore, ES/iPS [embryo stem/induced pluripotent stem] cells are an important tool for studying the molecular mechanisms underlying inner-ear pathology as well as for generating cells for replacement therapies.”

To culture the cells the researchers followed standard protocol for the first seven days at which point specific proteins were added to increase mRNA expression of connexins. On day 7-11 the cells were transferred to a flat 2D culture with inner-ear cells that are especially resistant to enzymes that break down proteins. They successfully cultured induced pluripotent stem cells that differentiated into gap junction plaque cells expressing connexin 26.

The researchers were also able to demonstrate that their stem-cell-derived gap junction cells were functionally and structurally characteristic of developing cochlear cells. Importantly the cells differentiated from mice that were deficient in connexin 26 reproduced cellular characteristics of congenital hearing loss. The researchers conclude, “It is expected, then, that these iPS derived cells, which can be obtained from patients, will be particularly useful for drug screening and inner-ear cell therapies targeting *GJB2*-related hearing loss.”

Background

Stem cells

Stem cells are a type of cell that can change into another type of more specialised cell through a process described as differentiation. They occur in embryos (embryonic stem cells), and adults as repair cells.

Embryonic stem cells can differentiate into a several different types of specialised cells to form the range of cells needed in the human body. The ability to differentiate into several different types of cell is described as pluripotency and can be induced in adult cells as well by reprogramming non-reproductive system cells (somatic cells) to produce “induced pluripotent stem cells”.

Structure of the ear

The ear comprises three main parts: outer, middle and inner. The ear canal in outer ear channels sound vibrations to the ear drum in the middle ear.

The middle ear contains three bones or ossicles that transfer the vibrations of the ear drum to the cochlea, a fluid filled spiral cavity in the inner ear. The movement of the fluid in the cochlea in response to these vibrations is detected by thousands of hair cells in the cochlea that convert this motion into electrical signals that are then communicated by nerve cells to the brain, which senses them as sound.

Function of connexin 26 and gap junction plaques

Connexins 26 and 30 form gap junctions that facilitate the movement of ions needed to maintain a balance in conditions - homeostasis – as well as developmental organization in the cochlea. The researchers were able to demonstrate that their stem-cell-derived gap junction cells were functional for forming gap junction intercellular communication networks typical of the developing cochlea. The cells differentiated from mice that were deficient in connexin 26

demonstrated a disruption in the formation of gap junction plaques.

Reference

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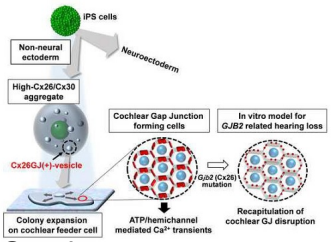
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iPS cells
Non-neural ectoderm
Neuroectoderm
High-Cx26/Cx30 aggregate
Cochlear Gap Junction forming cells
In vitro model for GJB2 related hearing loss
Cx26GJ(+)-vesicle
GJb2 (Cx26) mutation
Colony expansion on cochlear feeder cell
ATP/hemichannel mediated Ca2+ transients
Recapitulation of cochlear GJ disruption