PRESS RELEASE

Juntendo University

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Juntendo University research:
Stem cells provide sound in vitro models for deafness

(Juntendo, 11 November) **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 and transient ion species 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

Ichiro Fukunaga[1, 2], Ayumi Fujimoto[1], Kaori Hatakeyama[1], Toru Aoki[1], Atena Nishikawa[1], Tetsuo Noda[3, 4], Osamu Minowa[3, 4], Nagomi Kurebayashi[5], Katsuhisa Ikeda[1], Kazusaku Kamiya[1], *In vitro* models of *GJB2*-related hearing loss recapitulate Ca2+ transients via a gap junction characteristic of developing cochlea, 2016 *Stem Cell Reports* x y

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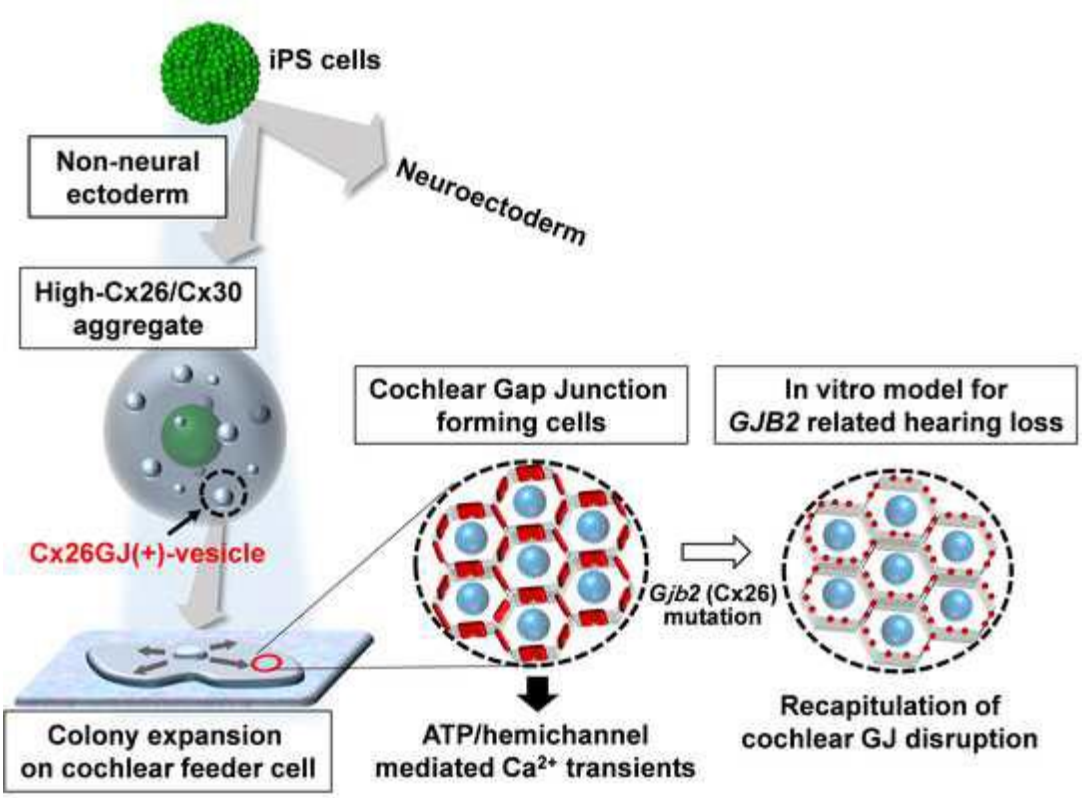
Figure 6



Caption

Schematic of the culture of connexin 26 expressing gap junction plaque forming cells and the recapitulation of disease symptoms in cells cultured from connexion deficient mice. Cx26 – connexin 26; Cx30 – connexin 30; GJ – gap junction. Courtesy Stem Cell Reports

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Further information

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About Juntendo University

Mission Statement

The mission of Juntendo University is to strive for advances in society through education, research, and healthcare, guided by the motto "Jin – I exist as you exist" and the principle of "Fudan Zenshin - Continuously Moving Forward". The spirit of "Jin", which is the ideal of all those who gather at Juntendo University, entails being kind and considerate of others. The principle of "Fudan Zenshin" conveys the belief of the founders that education and research activities will only flourish in an environment of free competition. Our academic environment enables us to educate outstanding students to become healthcare professionals patients can believe in, scientists capable of innovative discoveries and inventions, and global citizens ready to serve society.

About Juntendo

Juntendo was originally founded in 1838 as a Dutch School of Medicine at a time when Western medical education was not yet embedded as a normal part of Japanese society. With the creation of Juntendo, the founders hoped to create a place where people could come together with the shared goal of helping society through the powers of medical education and practices. Their aspirations led to the establishment of Juntendo Hospital, the first private hospital in Japan. Through the years the institution's experience and perspective as an institution of higher education and a place of clinical practice has enabled Juntendo University to play an integral role in the shaping of Japanese medical education and practices. Along the way the focus of the institution has also expanded, now consisting of four undergraduate programs and three graduate programs, the university specializes in the fields of health and sports science and nursing health care and sciences, as well as medicine. Today, Juntendo University continues to pursue innovative approaches to international level education and research with the goal of applying the results to society.