【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Medicine, dentistry, and pharmacy Ⅱ)

Title of Project : Elucidation of inner ear development mechanisms and its application to regenerative medicine

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Research Area : Medicine, Dentistry, and Pharmacology
Keyword : Otlology

【Purpose and Background of the Research】

In Japan more than six million people suffer from hearing loss. Although conductive hearing loss can be treated with surgery, it is very difficult to get complete recovery from sensorineural hearing loss (SNHL) including drug-induced hearing loss, idiopathic sudden sensorineural hearing loss, and age-related hearing loss. This is because most of SNHL are caused by impairment of cochlear sensory epithelia that are highly differentiated in the mammalian adult. Mammalian sensory epithelia stop their proliferation during later stage of their development and hardly regenerate after impaired at postnatal stage.

To regenerate cochlear sensory epithelia and establish treatment methods of SNHL, it is necessary to reproduce the development process in adult organs. However, the knowledge accumulation related to the development of inner ear is much poorer than that of retina that is necessary for vision.

The purpose of this study is to establish the methods to regenerate sensory epithelia by comprehensively elucidate the molecular mechanisms of cochlear sensory epithelia.

【Research Methods】

1. Elucidation of inner ear development mechanisms

We will take two strategies to elucidate the mechanisms of inner ear development.

Firstly, we will perform comprehensive analysis of gene expression patterns from a single cell that is dissociated from cochlear epithelia at various developmental stages. After classification of each single cell into several categories based on gene expression profiles, we will compare each profile to identify genes specific to each category of cells.

Secondly, we will collect DNA samples from patients with congenital SNHL, especially with inner ear anomaly and detect responsible genes for hearing loss. The identified genes should be important for inner ear development because most of congenital SNHL are caused by deficient inner ear development.

2. Morphological, chronological, and functional assessment of identified genes

After confirming where and when these genes are expressed in inner ears, we will make knockout mice of these genes to identify their functions.

3. Establishment of regeneration methods for cochlear sensory epithelia

To establish the regenerative medicine of cochlear sensory epithelia, we will over-express or inhibit the identified genes in ES or iPS cells, cochlear explant culture, or mammalian adult inner ears (in vivo). Especially inducing cochlear sensory epithelia from human iPS cells will bring us strong tools to achieve our goal.

【Expected Research Achievements and Scientific Significance】

We will elucidate whole mechanisms of inner ear development in this study, resulting in establishment of regenerative medicine for SNHL.

【Publications Relevant to the Project】

Ono K, Nakagawa T, Kojima K, Matsumoto M, Kawauchi T, Hoshino M, Ito J. Silencing p27 reverses post-mitotic state of supporting cells in neonatal mouse cochleae. Mol Cell Neurosci 42(4):391-8, 2009

Takebayashi S, Yamamoto N, Yabe D, Fukuda H, Kojima K, Ito J, Honjo T. Multiple roles of Notch signaling in cochlear development. Dev Biol. 1;307(1):165-78, 2007

【Term of Project】 FY2011-2015

【Budget Allocation】 151,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.kuhp.kyoto-u.ac.jp/~ent/InnerearRegeneration/InnerEarRegenerationTop.html