【Grant-in-Aid for Scientific Research (S)】

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Development of a Novel Strategy for Bone Regeneration with 'Small Molecule-mediated Osteo-reprogramming' and Understanding of Genomic Mechanisms Underlying the Process

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Research Area : Oral and maxillofacial surgery
Keyword : Oral surgery, bone regenerative medicine

【Purpose and Background of the Research】

We have been working on the direct reprogramming of somatic cells into osteoblasts, the identification of osteogenic small molecules, and the development of osteoconductive scaffolds. In this study, we aim to develop a novel platform for bone regeneration by the direct reprogramming toward osteoblasts with small molecules, which we call hereafter 'small molecule-mediated osteo-reprogramming.' Besides the osteo-reprogramming protocol, we will optimize scaffolds to appropriately apply the reprogrammed cells to living bodies (Figure 1). We also hope to gain epigenetic insights into the osteoblast differentiation program by exploring reprogramming mechanisms through genome-wide approaches.

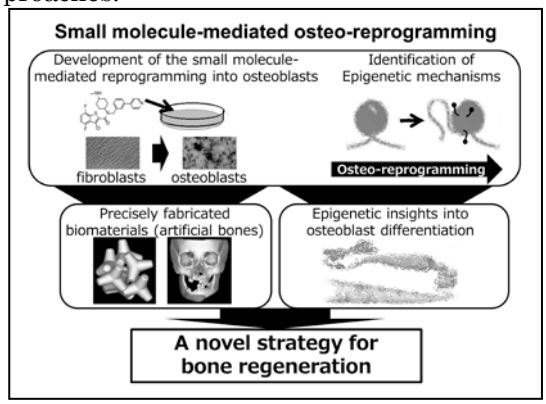

Figure 1 General flowchart of this study

【Research Methods】

1. Development of protocols for the small molecule-mediated osteo-reprogramming

Protocols for the small molecule-mediated osteo-reprogramming of mouse dermal fibroblasts are optimized. Optimized protocols are then verified in human dermal fibroblasts.

2. Investigation of epigenetic mechanisms underlying the osteo-reprogramming

We investigate the dynamics of the epigenetic status and gene expression profile during the osteo-reprogramming of human dermal fibroblasts, aiming to identify characteristics of reprogrammed cells and to obtain molecular basis of the reprogramming process in terms of epigenetics.

3. Evaluation of bone regeneration by the small molecule-mediated osteo-reprogramming

We assess bone regeneration by the fibroblast-derived osteoblasts in several animal models. Cellular mechanisms during the regeneration process are also examined.

【Expected Research Achievements and Scientific Significance】

There is no report available on the development of a platform for bone regeneration with small molecule-mediated direct reprogramming, or the creation of three-dimensional bone tissues based on the direct reprogramming. Therefore, this study will be a milestone in the field of skeletal regenerative medicine, contributing to the bone biology by clarifying epigenetic mechanisms during the reprogramming process. Given that basic and applied researches are cooperatively carried out in this study, one can expect that this is an important first step for generating novel research fields as well as therapeutic strategies that have never been established.

【Publications Relevant to the Project】

- Kanke K, Takato T et al. Stepwise differentiation of pluripotent stem cells into osteoblasts using four small molecules under serum-free and feeder-free conditions. *Stem Cell Rep* 2:751, 2014
- Saijo H, Takato T et al. A novel method for designing and fabricating custom-made artificial bones. *Int J Oral Maxillofac Surg* 40:955, 2011
- Ohba S, Takato T et al. Identification of a potent combination of osteogenic genes for bone regeneration using embryonic stem (ES) cell-based sensor. *FASEB J* 21(8):1777, 2007

【Term of Project】 FY2014-2018

【Budget Allocation】 136,100 Thousand Yen

【Homepage Address and Other Contact Information】

http://plaza.umin.ac.jp/~oralsurg/