Elucidation of the differentiation induction mechanism of ES cells and pancreatic stem cells to insulin-producing cells

Pancreatic b cells , Insulin , Diabetes , ES cells , Tissue stem cells

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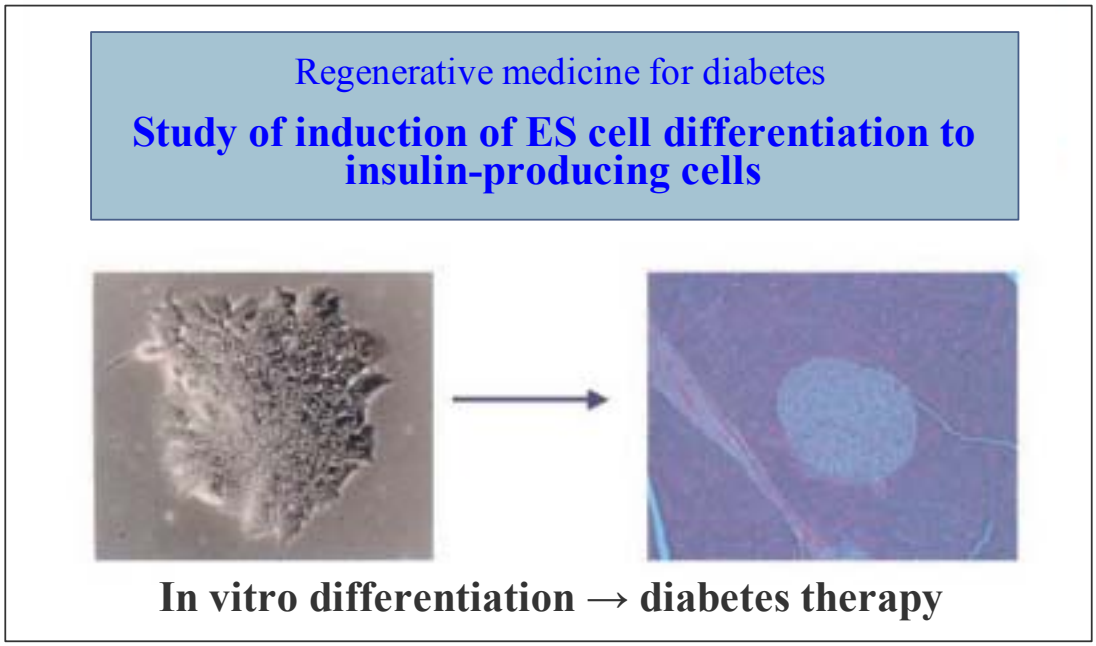
1 Induction of differentiation of ES cells to insulin-producing cells

Diabetes occurs due to relative or absolute insufficiency of insulin that decreases blood glucose. Transplantation of the pancreas or pancreatic islets is a radical therapeutic method, but lack of donors is a problem. Accordingly, studies of β cell regeneration raises great expectation. Several groups have recently succeeded in differentiation of mouse ES cells to insulin-producing cells. Various attempts have also been performed to increase the differentiation efficiency, suggesting that, for efficient induction of differentiation to insulin-producing cells (β cells), which are functionally highly differentiated, introduction of a new method is necessary, as opposed to the modification of culture conditions or addition of growth factors which are currently performed.

In this study, we will introduce genes of transcriptional factors considered to be related to the differentiation of β cells into ES cells in a manner that allows induction of expression of the genes, and the gene expression will be induced in the differentiation induction process in attempt to efficiently induce differentiation of b cells. For cell transplantation, efficient separation of β cells from ES cells is necessary.
For this purpose, we will establish a β cell purification method, in which a drug-resistance or reporter gene will be inserted in ES cells beforehand so as to specifically express the gene only in β cells, and the cells will be selected using the drug or reporter after induction of differentiation. Furthermore, we will study differentiation of human ES cells to β cells based on the results of the above studies.



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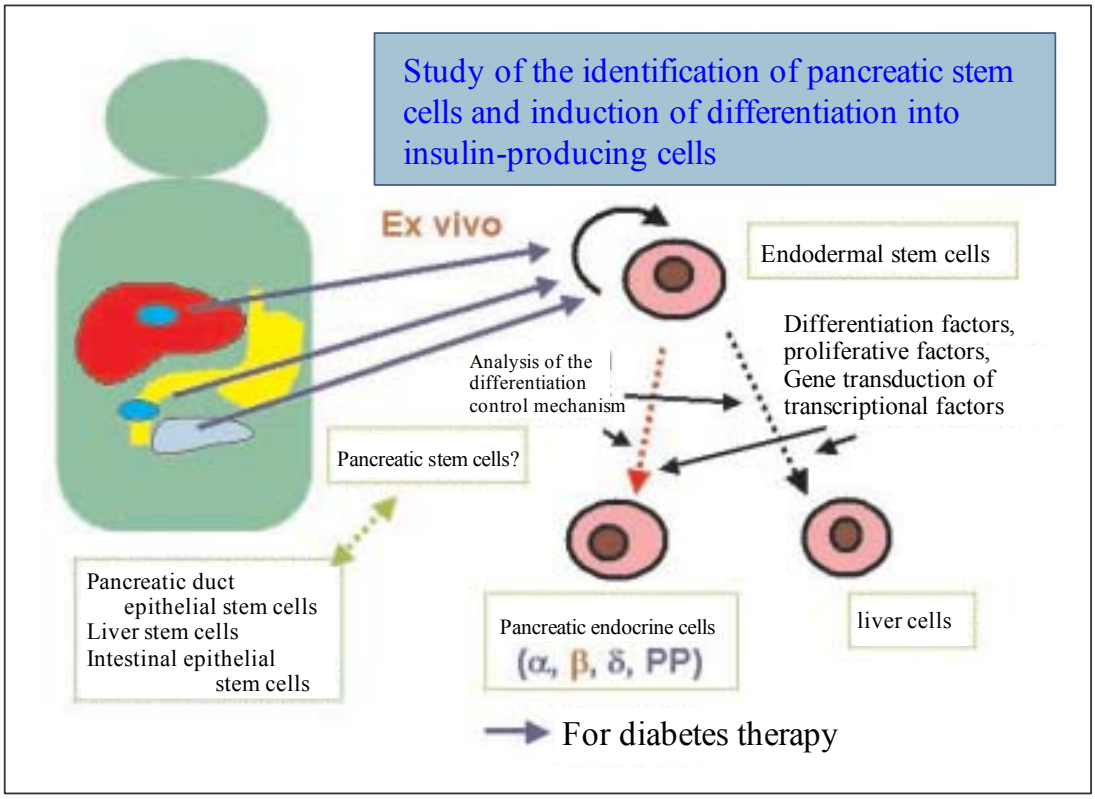
2 Identification of pancreatic stem cells and induction of differentiation to insulin-producing cells

It has recently been reported that pancreatic β cells have some proliferative ability. However, at present, it is difficult to proliferate β cells in vivo and in vitro. Partial excision of the pancreas and chronic destruction of β cells induce pdx-1-positive cells in the pancreas, and these cells may differentiate to β cells (pdx-1 is a transcriptional factor serving as the master-switch of pancreatic differentiation).

We have shown that new insulin-secreting cells appeared in the pancreas when pdx-1 was expressed in mouse pancreas using adenovirus vectors, suggesting that tissue stem cells present in the pancreas differentiated to β cells. In addition, our recent investigation of cells isolated from the pancreatic duct epithelium has shown that expression of insulin and albumin could be obtained by changing the culture conditions.

Therefore, these cells capable of differentiation into insulin-producing cells are assumed to be tissue stem cells. In this study, we will try to regenerate β cells using these tissue stem cells in the body. Since success of this study enables regeneration of β cells from patient's own cells, the study is raising high hopes.



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3 Elucidation of the mechanism of maintaining the undifferentiated state of ES cells

Regenerative medicine utilizing pluripotency of embryonic stem (ES) cells in in-vitro differentiation is raising high hopes. However, study of ES cells, that is how its omnipotency or pluripotency is maintained, has not made much progress.

This mechanism may be closely related to the re-programming mechanism of cloned embryos and the pluripotency maintenance mechanism of tissue stem cells, and thus, it is an important subject in embryology. The aim of this study is identification and analysis of novel genes involved in the maintenance of pluripotency and omnipotency.

The database of cDNA specific to the embryonic stage and EST sequence has been enriched, and we will select candidate genes using the information. For the candidate genes, genes expressed only in cells considered to maintain omnipotency and pluripotency.
Particularly, 3 types of genes: genes specifically expressed in ES cells, genes expressed between the egg cell stage and unfertilized egg cell stage in the maturation process, expression of which decreases upon fertilization, and genes persistently expressed only in germ cell lineages.

After confirmation of expression of these genes in ES cells and the early embryo, we will analyze their functions mainly using gene knockout technique, and clarify the molecular mechanism related to maintenance of the undifferentiated state.

Other study contents of Miyazaki laboratory
-Study of nuclear receptor function in pancreatic β cells