LONG-TERM IMPLANTATION OF PRIMARY ISLET CELL-ENCAPSULATING HYDROGEL MICROFIBERS IN DIABETIC MICE

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ABSTRACT

This paper describes long-term implantation of primary pancreatic islet cell fibers into diabetic mice. Primary rat pancreatic islet cells were encapsulated in core-shell hydrogel microfibers and implanted into renal capsular space of diabetic mice by using a microcatheter. The blood glucose concentration of the recipient mice were normalized for more than 36 days. This result shows that our cell fiber approach can be applied to long-term implantation and can provide primary islet cells with sufficient microenvironment to promote cellular functions *in vivo*.

KEYWORDS: Hydrogel, Microfiber, Implantation, Cell encapsulation, Diabetes mellitus

INTRODUCTION

For the treatment of diabetes mellitus, encapsulating beta-cells in hydrogel microbeads [1,2] has been studied for more than two decades to keep the implanted cells away from the recipient's immune system. However, those microbeads have a problem that it is difficult to trace and to keep within the implantation site. We here took an approach to change the shape of implantation materials, and developed fiber-shaped cell-laden hydrogel microfibers, termed "cell fiber" [3,4]; the fiber can stay at the implantation site and can easily be identified afterwards. Using this platform of cell fibers, we previously presented preliminary implantation results of large-scale hydrogel fibers using a MIN6m9 pancreatic beta-cell line [5] and recently reported the implantation of rat primary islet cell fibers [6] for the treatment of diabetic mice. In this paper, we first demonstrate the long-term (> month) implantation of primary islet cell fibers and the normalization of the blood glucose concentration of diabetic mice.

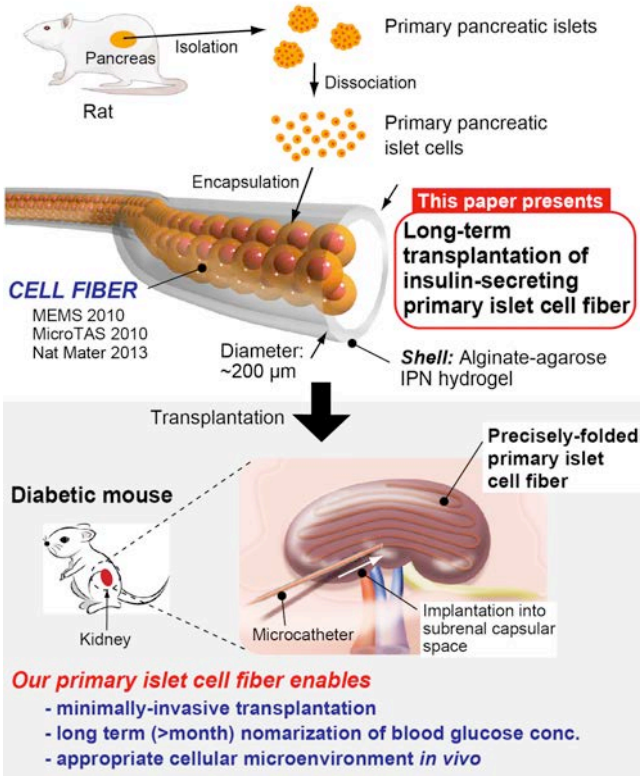

Figure 1: Concept of our work. Primary islet cells, which is isolated from rat pancreas, are encapsulated in a hydrogel microfiber termed "Cell fiber." The primary islet cell fiber secretes insulin depending on the surround glucose concentration. Transplantation of the primary islet cell fiber to a diabetic mouse normalizes the blood glucose concentration of the mouse for more than month.

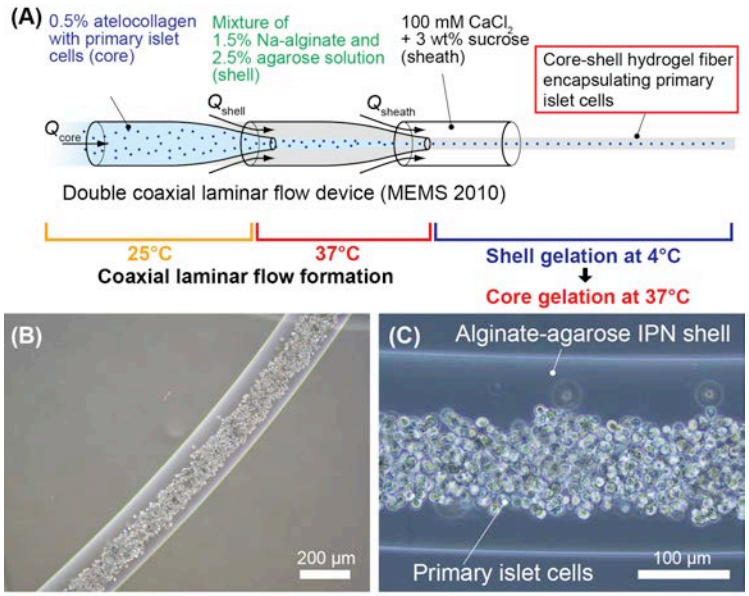

Figure 2: Formation of primary islet cell fibers. (A) Primary islet cell fiber was formed in a double coaxial microfluidic device with temperature control. (B)(C) Microscopic images of the formed primary islet cell fibers.

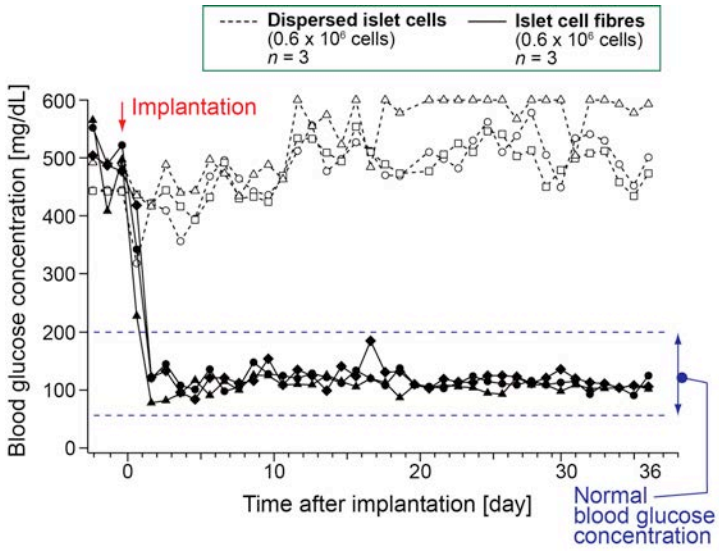

Figure 3: Change in the blood glucose concentration of three mice receiving 20-cm-long primary islet cell fibers (solid lines) and three mice receiving dispersed islet cells (dashed lines). Each symbols indicates an individual recipient. Even in 36 days after the implantation, the blood glucose concentration of the fiber-implanted mice were stable in the normal region.

FORMATION OF HYDROGEL MICROFIBERS ENCAPSULATING RAT PRIMARY ISLET CELLS

For long-term implantation, the use of primary beta cells is inevitable instead of cell lines. We isolated rat primary pancreatic islets from 10 adult rats and dissociated these islets to obtain single islet cells (~5.0×10^6 cells). Using the double coaxial laminar flow microfluidics [3,4], we encapsulated the obtained primary islet cells in core-shell hydrogel microfibers (Fig. 2 (A-C)). Stability of the shell in vivo is also important for ensuring the cell encapsulation for long term. Thus, as the shell of the cell fiber, we used alginate-agarose interpenetrating network (IPN) gel that can maintain the structure of the shell in vivo. Functionality of the primary islet cell fiber was evaluated by measuring glucose-induced insulin secreting ability of the cell fibers, resulting that our islet cell fibers produced insulin depending on surrounding glucose concentration.

IMPLANTATION OF PRIMARY ISLET CELL MICROFIBER TO DIABETIC MICE

Our cell fibers can easily be handled by using a microcatheter and fluid flow. Using this handling technique, the primary islet cell fiber encapsulated within the IPN gel was injected using a microcatheter and precisely folded into the subrenal capsular space of a diabetic mouse without damage. Section analysis revealed that the IPN hydrogel shell properly encapsulated the islet cells 15 days after the implantation. The implantation of a 20 cm-long primary islet cell fiber (~0.6×10^6 cells) normalized blood glucose concentrations stably for long term (more than 36 days, solid lines in Fig. 3), although simple injection of dispersed primary islet cells (~0.6×10^6 cells) failed to normalize the blood glucose concentrations (dashed lines in Fig. 3).

CONCLUSION

Implantation of rat primary islet cell fibers to diabetic mice stably normalized the blood glucose concentration of the mice for more than 36 days. This result showed that our cell fiber approach can be applied to long-term implantation and can provide primary islet cells with sufficient microenvironment to promote cellular functions *in vivo*. We believe that this fiber-based tissue transplantation would be compatible to minimally invasive therapeutic procedures such as catheter intervention and endoscopic surgery.

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