Method For Formation Of Peptide Functionalized Hydrogels By Native Chemical Ligation And Their Use In Preventing Cell Apoptosis

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Technology description

Novel in-situ hydrogels enabling islet cell encapsulation, stabilization and protection against cytokine induced cell apoptosis for improved tissue graft survival in transplantation applications.
#medicaldevice #biomedical #surgery #therapeutic #drugdelivery
Transplantation of pancreatic tissue is an effective method of restoring glycemic control in type I diabetic patients. Islet transplantation is attractive because it does not require major surgery and enables the potential storage of donor cells by cyropreservation. However, the major obstacles are the availability of islets and the maintenance of islet functions. Islet encapsulation uses an immuno-protective biomaterial to create a permselective membrane around a group of islet cells that enables islet transplantation in the absence of immunosuppression. Nevertheless encapsulated islet graft survival and function remain limited due to a lack of material biocompatibility, inefficient immunoprotection from small inflammatory factors and hypoxia.
This invention provides biocompatible hydrogels that protect islets from immunoreactive cells and antibodies, but also against cell apoptosis initiated by small inflammatory factors. Novel PEG hydrogels formed in-situ by native chemical ligation (NCL) are used to encapsulate the islet tissue. These hydrogels can be modified to incorporate peptides for improving cell adhesion and extending islet cell life by inhibiting surface receptors for IL-1b, a cytokine that mediates the inflammatory process causing islet death after transplantation. The anti-apoptosis effects of an IL-1r peptide antagonist immobilized on the hydrogels are highly localized to encapsulated islet cells. This approach of encapsulating tissues with hydrogels presenting anti-apoptotic reagents suggests a general, efficient solution to improve tissue graft survival in transplantation applications.
Rapid in-situ gel formation under physiological conditions was demonstrated. The gels are readily modified with suitable bioactive molecules and the chemoselective crosslinking shows minimal effect on cells during encapsulation. Mouse MIN 6 cells entrapped by NCL in PEG-hydrogels, incorporating cell adhesion (GRGDSPG) and an IL-1r antagonist (IL-1rA) peptides, reduced cell death upon exposure to low molecular weight cytokines by 60% compared to un-modified hydrogel (Figure 1). Encapsulated cells continued to secret insulin responsive to glucose stimulation, with enhanced sensitivity observed in the doubly modified PEG hydrogel (Figure 2). This invention provides a flexible hydrogel system addressing the key requirements for securing and managing islet cells for transplantation.

Figure 1.Peptide-functionalized hydrogels protect MIN 6 cells from cytokine-induced cell death. 24 hours after encapsulation, cells were treated with a combination of IL-1b (5 ng/ml), TNF-a (10 ng/ml) and INF-g (25 ng/ml) in serum-free DMEM for 1 hour.
Figure 2.Glucose-stimulated insulin release from peptide-functionalized hydrogel encapsulated MIN 6 cells, responsive to glucose concentration changes from 3.3 mM to 16.7 mM.

Advantages

A new and potentially general approach of encapsulating and maintaining transplant tissues with tailored hydrogels under biocompatible conditions.

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