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Pancreatic islet surface bioengineering with a heparin-incorporated starPEG nanofilm

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Cell surface engineering could protect implanted cells from host immune rejections while modify the cellular landscape for better post-transplantation graft function and survival. Islet transplantation is considered the most promising therapeutic option with the potential to cure diabetes. Current approach to improve clinical efficacy of pancreatic islet transplantation is alginate encapsulation. However, disappointing outcomes have been reported in clinical trials due to larger islet size resulted by encapsulation and alginate-elicited host immune responses. We have developed an ultrathin nanofilm of starPEG with incorporated heparin (Hep-PEG) that binds covalently to the amine groups of islet surface membrane via its *N*-hydroxysuccinimide groups. The Hep-PEG nanocoating elicited minimal alteration on islet volume in culture. Hep-PEG-coated islets exhibited robust islet viability accompanied by uncompromised islet insulin secretory function. Instant blood-mediated inflammatory reaction was also reduced by Hep-PEG islet coating, accompanied by enhanced intra-islet revascularization. In addition, despite its semi-permeability, Hep-PEG islet coating promoted the survival of islets exposed to pro-inflammatory cytokines. Considering that inflammation and hypoxia are primary causes of immediate cell loss for cell therapy, the Hep-PEG nanofilm represents a viable approach for cell surface engineering which would improve the clinical outcome of cell therapies.
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1. Introduction

Therapeutic efficacy of cell-based therapies is limited by poor engraftment and low cell retention [1,2]. Considering the rapid progress made in depicting roles of cell surface receptors, ligands and their downstream signalling cascades in regulating cellular activities, surface engineering of living cells via chemical biological approaches [3–11] or physical methods using natural and synthetic materials [12–18] have provided alternative ways to introduce functional groups or bioactive ligands to the cell surface for better cell function and survival. Furthermore, cell membrane is highly dynamic in mediating interactions between the cell and extracellular stimuli. Given the crucial role of cell-microenvironment interactions in tissue regeneration, remodelling of cell membrane could also control the in vivo microenvironment for donor cells and improve the therapeutic outcome of cell delivery.

Cell surface engineering has been implemented in a variety of cell therapies, including transplantation of stem cells, immune effector T cells [19] and hepatocytes [20]. Thus, enzymatic manipulation of cell surface receptor protein glycosylation has been reported, via which mesenchymal stem cell (MSCs) migration and homing for skeletal tissue regeneration could be directed [10,11]. Peptide conjugation to the outer cell membrane was later reported that facilitates MSCs navigation [9]. In addition, adjuvant-loaded nanoparticles were anchored to membranes of haematopoietic cells via maleimide-SH conjugation, which accelerated tumour elimination of adoptive T cell therapy [21]. In vivo cell tracking was also made possible by surface engineering of malignant cells, neurons, and cardiomyocytes using bioorthogonal chemistry [3].

Physical alteration of cell surface landscape was also demonstrated mainly by cell encapsulation with biocompatible nanofilms [8,12–14, 16–18,22,23]. One primary example of such approach is pancreatic islet encapsulation, which was designed to shield the implanted islets from host immune system. Rather different from stem cells or immune cells that are used for other type of cell therapies, the pancreatic islets are heterogenous in nature, composed of 3000–5000 cells per islet with an average size of ~100 μm in diameter [24–26]. Due to the scarcity of donor materials and low therapeutic efficacy, clinical islet transplantation is currently only available for selective patients with severe hypoglycaemia unawareness and poor glycaemia management [27]. Currently, alginate is the most commonly used biomaterial for islet encapsulation, generating alginate-islet microcapsules with average out diameters between 400 and 800 μm [15,24,28–30], which are less than ideal since it exceeds the physiological diffusing distance of oxygen. Disparaging outcomes from clinical trials using alginate encapsulated islet transplantation have also been reported and patients received infusion of alginate encapsulated islets all failed to achieve insulin independence, attributable to the chemical instability of alginate, inflammatory-related fibrosis and islet deaths as a result of insufficient

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revascularisation [24].Conformal islet coating was then developed by deposition of nanomembranes without affecting islet volume [13,15,26]. PEGylation, tetrafluoroethylene or silicon membrane nanoencapsulation of islets have been reported showing prolonged islet cell survival in vitro [13,15,23,24] and appropriate semi-permeability for immune protection. However, post-transplantation islet revascularisation remains to be addressed. Indeed, having previously been taken as a mere physical support of islets, the extracellular matrix (ECM), a dynamic structural scaffold composed of proteins and polysaccharides, has now been acknowledged to be essential for islet function and survival as disruption of which during isolation procedure is accountable for impaired islet engraftment, revascularisation and functional underperformance post-transplantation [31]. To address the issue of post-transplantation islet revascularisation, we have developed an ECM-mimicking nanofilm composed of star-shaped polyethylene glycol (starPEG) for its established biocompatibility and versatility as islet housing material [32]. Moreover, heparin, a highly sulphated glycosaminoglycan that resides in the ECM, was also incorporated in the starPEG nanofilm for its anti-inflammatory, anti-coagulant properties and ability to facilitate islet vascularisation by recruiting pro-angiogenic growth factors [33,34].Stability and efficacy of the Hep-PEG nanocoating were evaluated by assessing the viability and function of the coated islets. Performance of coated islets on intra-islet vascularisation was also investigated as well as islet survival against blood or pro-inflammatory cytokine-mediated inflammation.

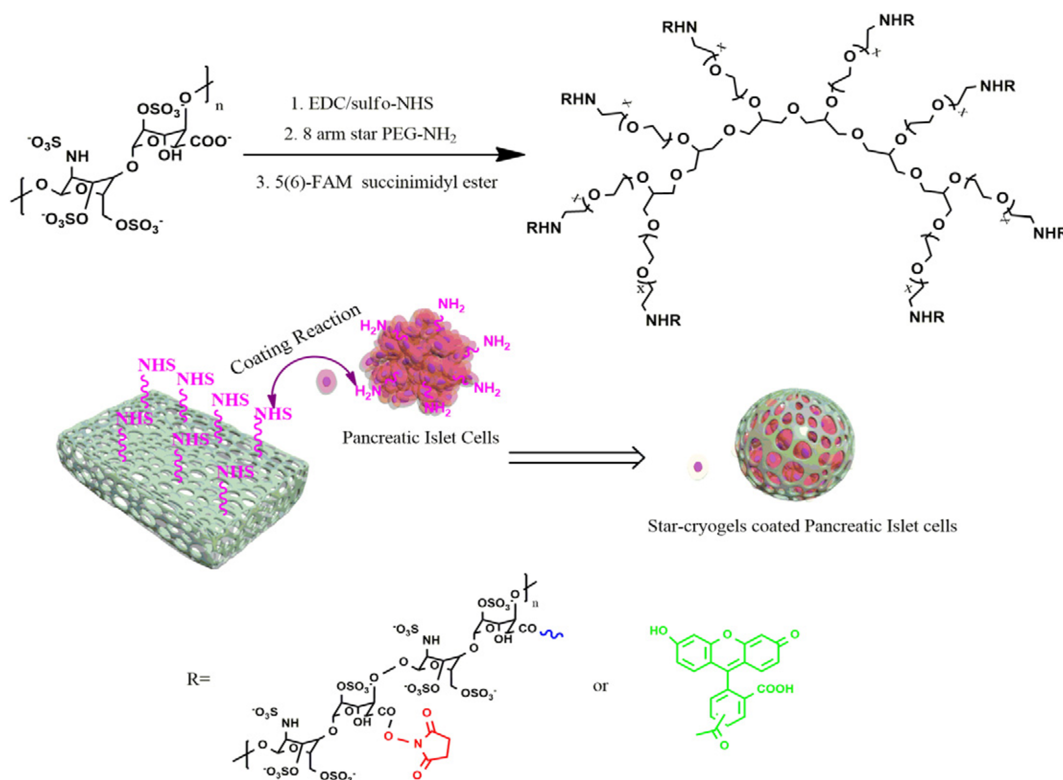
2. Experimental section

2.1. Materials

Heparin sodium salt (from porcine intestinal mucosa, Mw 12 kDa) and 8-arm poly(ethylene glycol) amine (8-arm PEG-NH_2, Mw 20 kDa), 5(6)-Carboxy fluorescein succinimidyl ester(5(6)-FAM-NHS), histopaque, collagenase V, LPS and TNF-α and DAPI were obtained from Sigma-Aldrich (Beijing, China). N-hydroxysuccinimide (NHS), N-(3-dimethylamino propyl)-*N′*-ethyl carbodiimide hydrochloride (EDC) and triethylamine (TEA) were purchased from J&K Scientific Ltd. (Beijing, China). All tissue culture reagents were obtained from Gibco (Beijing, China). The insulin ELISA kit was purchased from Merck Millipore (Shanghai, China). The life/dead cell staining kit and Annexin V/PI apoptosis kit was from BioVision (Milpitas CA, USA) and Dojindo (Shanghai, China), respectively. All animals were purchased from the Laboratory Animal Centre of the Academy of Military Medical Sciences (Beijing, China) and protocols employed for animal experiments included in the present study were in compliance with the regulations of the Tianjin Committee of Use and Care of Laboratory Animals and the Animal Ethics Committee of the Chinese Academy of Medical Science. Water that was used for all chemical reactions was purified by a Milli-Q system (Merckpore Ltd.) to a specific resistivity of ca. 18 MΩ cm.

2.2. Synthesis of heparin succinimidyl succinate

Heparin succinimidyl succinate (Heparin-NHS) was synthesized by modifying ca. 100% of the carboxylate group according to previously reported protocols [35]. Since each disaccharide repeat of heparin has one carboxylate group, the heparinised PEG polymer has one succinimidyl succinate group per ca.690 g/mol of heparin given 100% modification of heparin. Ratio of the carboxyl groups, NHS and EDC was kept at 1:2:4 (molar ratio). Reagents were dissolved in ice-cold deionised water, and allowed to react for 30 min. Excess EDC and NHS were separated by centrifugation (15,000 r, 10 min) followed by repeated washing with 30 mL cold ethanol for 3 times.



Scheme 1. Schematic illustration of Hep-PEG nanocoating preparation and pancreatic islet encapsulation. Islet coating was achieved by covalent crosslinking between the heparin-NHS and primary amines within the cell membrane and PEG-$(NH_2)_8$. Each heparin molecule possesses multiple carboxyl groups, part of which were modified to have an NHS group each. The NHS-activated carboxyl groups will react with primary amines of protein to form amide linkages, via which nanocoating of Hep-PEG and islets is stabilised.

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