Self-assembling glucagon-like peptide 1-mimetic peptide amphiphiles for enhanced activity and proliferation of insulin-secreting cells

Saahir Khan\textsuperscript{a,b,c}, Shantanu Sur\textsuperscript{a}, Christina J. Newcomb\textsuperscript{a,d}, Elizabeth A. Appelt\textsuperscript{a,b}, Samuel I. Stupp\textsuperscript{a,d,e,f,⇑}

\textsuperscript{a}Institute for BioNanotechnology in Medicine, Northwestern University, 303 E. Superior Ave., Rm. 11-123, Chicago, IL 60611, USA
\textsuperscript{b}Department of Biomedical Engineering, Northwestern University, Tech Building, Rm. E310, 2145 Sheridan Ave., Evanston, IL 60208, USA
\textsuperscript{c}Medical Scientist Training Program, Feinberg School of Medicine, Morton Building, Rm. 1-670, 1600 N. Michigan Ave., Chicago, IL 60611, USA
\textsuperscript{d}Department of Materials Science and Engineering, Northwestern University, Cook Hall, Rm. 1-3002, 2220 Campus Drive, Evanston, IL 60208, USA
\textsuperscript{e}Department of Chemistry, Northwestern University, Tech, Rm. K140, 2145 Sheridan Rd., Evanston, IL 60208, USA
\textsuperscript{f}Department of Biomedical Engineering, Northwestern University, Tech Building, Rm. E310, 2145 Sheridan Ave., Evanston, IL 60208, USA

Abstract

Current treatment for type 1 diabetes mellitus requires daily insulin injections that fail to produce physiological glycemic control. Islet cell transplantation has been proposed as a permanent cure but is limited by loss of β-cell viability and function. These limitations could potentially be overcome by relying on the activity of glucagon-like peptide 1 (GLP-1), which acts on β-cells to promote insulin release, proliferation and survival. We have developed a peptide amphiphile (PA) molecule incorporating a peptide mimetic for GLP-1. This GLP-1-mimetic PA self-assembles into one-dimensional nanofibers that stabilize the active secondary structure of GLP-1 and can be cross-linked by calcium ions to form a macroscopic gel capable of cell encapsulation and three-dimensional culture. The GLP-1-mimetic PA nanofibers were found to stimulate insulin secretion from rat insulinoma (RINm5F) cells, the GLP-1-mimetic PA also completely abrogates inflammatory cytokine-induced cell death to the level of untreated controls. When used as a PA gel to encapsulate RINm5F cells, the GLP-1-mimetic PA stimulates insulin secretion and proliferation in a cytokine-resistant manner that is significantly greater than a non-bioactive PA gel containing exendin-4. Due to its self-assembling property and bioactivity, the GLP-1-mimetic PA can be incorporated into previously developed islet cell transplantation protocols with the potential for significant enhancement of β-cell viability and function.

Keywords:
Self-assembly
Biomimetic material
Cell activation
Cell signaling
Diabetes

1. Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by immune-mediated cell death of insulin-producing β-cells of the pancreatic islets of Langerhans [1,2]. Current treatment with daily insulin injections fails to achieve the strict glycemic control observed in healthy individuals, leading to progressive secondary pathologies that decrease patient quality of life and lead to adverse clinical outcomes including kidney failure, blindness and limb amputation [3]. To alleviate these sequelae of inadequate glycemic control and to free patients from the burden of daily insulin injections, islet cell transplantation (ICT) has been proposed as a permanent treatment for T1DM [4]. The Edmonton protocol for intrahepatic ICT has achieved insulin independence in up to 80% of patients for a median of 3 years [5,6] but is limited by the loss of transplanted β-cell mass and function due to immune-mediated and inflammation-induced apoptosis [7,8], lack of vascularization [9], decreased proliferative potential [10] and impaired insulin secretion [11]. Current approaches to preventing the loss of β-cell mass and function resulting from these deleterious phenomena include the use of biomaterial scaffolds to control the islet microenvironment [12] and the addition of biological functionality to islets through genetic modification [13], substrate immobilization [14] or ligand presentation [15–17].

One source of biological functionality for the enhancement of ICT is the action of glucagon-like peptide 1 (GLP-1). GLP-1 is an

© 2012 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.