The effect of GLP-1 and Obestatin in the generation of insulin producing cells from Wharton’s jelly mesenchymal stem cells

Rana K. Al Asfar¹, Mohamed M. Kamal¹, Rania S. Abd-Elrazek¹, Ebtehal El Demerdash² and Hala O. El Mesallamy¹

¹Biochemistry Department, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt
²Pharmacology and Toxicology Department, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt

Introduction

➢ The number of patients suffering from Diabetes Mellitus (DM) is growing in an alarming rate
➢ In fact, insulin secreting β-cells are damaged to different extent in both type 1 and 2 diabetic patients
➢ The major goal of future diabetes therapy is to promote β-cell regeneration through stem cell therapy
➢ Recently, the umbilical cord (UC) has been proved to be a good source of mesenchymal stem cells (MSCs) especially from Wharton’s Jelly (WJ); the connective tissue surrounding the umbilical vessels
➢ Generation of Insulin producing cells (IPCs) from WJ-MSCs is still a challenge
➢ GLP-1, a gut hormone, has been implicated in the differentiation of MSCs into IPCs
➢ Obestatin, another gut hormone, has been recently shown to improve generation of functional β-cells from pancreatic mesenchymal stem cells

Objective

➢ In this study we aimed to
  ➢ Isolate, propagate and characterize MSCs from WJ as non-invasive and readily available source of stem cells
  ➢ Examine the effect of gut hormones including GLP-1 and obestatin in generation of IPCs in vitro from WJ-MSCs in comparison to exendin-4.

Materials and Methods

➢ The UCs were obtained from Obstetrics-Gynecology Department, Ain Shams University Hospitals.
➢ Isolation of WJ-MSCs by explant method
➢ Characterization of isolated MSCs from WJ:
  a) Adherent Culture in 10% FBS-LGMEM
  b) Immunophenotyping by Flowcytometry
  c) Adipogenic differentiation
➢ Effect of gut hormones on stem cell markers of WJ-MSCs: WJ-MSCs under proliferation conditions (10%FBS-DMEM) were incubated for 10 days with either:
  a) 10 nM Exendin-4
  b) 10 nM GLP-1
  c) 100 nM Obestatin
➢ Differentiation of WJ-MSCs into IPCs

Materials and Methods

➢ Effect of gut hormones on stem cell markers of WJ-MSCs: WJ-MSCs under proliferation conditions (10%FBS-DMEM) were incubated for 10 days with either:
  a) 10 nM Exendin-4
  b) 10 nM GLP-1
  c) 100 nM Obestatin

Results

➢ WJ is a sources of MSCs
➢ Freshly isolated WJ-MSCs showing homogenous fibroblast-like cells at (a) P0 and (b) P1
➢ WJ-MSCs lack hematopoietic CD markers and express mesenchymal CD markers
➢ Both GLP-1 and Obestatin decreased stem cell markers, nestin and Oct-4 expression in WJ-MSC under proliferation conditions, but failed to express β-cell markers
➢ Both short and long differentiation by GLP-1 and Obestatin induced morphological changes similar to exendin-4
➢ In long differentiation, Obestatin differentiate WJ-MSCs similarly to exendin-4, with higher expression of Pdx-1, as compared to GLP-1
➢ In vitro GSIS assay: Insulin release in response to low (5.5 mM) and high (16.7 mM) glucose concentrations of differentiated cells. IPCs generated from GLP-1 or obestatin showed higher insulin secretion but lack insulin responsiveness

Discussion

➢ WJ represents a source of MSCs which yields homogenous population that can be easily isolated and possesses all MSCs characteristics
➢ Under proliferation conditions, both gut hormones, GLP-1 and Obestatin, together with exendin-4, induced exit of WJ-MSC from stemness state
➢ WJ-MSCs can be differentiated to IPCs using exendin-4, GLP-1 and Obestatin using different protocols.
➢ Under short and long differentiation protocols, obestatin, as well as exendin-4, induced expression of β-cell markers, while GLP-1 failed to show similar effect.
➢ As for GSIS, IPCs generated with GLP-1 and obestatin showed higher secretion of insulin, while those generated by exendin-4 showed more glucose responsiveness than both.

Conclusions and Recommendations

➢ Gut hormones including GLP-1 and Obestatin can generate IPCs from WJ-MSCs.
➢ Obestatin is an effective differentiating factor comparable to exendin-4 and may be better than GLP-1.
➢ Obestatin should be considered a novel differentiating marker for optimization protocols.

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Author details

1. RANA K. AL ASFAR, EBTHEAL EL DEMERDASH, MOHAMED M. KAMAL, HALA O. EL MESALLAMY, RANIA S. ABDELRAZAK

1Biochemistry Department, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt
2Pharmacology and Toxicology Department, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt

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