

In-Vitro Differentiation Adipose-Derived Mesenchymal Stem Cells into Pancreatic Progenitor Cells

by Hermina Novida

Submission date: 27-May-2021 10:50AM (UTC+0800)

Submission ID: 1594979799

File name: Artikel.pdf (978.67K)

Word count: 3071

Character count: 17512

In-Vitro Differentiation Adipose-Derived Mesenchymal Stem Cells into Pancreatic Progenitor Cells

Hermina Novida¹, Agung Pranoto², Askandar Tjokroprawiro², Sony Wibisono^{1,3}, Purwati³

¹Lecturer, Division of Endocrinology, Metabolic and Diabetes, Department of Internal Medicine, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Hospital, Indonesia, ²Professor, Division of Endocrinology, Metabolic and Diabetes, Department of Internal Medicine, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Hospital, Indonesia, ³Lecturer, Stem Cells Research and Development Center Universitas Airlangga, Indonesia

Abstract

Background: Adult stem cells are currently reliable sources of mesenchymal stem cells for regenerative therapy, include diabetes mellitus. The aim of this study is to develop endocrine pancreatic progenitor cells characterized by Pdx1 and insulin expression from rat adipose-derived mesenchymal stem cells using two steps in-vitro differentiation.

Methods: In this experimental study ADMSCs were isolated from rat adipose tissue and exposed to insulinogenic differentiation medium containing nicotinamide, activin A and glucagon-like peptide-1 (GLP-1). After induction, the existence of pancreatic progenitor cells (PPCs) was confirmed by immune-staining assay of Pdx1 and insulin.

Results: After three weeks of in-vitro differentiation, expression of Pdx1 and insulin proteins showed up as green in the immunofluorescence assay. Immunofluorescence intensity of Pdx1 was higher in PPCs than in ADMSCs control ($p < 0.05$). Immunofluorescence intensity of insulin was also higher in PPCs than in ADMSCs control ($p < 0.05$). Therefore, in-vitro differentiation was successful to develop PPCs from rat ADMSCs

Conclusion: This study has demonstrated the in-vitro differentiation of ADMSCs into PPCs that expressed Pdx1 and insulin

Keywords: diabetes, adipose-derived mesenchymal stem cells, Pdx1, insulin

Introduction

According to a report by the WHO, 442 million people suffer from diabetes worldwide¹ and more than 8 million people have diabetes in Indonesia². Both type 1 and type 2 diabetes mellitus are characterized by destruction or dysfunction of pancreatic beta cells, regardless of the type of diabetes, the main focus of DM therapy is insulin therapy³. Currently, regenerative therapy is growing rapidly, including various studies

that investigate the formation of insulin-producing cells (IPCs) from embryonic stem cells, umbilical cord, and various adult tissues⁴.

Adult stem cells are currently reliable sources of mesenchymal stem cells for regenerative therapy. Among the various sources of adult stem cells, adipose tissue is an ideal population of stem cells. Adipose tissue contains an abundance of stem cells, which can be obtained by a procedure that is relatively easy, inexpensive and minimally invasive^{5,6}. Several studies were conducted to differentiate MSCs into cells that were similar to pancreatic islets and which, when transplanted, proved to be functional and producing insulin in diabetic rats⁶. Pancreatic progenitor cells (PPCs) give rise to all cell

Corresponding Author:

Hermina Novida,
dr., SpPD., K-EMD, FINASIM
Email: hermina-n@fk.unair.ac.id

types in the pancreas during development⁷. Pancreatic progenitors cells expressing the key transcription factor Pdx1 are recognized as the indispensable precursors of functional pancreatic β cells^{7,8}.

There are several main mechanisms of pancreatic regeneration such as replication of mature beta cells, differentiation of stem cells, cell fusion, and trans-differentiation of one type of stem cells to another type⁹. Adipose-derived mesenchymal stem cells (ADMSCs) are mesenchymal stem cells (MSCs) which obtained from adipose tissue and had unique characteristics making them suitable for differentiation into endocrine pancreatic progenitor^{10,11}. Differentiation MSCs into endocrine progenitor pancreas can be carried out using many extrinsic factors such as nicotinamide, exendin-4, and GLP-1 receptor agonist⁶.

The aim of this study is to develop endocrine pancreatic progenitor cells characterized by Pdx1 and insulin expression from rat adipose-derived mesenchymal stem cells using two steps in-vitro differentiation.

Materials and Methods

Isolation, culture and characterization of cells

Rats were obtained from Stem Cells Research Development Center Universitas Airlangga, and this study was approved by the Ethics Committee of the same University. Subcutaneous adipose tissue from male Wistar rats was removed under sterile conditions, cut into small pieces and incubated to liberate the cells in 25 cm² flasks containing Dulbecco's Modified Eagle's Medium (DMEM) and 1.0 mg/ml of collagenase. The cell suspension was centrifuged at 3500 rpm for 5 minutes at room temperature to obtain pellets containing cells from the stroma. Furthermore, erythrocyte lysis was carried out with ammonium chloride lysis buffer then washed with phosphate-buffered saline. Cells were maintained in DMEM (Invitrogen, Carlsbad, CA, USA) which had been supplemented with 20% Fetal Bovine Serum (FBS; Gibco, USA), 1% penicillin-streptomycin (Invitrogen) and 1% Amphotericin B (Gibco, USA). The cultures of ADMSCs were inspected every three days and passaged when the ADMSCs had reached approximately 80% confluence. The mesenchymal stem cells were isolated based on their ability to adhere to the bottom of the flask. The ADMSCs appeared spindle-shaped in the culture.

They were harvested in passage 3 and characterized as mesenchymal stem cells using CD73 (1 mg/mL; BD Pharmingen), CD90 (1 mg/mL; BD Pharmingen, San Diego, CA, USA), CD105 (1mg/mL; BD Pharmingen), and CD34 (1mg/mL; BD Pharmingen).

In-vitro differentiation ADMSCs into PPCs

We performed the two-step differentiation protocol in this study for three weeks¹². The cells that had been placed on multiwell plate M 24, each 5x10³ cells per well then cultured on insulinogenic differentiation medium containing 10 mmol nicotinamide (Sigma), 4 nmol activin A (Peprotech, Rocky Hill, NJ, USA), and 10 nmol glucagon-like peptide-1 (GLP-1, Sigma). During the first week of culture, cells were cultured in DMEM-high glucose (DMEM-HG) medium containing 10% FBS. Then two weeks later, culture in DMEM-low glucose (DMEM-LG) medium containing 10% FBS.

Characterization of Pdx1 and Insulin

The progenitor cells were placed on a multiwell plate M24 containing slides that were coated with poly-L-lysine with 6 slides of replication slides for each marker. The slides were fixed in 4% paraformaldehyde for 20 minutes, then added with Triton X-100 0.2% for 30 minutes and blocked with 5% normal goat serum (Sigma) for 20 minutes. Incubation of primary antibodies has been labelled with Pdx1 or insulin. It was continued with incubation of antibodies labelled FITC for 1 hour at room temperature, then washed with PBS-Tween 0.5% 2 times before reading it under a microscope. Images were captured using an Olympus CKX53 fluorescent microscope (Olympus, Japan). From each group, a minimum of ten slides were examined. Immunostaining intensity was estimated using quantitative score using digital software program ImageJ.

Statistical Analysis

Data distribution was analyzed using the Kolmogorov-Smirnov test. The comparisons of two group means of intensity were performed using Mann-Whitney tests, and P<0.05 was considered statistically significant.

Results

Cell surface markers of ADMSCs detected by

immune-staining revealed that ADMSCs expressed CD73, CD90 and CD105, whereas expression of CD34 was negative (Figure 1).

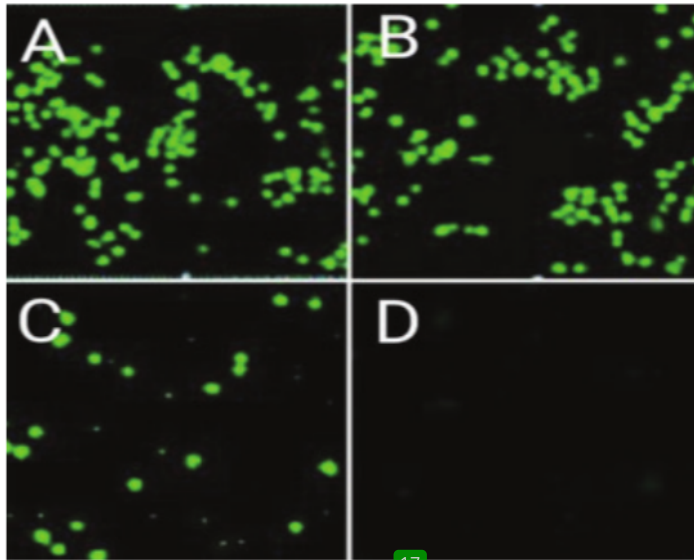


Figure 1. Immunofluorescence of cell surface markers. A. Expression of CD73, B. Expression of CD90, C. Expression of CD105, D. Expression of CD34 (magnifications: ×200).

After three weeks of in-vitro differentiation, expression of Pdx1 and insulin proteins showed up as green in the immunofluorescence assay (figure 2C and 2E). The ADMSCs cultured in non-differentiation inducing media (control group) showed very low expression of Pdx1 and insulin proteins (figure 2D and 2F).

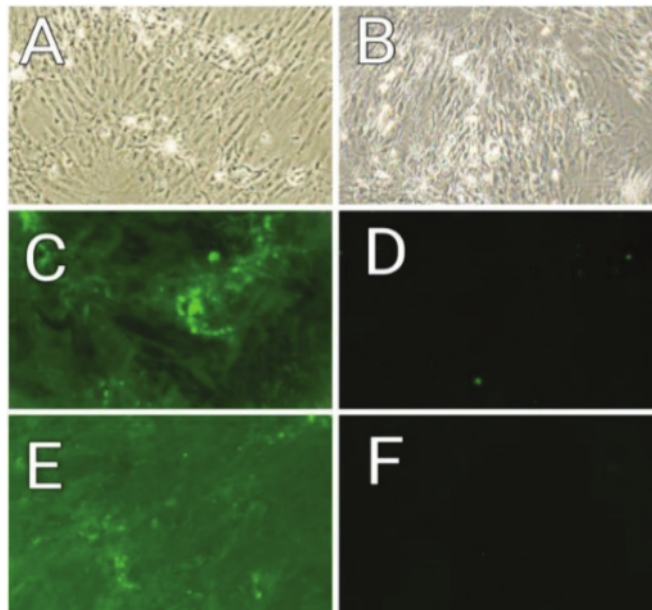


Figure 2. Progenitor cell identification and comparison with control. A. Progenitor cell proliferation. B. Control cell proliferation. C. Expression of Pdx1 on progenitor cells. D. Expression of Pdx1 on control cells. E. Expression of insulin on progenitor cells. F. Expression of insulin on control cells (magnifications: ×200).

Distribution of data was analysed using the Kolmogorov-Smirnov test and revealed that the distribution was not normal. Then the data were analysed using the Mann-Whitney test to compare immunofluorescence intensities of Pdx1 and insulin between PPCs and ADMSCs (control).

Immunofluorescence intensity of Pdx1 was higher in PPCs than in ADMSCs control ($p=0.0001$). Immunofluorescence intensity of insulin was also higher in PPCs than in ADMSCs control ($p=0.0001$). Therefore, in-vitro differentiation was successful to develop PPCs from rat ADMSCs (table 1).

Table 1. Immunofluorescence intensities of Pdx1 and Insulin

Markers	PPCs		ADMSCs (Control)		Mann-Whitney Test
	Median	Range	Median	Range	
Expression of Pdx1 (/mm ²)	12.455	8.479 - 15.547	5.486	4.263 - 6.187	P = 0.0001*
Expression of Insulin (/mm ²)	31.785	24.407 - 35.918	4.015	3.163 - 5.873	P = 0.0001*

*statistically significant ($p<0.005$)

Discussion

Stem cells are currently becoming the focus of beta cell replacement, due to flexibility and abundant sources. Stem cells derived from pluripotent embryonic stem cells (ESCs) have great differentiation potential, but ethical issues and malignant transformation are still the main problems¹³. Mesenchymal stem cells (MSCs) are found in various body tissues such as bone marrow, umbilical cord and adipose tissue and are immune-naive. MSCs derived from adipose tissue or called adipose-derived mesenchymal stem cells (ADMSCs) have the advantage of being easily obtained in abundance and have the potential to differentiate into various pathways, both mesoderm, ectoderm and endoderm¹⁴. Approximately 1-10% of the stromal fraction of adipose tissue are MSCs and they are capable to differentiate into multiple pathway¹⁵. Standard criteria for MSCs are positive phenotypes for CD105, CD73 and CD90, and negative phenotype for CD45, CD34, CD14 or CD11b, CD79 alpha or CD19^{13,16}. The phenotypes characterization of MSCs in this study showed positive staining results for CD73, CD90 and CD105, as well as negative staining for CD34, according to the existing theory.

Pancreatic progenitor cells are multipotent cells derived from the endoderm that have the ability to differentiate into specific progenitor pathways that are responsible for pancreatic development^{17,18}. In this study, ADMSCs were differentiated into pancreatic progenitor cells which later became insulin-producing cells. The induction of stem cells to become insulin-producing cells requires a multi-stage protocol. Most protocols require at least a two-stage protocol, while others can go up to 5-6 stages. It can last from several days to several months. Finally, the addition of combination extrinsic factors can stimulate the proliferation and differentiation of beta cells^{19,20}.

In this study, the differentiation of ADMSCs into progenitor cells was performed in two stages. The first stage used insulinogenic differentiation medium containing nicotinamide, activin A and glucagon-like peptide-1 (GLP-1) with DMEM-high glucose (DMEM-HG) medium containing 10% FBS for one week. Meanwhile, the second stage of the insulinogenic medium was cultured in DMEM-low glucose (DMEM-LG) medium containing 10% FBS for two weeks. Therefore, it needed a total of three weeks for the

differentiation of ADMSCs into insulin-producing cells^{13,21}. The glucose medium had a function to increase beta-cell replication and hypertrophy. Nicotinamide is associated with the development of beta-cell outgrowth from the undifferentiated epithelial cell cluster. The growth factor activin A triggered beta cell regeneration by increasing the mass of beta cells. Meanwhile, GLP-1 accelerated the functional maturation of beta cells by secreting insulin^{22,23}.

Pancreatic and duodenal homeobox1 (Pdx1) is the first transcription factor produced by the pancreas. Loss of expression of this factor in humans and mice will lead to pancreatic agenesis due to the absence of endocrine, exocrine or pancreatic duct cells²⁴. However, Pdx1 expression became limited to pancreatic beta cells only. If Pdx1 is removed from pancreatic beta cells, hyperglycaemia will occur due to reduced insulin-producing cells and an increase in glucagon-producing cells²⁵⁻²⁷. Pancreatic progenitor cells were characterized by expression of Pdx1, Myc and Ptf1A. Furthermore, cells expressing Ptf1A will differentiate into exocrine pancreatic cells²⁸. In this study, the expression of Pdx1 and insulin were marker that showed ADMSCs differentiated into pancreatic progenitor cells. Expression of Pdx1 is a key factor that determines the fate and development of the pancreas, meanwhile, insulin was the target of progenitor cell treatment.

Conclusion

This study has demonstrated the in-vitro differentiation of ADMSCs into pancreatic progenitor cells that expressed Pdx1 and insulin. This method may help the formation of an unlimited source of cells for pancreas transplantation.

Acknowledgement: I sincerely thank Stem Cells Research and Development Center Universitas Airlangga. My sincere thanks to Helen Susilowati, Deya Karsari, Igo S. Ihsan, Eryk Hendrianto for helping me in this study.

Conflict of Interest: No conflict of interest regarding the publication.

Source of Funding: This research was fund by the author.

Ethical Clearance: Taken from Ethical Committee

in Universitas Airlangga, Surabaya, Indonesia (183/EC/KEPK/FKUA/2019).

References

1. WHO. Global Report on Diabetes. World Heal Organ 2016 [Internet]. 2016;978:6-86. Available from: http://www.who.int/about/licensing/copyright_form/index.htmlhttp://www.who.int/about/licensing/copyright_form/index.html<https://apps.who.int/iris/handle/10665/204871><http://www.who.int/about/licensing/>
2. IDF. IDF Diabetes Atlas - 2019. International Diabetes Federation. 2019. 144 p.
3. Bhansali S, Kumar V, Saikia UN, Medhi B, Jha Bhansali A, et al. Effect of mesenchymal stem cells transplantation on glycaemic profile & their localization in streptozotocin induced diabetic Wistar rats. *Indian J Med Res.* 2015;142(JULY):63-71.
4. Aguayo-mazzucato C, Bonner-weir S, States U. Pancreatic β -cell regeneration as a possible therapy for diabetes Cristina. *Cell Metab.* 2018;27(1):57-67.
5. Jickka M, Major P, Wysocki M, Marycz K. Adipose-Derived Mesenchymal Stem Cells Isolated from Patients with Type 2 Diabetes Show Reduced "Stemness" through an Altered Secretome Profile, Impaired Anti-Oxidative Protection, and Mitochondrial Dynamics Deterioration. *J Clin Med.* 2019;8(6):765.
6. Wartchow KM, Rodrigues L, Suardi LZ, Federhen BC, Selistre NG, Gonçalves CA, et al. Short-Term Protocols to Obtain Insulin-Producing Cells from Rat Adipose Tissue: Signaling Pathways and In Vivo Effect. *Int J Mol Sci.* 2019;20(10):1-18.
7. Kimura A, Toyoda T, Nishi Y, Nasu M, Ohta A, Osafune K. Small molecule AT7867 proliferates PDX1-expressing pancreatic progenitor cells derived from human pluripotent stem cells. *Stem Cell Res* [Internet]. 2017;24:61-8. Available from: <https://doi.org/10.1016/j.scr.2017.08.010>
8. Memon B, Karam M, Al-Khawaga S, Abdelalim M. Enhanced differentiation of human pluripotent stem cells into pancreatic progenitors co-expressing PDX1 and NKX6.1. *Stem Cell Res Ther.* 2018;9(1):1-15.
9. Kodama S, Faustman DL. Routes to regenerating

- islet cells: Stem cells and other biological therapies for type 1 diabetes. *Pediatric Diabetes*, Supplement. 2004.
10. Paek HJ. Adipose stem cell-based regenerative medicine for reversal of diabetic hyperglycemia. *World J Diabetes*. 2014;5(3):235.
 11. Qi Y, Ma J, Li S, Liu W. Applicability of adipose-derived mesenchymal stem cells in treatment of patients with type 2 diabetes. *Stem Cell Res Ther*. 2019;10(1):1–13.
 12. Mohamad Buang ML, Seng HK, Chung LH, Saim A Bin, Idrus RBH. In vitro generation of functional insulin-producing cells from lipoaspirated human adipose tissue-derived stem cells. *Arch Med Res*. 2012 Jan;43(1):83–8.
 13. Rekitke NE, Ang M, Rawat D, Khatri R, Linn T. Regenerative therapy of type 1 diabetes mellitus: From pancreatic islet transplantation to mesenchymal stem cells. *Stem Cells Int*. 2016;2016.
 14. Thadani J, Anant M, Bhaskar V, Rajni V, 11sarullah A, Prasant K, et al. Therapeutic Application of Autologous ADMSCS (Adipose Derived Mesenchymal Stem Cells) and Islet like Cell Aggregates (ICAS) Derived from them in Type 1 and 2 Diabetes Mellitus - A Proof of Concept Study. *Stem Cells Res Dev Ther*. 2016;3(1):1–6.
 15. Camilleri ET, Gustafson MP, Dudakovic A, Riestler 9M, Garces CG, Paradise CR, et al. Identification and validation of multiple cell surface markers of clinical-grade adipose-derived mesenchymal stromal cells as novel release criteria for good manufacturing practice-compliant production. *Stem Cell Res Ther* [Internet]. 2016;7(1):1–16. Available from: <http://dx.doi.org/10.1186/s13287-016-0370-8>
 16. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini FC, Krause DS, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy*. 2006;
 17. Noguchi H. Pancreatic stem/progenitor cells for the treatment of diabetes. *Rev Diabet Stud*. 2010;7(2):105–11.
 18. Domínguez-Bendala J, Inverardi L, Ricordi C. Stem cell-derived islet cells for transplantation. *Curr Opin Organ Transplant*. 2011;16(1):76–82.
 19. Wong RSY. Extrinsic Factors Involved in the Differentiation of Stem Cells into Insulin-Producing Cells: An Overview. *Exp Diabetes Res*. 2011;2011:15.
 20. Açiksari A, Duruksu G, Karaöz E. Improved insulin-secreting properties of pancreatic islet mesenchymal stem cells by constitutive expression of Pax4 and MafA. *Turkish J Biol*. 2017;
 21. Jara C, Oyarzun-Ampuero F, Carrión F, González-Echeverría E, Cappelli C, Caviedes 7 Microencapsulation of cellular aggregates composed of differentiated insulin and glucagon-producing cells from human mesenchymal stem cells derived from adipose tissue. *Diabetol Metab Syndr* [Internet]. 2020;12(1):1–11. Available from: <https://doi.org/10.1186/s13098-020-00573-9>
 22. Dave S. Mesenchymal stem cells derived in vitro transdifferentiated insulin-producing cells: A new approach to treat type 1 diabetes. *Adv Biomed Res*. 2014;3(1):266.
 23. Jiang WJ, Peng YC, Yang KM. Cellular signaling pathways regulating β -cell proliferation as a promising therapeutic target in the treatment of diabetes (Review). *Exp Ther Med*. 2018;16(4):3275–85.
 24. Zhong F, Jiang Y. Endogenous pancreatic β cell regeneration: A potential strategy for the recovery of β cell deficiency in diabetes. *Front Endocrinol (Lausanne)*. 2019;10(FEB):1–14.
 25. Gao T, Mckenna B, Li C, Reichert M, Nguyen J, Singh T, et al. Pdx1 maintains β -cell identity and function by repressing an α -cell program. *Cell Metab*. 2014;19(2):259–71.
 26. Ruben Martin and Stephen L. Buchwald, Rukstalis 22. Habener JF, Lee YN, Yi H-J, Seo EH, et al. Improvement of therapeutic capacity of insulin-producing cells trans-differentiated from human liver cells using engineered cell sheet. *Dev Cell* [Internet]. 2017 Nov;9(1):1607–11. Available from: <https://doi.org/10.1016/j.scr.2018.04.010>
 27. Zhu Y, Liu Q, Zhou Z, Ikeda Y. PDX1, Neurogenin-3, and MAFA: Critical transcription regulators for beta cell development and regeneration. *Stem Cell Res Ther*. 2017;8(1):1–7.
 28. Loomans CJM, Williams Giuliani N, Balak 8 Ringnalda F, van Gurp L, Huch M, et al. Expansion of Adult Human Pancreatic Tissue Yields Organoids Harboring Progenitor Cells with Endocrine Differentiation Potential. *Stem Cell Reports*. 2018;10(3):712–24.

In-Vitro Differentiation Adipose-Derived Mesenchymal Stem Cells into Pancreatic Progenitor Cells

ORIGINALITY REPORT

21 %
SIMILARITY INDEX

%
INTERNET SOURCES

21 %
PUBLICATIONS

%
STUDENT PAPERS

PRIMARY SOURCES

- 1** I. M. Ghoneim, J. A. AL-Ahmad, M. M. Fayez, I. M. El-Sabagh, N. A. A. Humam, M. M. Al-EknaH. "Characterization of microbes associated with cervico-vaginal adhesion in the reproductive system of camels (Camelus dromedaries)", Tropical Animal Health and Production, 2021
Publication **1** %

- 2** Paul Holvoet. "Non-coding RNAs at the Cross-Road of Cardiometabolic Diseases and Cancer", Springer Science and Business Media LLC, 2021
Publication **1** %

- 3** Shruti Dave. "Extrinsic Factors Promoting Insulin Producing Cell-Differentiation and Insulin Expression Enhancement-Hope for Diabetics.", Current Stem Cell Research & Therapy, 2013
Publication **1** %

4

Nadine E. Rekittke, Meidjie Ang, Divya Rawat, Rahul Khatri, Thomas Linn. "Regenerative Therapy of Type 1 Diabetes Mellitus: From Pancreatic Islet Transplantation to Mesenchymal Stem Cells", *Stem Cells International*, 2016

Publication

1 %

5

B.O.S. Camara, N.M. Ocarino, Bruno M. Bertassoli, C. Malm, F.R. Araújo, A.M.S. Reis, E.C. Jorge, E.G.L. Alves, R. Serakides. "Differentiation of canine adipose mesenchymal stem cells into insulin-producing cells: comparison of different culture medium compositions", *Domestic Animal Endocrinology*, 2020

Publication

1 %

6

Mohammad Ojaghi, Fatemeh Soleimanifar, Alireza Kazemi, Marzieh Ghollasi, Masoud Soleimani, Nikoo Nasoohi, Seyed Ehsan Enderami. " Electrospun poly - - lactic acid/polyvinyl alcohol nanofibers improved insulin - producing cell differentiation potential of human adipose - derived mesenchymal stem cells ", *Journal of Cellular Biochemistry*, 2018

Publication

1 %

7

Claudia Jara, Felipe Oyarzun-Ampuero, Flavio Carrión, Esteban González-Echeverría, Claudio

1 %

Cappelli, Pablo Caviedes. "Microencapsulation of cellular aggregates composed of differentiated insulin and glucagon-producing cells from human mesenchymal stem cells derived from adipose tissue", *Diabetology & Metabolic Syndrome*, 2020

Publication

8

Islets of Langerhans, 2015.

Publication

1 %

9

Mario Barilani, Federica Banfi, Silvia Sironi, Enrico Ragni et al. "Low-affinity Nerve Growth Factor Receptor (CD271) Heterogeneous Expression in Adult and Fetal Mesenchymal Stromal Cells", *Scientific Reports*, 2018

Publication

1 %

10

Mesenchymal Stromal Cells, 2013.

Publication

1 %

11

"Progenitor Cells", Springer Science and Business Media LLC, 2019

Publication

1 %

12

Saber Khazaei, Ghazal Keshavarz, Azam Bozorgi, Hamed Nazari, Mozafar Khazaei. "Adipose tissue-derived stem cells: a comparative review on isolation, culture, and differentiation methods", *Cell and Tissue Banking*, 2021

Publication

13

Meity Ardiana, Anwar Santoso, Hanestya O. Hermawan, Ricardo A. Nugraha, Budi S. Pikir, I Gde Rurus Suryawan. "Acute Effects of Cigarette on Endothelial Nitric Oxide Synthase, Vascular Cell Adhesion Molecule 1 and Aortic Intima Media Thickness "Cigarette smoke-induced pro-atherogenic changes"", Cold Spring Harbor Laboratory, 2021

Publication

1 %

14

Yoshio Sakai, Shuichi Kaneko. "Chapter 17 Mesenchymal Stem Cell Therapy on Murine Model of Nonalcoholic Steatohepatitis", Springer Science and Business Media LLC, 2012

Publication

1 %

15

Azuma Kimura, Taro Toyoda, Yohei Nishi, Makoto Nasu, Akira Ohta, Kenji Osafune. "Small molecule AT7867 proliferates PDX1-expressing pancreatic progenitor cells derived from human pluripotent stem cells", Stem Cell Research, 2017

Publication

1 %

16

Agus Turchan, Taufiq Fatchur Rochman, Arie Ibrahim, Dyah Fauziah et al. "Duraplasty using amniotic membrane versus temporal muscle fascia: A clinical comparative study", Journal of Clinical Neuroscience, 2018

Publication

1 %

17

Guanghai Cui, Zhengyu Qi, Xin Guo, Jie Qin, Yaoting Gui, Zhiming Cai. "Rat bone marrow derived mesenchymal progenitor cells support mouse ES cell growth and germ-like cell differentiation", *Cell Biology International*, 2009

Publication

1 %

18

"Pancreas, Kidney and Skin Regeneration", Springer Science and Business Media LLC, 2017

Publication

1 %

19

Claudia Jara, Felipe Oyarzun-Ampuero, Flavio Carrión, Esteban González-Echeverría, Claudio Cappelli, Pablo Caviedes. "Microencapsulation of cellular aggregates composed of differentiated insulin and glucagon-producing cells from human mesenchymal stem cells derived from adipose tissue.", *Research Square*, 2020

Publication

1 %

20

Rebecca S. Y. Wong. "Extrinsic Factors Involved in the Differentiation of Stem Cells into Insulin-Producing Cells: An Overview", *Experimental Diabetes Research*, 2011

Publication

1 %

21

Mengmeng Wang, Lili Song, Charlie Strange, Xiao Dong, Hongjun Wang. "Therapeutic Effects of Adipose Stem Cells from Diabetic

1 %

Mice for the Treatment of Type 2 Diabetes",
Molecular Therapy, 2018

Publication

22

Yu Na Lee, Hye-Jin Yi, Eun Hye Seo, Jooyun Oh, Song Lee, Sarah Ferber, Teruo Okano, Inkyong Shim, Song Cheol Kim. "Improvement of the therapeutic capacity of insulin-producing cells trans-differentiated from human liver cells using engineered cell sheet ", Research Square, 2020

Publication

1 %

23

Bushra Memon, Manale Karam, Sara Al-Khawaga, Essam M. Abdelalim. "Enhanced differentiation of human pluripotent stem cells into pancreatic progenitors co-expressing PDX1 and NKX6.1", Stem Cell Research & Therapy, 2018

Publication

<1 %

24

Lin, T.M.. "Isolation and identification of mesenchymal stem cells from human lipoma tissue", Biochemical and Biophysical Research Communications, 20071005

Publication

<1 %

25

"Cell Biology and Translational Medicine, Volume 4", Springer Science and Business Media LLC, 2018

Publication

<1 %

26

AÇIKSARI, Ayşegül, DURUKSU, Gökhan and KARAÖZ, Erdal. "Improved insulin-secreting properties of pancreatic islet mesenchymal stem cells by constitutive expression of Pax4 and MafA", TÜBİTAK, 2017.

Publication

<1 %

27

Feng Zhou, Yu Hui, Yongde Xu, Hongen Lei, Bicheng Yang, Ruili Guan, Zhezhu Gao, Zhongcheng Xin, Jianquan Hou. "Effects of adipose-derived stem cells plus insulin on erectile function in streptozotocin-induced diabetic rats", International Urology and Nephrology, 2016

Publication

<1 %

28

NA. "Supplement 2, Proceedings of the 14th World Conference on Lung Cancer, Book 2", Journal of Thoracic Oncology, 2011

Publication

<1 %

29

Tarek Khamis, Abdelalim F. Abdelalim, Ahmed A. Saeed, Nagah M. Edress et al. "Breast milk MSCs upregulated β -cells PDX1, Ngn3, and PCNA expression via remodeling ER stress /inflammatory /apoptotic signaling pathways in type 1 diabetic rats", European Journal of Pharmacology, 2021

Publication

<1 %

30

Xing-Hua Xiao, Qi-Yuan Huang, Xian-Ling Qian, Jing Duan et al. "

<1 %

Cdc42 Promotes ADSC-Derived IPC Induction, Proliferation, And Insulin Secretion Via Wnt/ β -Catenin Signaling

", Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, 2019

Publication

Exclude quotes Off

Exclude matches < 10 words

Exclude bibliography On