Aberrant DNA methylation reprogramming during induced pluripotent stem cell generation is dependent on the choice of reprogramming factors

The conversion of somatic cells into pluripotent stem cells via overexpression of reprogramming factors involves epigenetic remodeling. DNA methylation at a significant proportion of CpG sites in induced pluripotent stem cells (iPSCs) differs from that of embryonic stem cells (ESCs). Whether different sets of reprogramming factors influence the type and extent of aberrant DNA methylation in iPSCs differently remains unknown. In order to help resolve this critical question, we generated human iPSCs from a common fibroblast cell source using either the Yamanaka factors (OCT4, SOX2, KLF4 and cMYC) or the Thomson factors (OCT4, SOX2, NANOG and LIN28), and determined their genome-wide DNA methylation profiles. In addition to shared DNA methylation aberrations present in all our iPSCs, we identified Yamanaka-iPSC (Y-iPSC)-specific and Thomson-iPSC (T-iPSC)-specific recurrent aberrations. Strikingly, not only were the genomic locations of the aberrations different but also their types: reprogramming with Yamanaka factors mainly resulted in failure to demethylate CpGs, whereas reprogramming with Thomson factors mainly resulted in failure to methylate CpGs. Differences in the level of transcripts encoding DNMT3b and TET3 between Y-iPSCs and T-iPSCs may contribute partially to the distinct types of aberrations. Finally, de novo aberrantly methylated genes in Y-iPSCs were enriched for NANOG targets that are also aberrantly methylated in some cancers. Our study thus reveals that the choice of reprogramming factors influences the amount, location, and class of DNA methylation aberrations in iPSCs. These findings may provide clues into how to produce human iPSCs with fewer DNA methylation abnormalities.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Computational Science X (CompX), University of Campinas, Zhejiang University, Ontario Institute for Cancer Research, National Cancer Institute, Ontario Cancer Institute University of Toronto, Max Planck Institute for Informatics, University of Toronto, Canada, Medical University of Vienna
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Publication date: 7 Feb 2014
Peer-reviewed: Yes

Publication information

Journal: Cell Regeneration
Volume: 3
Issue number: 1
Article number: 4
Ratings:

Scopus rating (2014): CiteScore 0 SJR 0.387 SNIP 0.199
Original language: English
ASJC Scopus subject areas: Cell Biology, Developmental Biology
URLs:

http://www.scopus.com/inward/record.url?scp=84988287132&partnerID=8YFLogxK (Link to publication in Scopus)
Source: Scopus
Source ID: 84988287132
Research output: Contribution to journal › Article › Scientific › peer-review

Antioxidant supplementation reduces genomic aberrations in human induced pluripotent stem cells

Somatic cells can be reprogrammed to induced pluripotent stem cells (iPSCs) using oncogenic transcription factors. However, this method leads to genetic aberrations in iPSCs via unknown mechanisms, which may limit their clinical use. Here, we demonstrate that the supplementation of growth media with antioxidants reduces the genome instability of cells transduced with the reprogramming factors. Antioxidant supplementation did not affect transgene expression level or silencing kinetics. Importantly, iPSCs made with antioxidants had significantly fewer de novo copy number variations, but not fewer coding point mutations, than iPSCs made without antioxidants. Our results suggest that the quality and safety of human iPSCs might be enhanced by using antioxidants in the growth media during the generation and maintenance of iPSCs.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Computational Science X (CompX), Zhejiang University, Ontario Institute for Cancer Research, National Cancer Institute, Shanghai Institute of Ceramics Chinese Academy of Sciences, Key Laboratory of Regenerative Biology of the Chinese Academy of Sciences, University of Toronto, Canada
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Number of pages: 8
Pages: 44-51
Publication date: 14 Jan 2014

Peer-reviewed: Yes

Publication information
Journal: Stem Cell Reports
Volume: 2
Issue number: 1
ISSN (Print): 2213-6711
Ratings:

Scopus rating (2014): CiteScore 2.3 SJR 5.123 SNIP 1.457
Original language: English
ASJC Scopus subject areas: Biochemistry, Cell Biology, Developmental Biology, Genetics, Medicine(all)
DOIs:

10.1016/j.stemcr.2013.11.004
URLs:

http://www.scopus.com/inward/record.url?scp=84892598278&partnerID=8YFLogxK (Link to publication in Scopus)
Source: Scopus
Source ID: 84892598278
Research output: Contribution to journal › Article › Scientific › peer-review

Autologous adipose stem cells in treatment of female stress urinary incontinence: Results of a pilot study
The purpose of our study was to find out whether transurethral injections of autologous adipose stem cells (ASCs) are an effective and a safe treatment for female stress urinary incontinence (SUI). We treated five SUI patients with ASCs combined with bovine collagen gel and saline. Prior to the treatment, the ASCs were isolated from subcutaneous fat and expanded for 3 weeks in a good manufacturing practice-level laboratory. The mixture of ASCs and collagen was injected transurethrally via cystoscope. Additionally, viability, multipotency, and surface marker profile of ASCs were analyzed in vitro. We followed up with patients 3, 6, and 12 months after the injections. The primary endpoint was a cough test to measure objectively the effect of the treatment. Validated questionnaires were used to determine the subjective cure rate. After 6 months, 1 of 5 patients displayed a negative cough testwith full bladder filledwith 500 ml of saline. At 1 year, the cough testwas negative with three patients; two of themwere satisfied with the treatment and did notwish further treatment for SUI. Validated questionnaires showed some subjective improvement in all five patients. This is the first study describing the use of autologous ASCs in combination with collagen gel for female SUI treatments. Thus far, the treatment with autologous ASCs has proven safe and well tolerated. However, the feasibility and efficacy of the treatment were not optimal; therefore, additional research is needed to develop SUI injection therapies.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), School of Management (JKK), Tampere University Hospital, University of Twente
Contributors: Kuismanen, K., Sartoneva, R., Haimi, S., Mannerström, B., Tomás, E., Miettinen, S., Nieminen, K.
Number of pages: 6
Pages: 936-941
Publication date: 2014
Peer-reviewed: Yes

Publication information
Journal: Stem Cells Translational Medicine
Volume: 3
Issue number: 8
ISSN (Print): 2157-6564
Ratings:

Scopus rating (2014): CiteScore 5.1 SJR 2.308 SNIP 1.596
Original language: English
ASJC Scopus subject areas: Cell Biology, Developmental Biology
Keywords: Adipose stem cells, Female incontinence, Injection therapy, Stress urinary incontinence, Tissue engineering
DOIs:

10.5966/sctm.2013-0197
URLs:

http://www.scopus.com/inward/record.url?scp=84905509493&partnerID=8YFLogxK (Link to publication in Scopus)
Source: Scopus
Source ID: 84905509493
Research output: Contribution to journal › Article › Scientific › peer-review

Bone morphogenetic protein-2 induces donor-dependent osteogenic and adipogenic differentiation in human adipose stem cells

Bone morphogenetic protein-2 (BMP-2) is a growth factor used to stimulate bone regeneration in clinical applications. However, there are contradicting reports on the functionality of BMP-2 in human adipose stem cells (hASCs), which are frequently used in tissue engineering. In this study, we analyzed the effects of BMP-2 on SMAD1/5 signaling, proliferation, and differentiation in hASCs. Our results indicated that BMP-2 induced dose-dependent (25–100 ng/ml) activation of SMADsignaling. Furthermore, the cell proliferation analysis revealed that BMP-2 (100 ng/ml) consistently decreased the proliferation in all the cell lines studied. However, the analysis of the differentiation potential revealed that BMP-2 (100 ng/ml) exhibited a donor-dependent dual role, inducing both osteogenic and adipogenic differentiation in hASCs. The quantitative alkaline phosphatase (qALP) activity and mineralization levels were clearly enhanced in particular donor cell lines by BMP-2 stimulus. On the contrary, in other cell lines, qALP and mineralization levels were diminished and the lipid formation was enhanced. The current study also suggests that hASCs have accelerated biochemical responsiveness to BMP-2 stimulus in human serum-supplemented culture medium compared with fetal bovine serum. The production origin of the BMP-2 growth factor is also important for its response: BMP-2 produced in mammalian cells enhanced signaling and differentiation responses compared with BMP-2 produced in Escherichia coli. These results explain the existing contradiction in the reported BMP-2 studies and indicate the variability in the functional end mechanism of BMP-2-stimulated hASCs.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Tampere University Hospital, Adult Stem Cell Research Group, National Center of Science and Technology, Ministry of Education and Science, Republic of Kazakhstan, Pirkanmaa Hospital District and School of Health Sciences
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Number of pages: 12
Pages: 1391-1402
Publication date: 1 Dec 2015
Peer-reviewed: Yes

Publication information

Journal: Stem Cells Translational Medicine
Volume: 4
Issue number: 12
ISSN (Print): 2157-6564
Ratings:

Scopus rating (2015): CiteScore 8 SJR 2.104 SNIP 1.218
Original language: English
ASJC Scopus subject areas: Cell Biology, Developmental Biology
Keywords: Adipose stem cell, Bone morphogenetic protein 2, Bone tissue engineering, Cell signaling, Differentiation, SMAD-1/5
DOIs:

10.5966/sctm.2015-0042
URLs:

http://www.scopus.com/inward/record.url?scp=84949660886&partnerID=8YFLogxK (Link to publication in Scopus)
Source: Scopus
Source ID: 84949660886
Research output: Contribution to journal › Article › Scientific › peer-review

Calcium transients closely reflect prolonged action potentials in iPSC models of inherited cardiac arrhythmia

Long-QT syndrome mutations can cause syncope and sudden death by prolonging the cardiac action potential (AP). Ion channels affected by mutations are various, and the influences of cellular calcium cycling on LQTS cardiac events are unknown. To better understand LQTS arrhythmias, we performed current-clamp and intracellular calcium ($[Ca^{2+}]_i$) measurements on cardiomyocytes differentiated from patient-derived induced pluripotent stem cells (iPS-CM). In myocytes carrying an LQT2 mutation (HERG-A422T), APs and $[Ca^{2+}]_i$ transients were prolonged in parallel. APs were abbreviated by nifedipine exposure and further lengthened upon releasing intracellularly stored Ca^{2+}. Validating this model, control iPS-CM treated with HERG-blocking drugs recapitulated the LQT2 phenotype. In LQT3 iPS-CM, expressing $Na_V1.5$-N406K, APs and $[Ca^{2+}]_i$ transients were markedly prolonged. AP prolongation was sensitive to tetrodotoxin and to inhibiting Na^+-Ca^{2+} exchange. These results suggest that LQTS mutations act partly on cytosolic Ca^{2+} cycling, potentially providing a basis for functionally targeted interventions regardless of the specific mutation site.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Gladstone Institute of Cardiovascular Disease, University of California San Francisco, Berkeley, University of Wisconsin School of Medicine and Public Health,

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Number of pages: 13
Pages: 269-281
Publication date: 12 Aug 2014
Peer-reviewed: Yes

Publication information
Journal: Stem Cell Reports
Volume: 3
Issue number: 2
ISSN (Print): 2213-6711
Ratings:

Scopus rating (2014): CiteScore 2.3 SJR 5.123 SNIP 1.457
Original language: English
ASJC Scopus subject areas: Biochemistry, Cell Biology, Developmental Biology, Genetics, Medicine(all)
DOIs:

10.1016/j.stemcr.2014.06.003
URLs:

http://www.scopus.com/inward/record.url?scp=84924219943&partnerID=8YFLogxK (Link to publication in Scopus)
Source: Scopus
Source ID: 84924219943
Research output: Contribution to journal › Article › Scientific › peer-review

Comparative analysis of targeted differentiation of human induced pluripotent stem cells (hiPSCs) and human embryonic stem cells reveals variability associated with incomplete transgene silencing in retrovirally derived hiPSCs lines
Functional hepatocytes, cardiomyocytes, neurons, and retinal pigment epithelial (RPE) cells derived from human embryonic stem cells (hESCs) or human induced pluripotent stem cells (hiPSCs) could provide a defined and renewable source of human cells relevant for cell replacement therapies, drug discovery, toxicology testing, and disease modeling. In this study, we investigated the differences between the differentiation potentials of three hESC lines, four retrovirally derived hiPSC lines, and one hiPSC line derived with the nonintegrating Sendai virus technology. Four independent protocols were used for hepatocyte, cardiomyocyte, neuronal, and RPE cell differentiation. Overall, cells differentiated from hESCs and hiPSCs showed functional similarities and similar expression of genes characteristic of specific cell types, and differences between individual cell lines were also detected. Reactivation of transgenic OCT4 was detected specifically during RPE differentiation in the retrovirally derived lines, which may have affected the outcome of differentiation with these hiPSCs. One of the hiPSC lines was inferior in all directions, and it failed to produce hepatocytes. Exogenous KLF4 was incompletely silenced in this cell line. No transgene expression was detected in the Sendai virus-derived hiPSC line. These findings highlight the problems related to transgene expression in retrovirally derived hiPSC lines.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), University of Helsinki, Tampere University Hospital, Children’s Hospital, Helsinki University Central Hospital
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Number of pages: 11
Pages: 83-93
Publication date: 2013
Peer-reviewed: Yes

Publication information
Journal: Stem Cells Translational Medicine
Volume: 2
Issue number: 2
ISSN (Print): 2157-6564
Ratings:

Scopus rating (2013): CiteScore 2.7 SJR 1.303 SNIP 1.033
Original language: English
ASJC Scopus subject areas: Cell Biology, Developmental Biology
Keywords: Cardiac, Differentiation, Embryonic stem cells, Hepatocyte differentiation, Neural differentiation, Pluripotent stem cells, Retinal pigmented epithelium

DOIs:
10.5966/sctm.2012-0047
URLs:
http://www.scopus.com/inward/record.url?scp=84876509620&partnerID=8YFLogxK (Link to publication in Scopus)
Source: Scopus
Source ID: 84876509620
Research output: Contribution to journal › Article › Scientific › peer-review

Different culture conditions modulate the immunological properties of adipose stem cells

The potential of human adipose stem cells (ASCs) for regenerative medicine has received recognition owing to their ease of isolation and their multilineage differentiation capacity. Additionally, low immunogenicity and immunosuppressive properties make them a relevant cell source when considering immunomodulation therapies and allogeneic stem cell treatments. In the current study, immunogenicity and immunosuppression of ASCs were determined through mixed lymphocyte reactions. The immunogenic response was analyzed after cell isolation and expansion in fetal bovine serum (FBS), human serum (HS)-supplemented medium, and xeno-free and serum-free (XF/SF) conditions. Additionally, the immunophenotype and the secretion of CXC chemokine ligand 8 (CXCL8), CXCL9, CXCL10, C-C chemokine ligand 2 (CCL2), CCL5, interleukin 2 (IL-2), IL-4, IL-6, IL-10, IL-17A, tumor necrosis factor-α, interferon-γ, transforming growth factor-β1, indoleamine 2,3-deoxygenase, Galectin-1, and Galectin-3 were analyzed. The results showed that ASCs were weakly immunogenic when expanded in any of the three conditions. The significantly strongest suppression was observed with cells expanded in FBS conditions, whereas higher ASC numbers were required to display suppression in HS or XF/SF conditions. In addition, statistically significant differences in protein secretion were observed between direct versus indirect cocultures and between different culture conditions. The characteristic immunophenotype of ASCs was maintained in all conditions. However, in XF/SF conditions, a significantly lower expression of CD54 (intercellular adhesion molecule 1) and a higher expression of CD45 (lymphocyte common antigen) was observed at a low passage number. Although culture conditions have an effect on the immunogenicity, immunosuppression, and protein secretion profile of ASCs, our findings demonstrated that ASCs have low immunogenicity and promising immunosuppressive potential whether cultured in FBS, HS, or XF/SF conditions.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Tampere University Hospital
Contributors: Patrikoski, M., Sivula, J., Huhtala, H., Helminen, M., Salo, F., Mannerström, B., Miettinen, S.
Number of pages: 11
Pages: 1220-1230
Publication date: 2 Oct 2014
Peer-reviewed: Yes

Publication information

Journal: Stem Cells Translational Medicine
Volume: 3
Issue number: 10
ISSN (Print): 2157-6564
Ratings:
Scopus rating (2014): CiteScore 5.1 SJR 2.308 SNIP 1.596
Original language: English
ASJC Scopus subject areas: Developmental Biology, Cell Biology
Keywords: Adipose stem cells, Cellular therapy, Cytokines, Immunogenicity, Immunosuppression, Serum-free
DOIs:
10.5966/sctm.2013-0201
URLs:
http://www.scopus.com/inward/record.url?scp=84908028028&partnerID=8YFLogxK (Link to publication in Scopus)
Source: Scopus
Source ID: 84908028028
Research output: Contribution to journal › Article › Scientific › peer-review

Elevated coding mutation rate during the reprogramming of human somatic cells into induced pluripotent stem cells

Mutations in human induced pluripotent stem cells (iPSCs) pose a risk for their clinical use due to preferential reprogramming of mutated founder cell and selection of mutations during maintenance of iPSCs in cell culture. It is unknown, however, if mutations in iPSCs are due to stress associated with oncogene expression during reprogramming. We performed whole exome sequencing of human foreskin fibroblasts and their derived iPSCs at two different passages. We found that in vitro passaging contributed 7% to the iPSC coding point mutation load, and ultradeep amplicon sequencing revealed that 19% of the mutations preexist as rare mutations in the parental fibroblasts suggesting that the remaining 74% of the mutations were acquired during cellular reprogramming. Simulation suggests that the mutation intensity during reprogramming is ninefold higher than the background mutation rate in culture. Thus the factor induced

reprogramming stress contributes to a significant proportion of the mutation load of iPSCs.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Computational Science X (CompX), Ontario Institute for Cancer Research, Mount Sinai Hospital, Harvard Medical School
Contributors: Ji, J., Ng, S., Sharma, V., Neculai, D., Hussein, S., Sam, M., Trinh, Q., Church, G. M., McPherson, J. D., Nagy, A., Batada, N. N.
Number of pages: 6
Pages: 435-440
Publication date: Mar 2012
Peer-reviewed: Yes

Publication information
Journal: Stem Cells
Volume: 30
Issue number: 3
ISSN (Print): 1066-5099
Ratings:

Scopus rating (2012): CiteScore 14.5 SJR 4.083 SNIP 1.781
Original language: English
ASJC Scopus subject areas: Cell Biology, Developmental Biology, Molecular Medicine
Keywords: Exome sequencing, Genome instability, Induced pluripotent stem cells, Mutations, Reprogramming, Stem cells
DOIs:

10.1002/stem.1011
URLs:

http://www.scopus.com/inward/record.url?scp=84857496469&partnerID=8YFLogxK (Link to publication in Scopus)
Source: Scopus
Source ID: 84857496469
Research output: Contribution to journal › Article › Scientific › peer-review

Ensuring Quality Standards and Reproducible Research for Data Analysis Services in Oncology: A Cooperative Service Model
Modern molecular high-throughput devices, e.g., next-generation sequencing, have transformed medical research. Resulting data sets are usually high-dimensional on a genomic-scale providing multi-factorial information from intertwined molecular and cellular activities of genes and their products. This genomics-revolution installed precision medicine offering breathtaking opportunities for patient's diagnosis and treatment. However, due to the speed of these developments the quality standards of the involved data analyses are lacking behind, as exemplified by the infamous Duke Saga. In this paper, we argue in favor of a two-stage cooperative serve model that couples data generation and data analysis in the most beneficial way from the perspective of a patient to ensure data analysis quality standards including reproducible research.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Research group: Predictive Society and Data Analytics (PSDA), Computing Sciences, BioMediTech, University of Applied Sciences Upper Austria, School of Management, Nankai University, Institute for Systems Biology, Seattle, Washington, USA
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Publication date: 17 Dec 2019
Peer-reviewed: Yes

Publication information
Journal: Frontiers in cell and developmental biology
Volume: 7
Article number: 349
ISSN (Print): 2296-634X
Ratings:

Scopus rating (2019): CiteScore 5.8 SJR 2.572 SNIP 1.288
Original language: English
ASJC Scopus subject areas: Developmental Biology, Cell Biology
Keywords: biostatistics, computational biology, data science, genomics, oncology, precision medicine, reproducible research
Electronic versions:

fcell-07-00349
DOIs:
10.3389/fcell.2019.00349
URLs:
http://urn.fi/URN:NBN:fi:tuni-202001201401
Source: Scopus
Source ID: 85077340569
Research output: Contribution to journal › Article › Scientific › peer-review

Functional Outcome of Human Adipose Stem Cell Injections in Rat Anal Sphincter Acute Injury Model

Anal incontinence is a devastating condition that significantly reduces the quality of life. Our aim was to evaluate the effect of human adipose stem cell (hASC) injections in a rat model for anal sphincter injury, which is the main cause of anal incontinence in humans. Furthermore, we tested if the efficacy of hASCs could be improved by combining them with polyacrylamide hydrogel carrier, Bulkamid. Human ASCs derived from a female donor were culture expanded in DMEM/F12 supplemented with human platelet lysate. Female virgin Sprague-Dawley rats were randomized into four groups (n = 14–15/group): hASCs in saline or Bulkamid (3×10^5/60 µl) and saline or Bulkamid without cells. Anorectal manometry (ARM) was performed before anal sphincter injury, at two (n = 58) and at four weeks after (n = 33). Additionally, the anal sphincter tissue was examined by micro-computed tomography (µCT) and the histological parameters were compared between the groups. The median resting and peak pressure during spontaneous contraction measured by ARM were significantly higher in hASC treatment groups compared with the control groups without hASCs. There was no statistical difference in functional results between the hASC-carrier groups (saline vs. Bulkamid). No difference was detected in the sphincter muscle continuation between the groups in the histology and µCT analysis. More inflammation was discovered in the group receiving saline with hASC. The hASC injection therapy with both saline and Bulkamid is a promising nonsurgical treatment for acute anal sphincter injury. Traditional histology combined with the 3D µCT image data lends greater confidence in assessing muscle healing and continuity. Stem Cells Translational Medicine 2018;7:295–304.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Faculty of Biomedical Sciences and Engineering, Research group: Computational Biophysics and Imaging Group, Tampere University Hospital
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Number of pages: 10
Pages: 295-304
Publication date: 1 Mar 2018
Peer-reviewed: Yes

Publication information

Journal: Stem Cells Translational Medicine
Volume: 7
Issue number: 3
ISSN (Print): 2157-6564
Ratings:
Scopus rating (2018): CiteScore 10 SJR 2.145 SNIP 1.384
Original language: English
ASJC Scopus subject areas: Developmental Biology, Cell Biology
Keywords: Adipose stem cells, Anal incontinence, Anal sphincter injury, Mesenchymal stem cells, Micro-computed tomography, Polyacrylamide hydrogel Bulkamid, Tissue engineering
Electronic versions:
Kuismanen_et_al-2018-STEM_CELLS_Translational_Medicine
DOIs:
10.1002/sctm.17-0208
URLs:
http://urn.fi/URN:NBN:fi:tty-201901181121
Source: Scopus
Source ID: 85041170829
Research output: Contribution to journal › Article › Scientific › peer-review

Novel in vitro cardiovascular constructs composed of vascular-like networks and cardiomyocytes

The interaction between different cardiac cells has shown to be important for critical biological properties including cell survival, proliferation, differentiation and function. The improvement of culture conditions with different cell types and to study their effects on cardiomyocyte viability and functionality is essential. For practical applications including general

toxicity testing, drug development and tissue engineering it is important to study whether co-cultures have additional advantages over cardiomyocyte monoculture. Two multicellular in vitro cardiovascular constructs devoid of added biomaterial were developed in this study. In the first construct, neonatal rat cardiomyocytes (CM) were seeded on vascular-like network formed by human umbilical vein endothelial cells (HUVEC) and human adipose stromal cells (hASC). In the second construct, CMs were seeded on vascular-like network formed by HUVECs and human foreskin fibroblasts. The ability of these two vascular-like networks to support the viability and functionality of CMs was analyzed. Different culture media compositions were evaluated to support the development of optimal cardiovascular construct. Our results demonstrate that both vascular-like networks markedly improved CM viability and functionality. In the constructs, co-localization of CMs and vascular-like networks was seen. Multicellular constructs also allowed synchronized contractility of CMs. Serum-free medium supplemented with vascular endothelial growth factor and basic fibroblast growth factor was found to provide the most optimal conditions for cardiovascular construct as an entity. In conclusion, when combining a vascular-like network with CMs, the viability and functionality of CMs was markedly improved. The results suggest that the cardiovascular constructs developed provide a promising new tool for the assessment of toxicological and safety pharmacological effects of compounds in vitro.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: BioMediTech, Integrated Technologies for Tissue Engineering Research (ITTE), Adult Stem Cells, BioMediTech, Tampere University Hospital
Contributors: Vuorenpää, H., Ikonen, L., Kujala, K., Huttala, O., Sarkanen, J. R., Ylikomi, T., Aalto-Setälä, K., Heinonen, T.
Number of pages: 12
Pages: 275-286
Publication date: 2014
Peer-reviewed: Yes

Publication information
Journal: IN VITRO CELLULAR AND DEVELOPMENTAL BIOLOGY: ANIMAL
Volume: 50
Issue number: 4
ISSN (Print): 1071-2690
Ratings:

Scopus rating (2014): CiteScore 2.3 SJR 0.549 SNIP 0.572
Original language: English
ASJC Scopus subject areas: Developmental Biology, Cell Biology, Medicine(all)
Keywords: Angiogenesis, Human adipose stromal cells, in vitro cardiotoxicity, Primary cardiomyocytes
DOIs:

10.1007/s11626-013-9703-4
URLs:

http://www.scopus.com/inward/record.url?scp=84898596867&partnerID=8YFLogxK (Link to publication in Scopus)
Source: Scopus
Source ID: 84898596867
Research output: Contribution to journal › Article › Scientific › peer-review

Small-molecule induction promotes corneal epithelial cell differentiation from human induced pluripotent stem cells
Human induced pluripotent stem cells (hiPSCs) offer unique opportunities for developing novel cell-based therapies and disease modeling. In this study, we developed a directed differentiation method for hiPSCs toward corneal epithelial progenitor cells capable of terminal differentiation toward mature corneal epithelial-like cells. In order to improve the efficiency and reproducibility of our method, we replicated signaling cues active during ocular surface ectoderm development with the help of two small-molecule inhibitors in combination with basic fibroblast growth factor (bFGF) in serum-free and feeder-free conditions. First, small-molecule induction downregulated the expression of pluripotency markers while upregulating several transcription factors essential for normal eye development. Second, protein expression of the corneal epithelial progenitor marker p63 was greatly enhanced, with up to 95% of cells being p63 positive after 5 weeks of differentiation. Third, corneal epithelial-like cells were obtained upon further maturation.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), BioMediTech, Tampere University Hospital
Contributors: Mikhailova, A., Ilmarinen, T., Uusitalo, H., Skottman, H.
Number of pages: 13
Pages: 219-231
Publication date: 11 Feb 2014
Peer-reviewed: Yes

Publication information
Journal: Stem Cell Reports
Volume: 2
Issue number: 2
ISSN (Print): 2213-6711
Ratings:

Scopus rating (2014): CiteScore 2.3 SJR 5.123 SNIP 1.457
Original language: English
ASJC Scopus subject areas: Biochemistry, Cell Biology, Developmental Biology, Genetics, Medicine(all)
DOIs:

10.1016/j.stemcr.2013.12.014
URLs:

http://www.scopus.com/inward/record.url?scp=84893769217&partnerID=8YFLogxK (Link to publication in Scopus)
Source: Scopus
Source ID: 84893769217
Research output: Contribution to journal › Article › Scientific › peer-review

Sodium channels enable fast electrical signaling and regulate phagocytosis in the retinal pigment epithelium
Background: Voltage-gated sodium (Na_V) channels have traditionally been considered a trademark of excitable cells. However, recent studies have shown the presence of Na_V channels in several non-excitable cells, such as astrocytes and macrophages, demonstrating that the roles of these channels are more diverse than was previously thought. Despite the earlier discoveries, the presence of Na_V channel-mediated currents in the cells of retinal pigment epithelium (RPE) has been dismissed as a cell culture artifact. We challenge this notion by investigating the presence and possible role of Na_V channels in RPE both ex vivo and in vitro. Results: Our work demonstrates that several subtypes of Na_V channels are found in human embryonic stem cell (hESC)-derived and mouse RPE, most prominently subtypes $Na_V1.4$, $Na_V1.6$, and $Na_V1.8$. Whole cell patch clamp recordings from the hESC-derived RPE monolayers showed that the current was inhibited by TTX and QX-314 and was sensitive to the selective blockers of the main Na_V subtypes. Importantly, we show that the Na_V channels are involved in photoreceptor outer segment phagocytosis since blocking their activity significantly reduces the efficiency of particle internalization. Consistent with this role, our electron microscopy results and immunocytochemical analysis show that $Na_V1.4$ and $Na_V1.8$ accumulate on phagosomes and that pharmacological inhibition of Na_V channels as well as silencing the expression of $Na_V1.4$ with shRNA impairs the phagocytosis process. Conclusions: Taken together, our study shows that Na_V channels are present in RPE, giving this tissue the capacity of fast electrical signaling. The channels are critical for the physiology of RPE with an important role in photoreceptor outer segment phagocytosis.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: BioMediTech, Tampere University, University of Jyvaskyla, Tampere University Hospital
Contributors: Johansson, J. K., Karema-Jokinen, V. I., Hakanen, S., Jylhä, A., Uusitalo, H., Vihinen-Ranta, M., Skottman, H., Ihalainen, T. O., Nymark, S.
Publication date: 15 Aug 2019
Peer-reviewed: Yes

Publication information
Journal: BMC BIOLOGY
Volume: 17
Issue number: 1
Article number: 63
ISSN (Print): 1741-7007
Ratings:

Scopus rating (2019): CiteScore 9.5 SJR 3.698 SNIP 1.604
Original language: English
ASJC Scopus subject areas: Biotechnology, Structural Biology, Ecology, Evolution, Behavior and Systematics, Physiology , Biochemistry, Genetics and Molecular Biology(all), Agricultural and Biological Sciences(all), Plant Science, Developmental Biology, Cell Biology
Keywords: Ion channels, Na, Patch clamp, Phagocytosis, Photoreceptors, Retina, RPE
Electronic versions:

s12915-019-0681-1
DOIs:

10.1186/s12915-019-0681-1
URLs:

http://urn.fi/URN:NBN:fi:tuni-201909173353
Source: Scopus
Source ID: 85071165212

Research output: Contribution to journal › Article › Scientific › peer-review

Named Entity Recognition and Relation Detection for Biomedical Information Extraction

The number of scientific publications in the literature is steadily growing, containing our knowledge in the biomedical, health, and clinical sciences. Since there is currently no automatic archiving of the obtained results, much of this information remains buried in textual details not readily available for further usage or analysis. For this reason, natural language processing (NLP) and text mining methods are used for information extraction from such publications. In this paper, we review practices for Named Entity Recognition (NER) and Relation Detection (RD), allowing, e.g., to identify interactions between proteins and drugs or genes and diseases. This information can be integrated into networks to summarize large-scale details on a particular biomedical or clinical problem, which is then amenable for easy data management and further analysis. Furthermore, we survey novel deep learning methods that have recently been introduced for such tasks.

General information

Publication status: Published
MoE publication type: A2 Review article in a scientific journal
Organisations: Computing Sciences, Research group: Predictive Society and Data Analytics (PSDA), Research group: Computational Medicine and Statistical Learning Laboratory (CMSL), BioMediTech, Nankai University, UMIT
Contributors: Perera, N., Dehmer, M., Emmert-Streib, F.
Number of pages: 26
Publication date: 28 Aug 2020
Peer-reviewed: Yes

Publication information

Journal: Frontiers in cell and developmental biology
Volume: 8
Article number: 673
ISSN (Print): 2296-634X
Original language: English
ASJC Scopus subject areas: Developmental Biology, Cell Biology
Keywords: artificial intelligence, deep learning, information extraction, named entity recognition, natural language processing, relation detection, text analytics, text mining
Electronic versions:

Named Entity Recognition and Relation 2020
DOIs:

10.3389/fcell.2020.00673
URLs:

http://urn.fi/URN:NBN:fi:tuni-202009227081

Bibliographical note

INT=comp,"Perera, Nadeesha"
Source: Scopus
Source ID: 85090794274
Research output: Contribution to journal › Review Article › Scientific › peer-review