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Stem Cell Research





Lab resource: Stem Cell Line

Generation of WAe001-A-58 human embryonic stem cell line with inducible expression of the SARS-CoV-2 nucleocapsid protein

Feima Wu^a, Yan Chen^{b,c,d}, Kai You^{b,c,d}, Shenglin Tan^{b,c}, Yingying Xu^{b,c,d}, Pei-Hui Wang^e, Shiming Liu^{a,*}, Yin-xiong Li^{b,c,d,*}

^a Guangzhou Institute of Cardiovascular Disease, Guangdong Key Laboratory of Vascular Diseases, State Key Laboratory of Respiratory Disease, the Second Affiliated Hospital, Guangzhou Medical University, Guangzhou, China

^b Institute of Public Health, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, China

^c Guangdong Provincial Key Laboratory of Biocomputing, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, China

^d Key Laboratory of Regenerative Biology, South China Institute for Stem Cell Biology and Regenerative Medicine, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, China

e Advanced Medical Research Institute, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China

ABSTRACT

Excessive prostaglandin E2 (PGE2) is the key pathological basis for COVID-19 and a Celebrex treatment of hospitalized COVID-19 patients with comorbidities led to 100% discharged rate and zero death (Hong et al. 2020). It is also suggested that SARS-CoV-2 infected multiple organs and the SARS-CoV nucleocapsid (N) protein transcriptionally drives the expression of the host COX-2 gene. In order to test whether SARS-CoV-2 N protein activates COX-2 transcription in multiple human relevant cell types, an expression inducible human embryonic stem cell line was generated by piggyBac transposon system. This cell line maintained its pluripotency, differentiation potentials, normal morphology and karyotype.

(continued)

Resource table

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		Unique stem cell line	WAe001-A-58		
Unique stem cell line	WAe001-A-58	identifier			
identifier		Name of transgene or			
Alternative name(s) of stem	H1-SARS-CoV-2-N-Teton	resistance			
cell line		Inducible/constitutive	TET		
Institution	Guangzhou Institute of Biomedicine and Health,	system			
	Chinese Academy of Sciences	Date archived/stock date	December 17, 2020		
Contact information of	Yin-xiong Li, li_yinxiong@gibh.ac.cn	Cell line repository/bank	N/A		
distributor		Ethical approval	Cell line was used according to institutional ethical		
Type of cell line	Embryonic stem cell		guidelines		
Origin	Human				
Additional origin info	Age: blastocyst stage				
	Sex: Male, 46, XY				
Cell Source	N/A				
Clonality	Clonal				
Method of reprogramming	N/A	2 Resource utility			
Genetic Modification	YES	SARS-CoV-2 could infect multiple human stem cell-derived cells and			
Type of Modification	Transgene expression				
Associated disease	Coronavirus disease 2019 (COVID-19)				
Gene/locus	N/GU280_gp10	organoids <i>in vitro</i> (Yang et al., 2020). Therefore, this cell line provides an ideal platform to illustrate the pathological role of SARS-CoV-2 N pro			
Method of modification	piggyBac				
	puromycin	tein in multiple organoi	de and cell types as well as to screen inhibitor		

(continued on next column)

* Corresponding authors at: 190 Kai Yuan Avenue, Science Park, Guangzhou 510530, China. Tel.: 86 (020)3201-5207 (Y.-X. Li), 250 Chang gang dong Road, Guangzhou 510260, China. Tel.: 86 (020) 34153522 (S. Liu).

E-mail addresses: liushiming@gzhmu.edu.cn (S. Liu), li_yinxiong@gibh.ac.cn (Y.-x. Li).

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d n tein in multiple organoids and cell types, as well as to screen inhibitors for COX-2 and prostaglandins production (Table 1).

3. Resource details

SARS-CoV-2 causes severe inflammation and damage to the lungs as well as other organs resulting in high mortality of COVID-19 patients. The molecular mechanism behind this event remained to be elucidated. Our recent study found that PGE₂ concentration was significantly elevated in COVID-19 and COX-2 specific inhibitor promoted recovery of this disease (Hong et al., 2020). Previous studies shown that SARS-CoV N protein could directly bind to the promoter of COX-2 gene and stimulate COX-2 expression in a dose-dependent manner (Yan et al., 2006). The SARS-CoV-2 N protein shares high similarity with SARS-CoV N protein in the amino acid sequence and enhance nuclear localization signals (NLS) that may contribute to virus pathogenicity were identified in this protein (Gussow et al., 2020). Therefore, we speculate that SARS-CoV-2 N protein holds the potential to activate COX-2 expression and subsequently leads to excessive prostaglandin E₂ production. Moreover, SARS-CoV-2-N could also interact with the host translation machinery by binding the stress granule (SG) proteins G3BP1/2, host mRNA binding proteins LARP1 and protein kinases CK2, and mRNA decay factors UPF1 and MOV10 (Gordon et al., 2020), which may further regulate the host antivirus response and viral replication.

The cell line WAe001-A-58 was generated from the human embryonic stem cell line WA01 (H1), with the Tet-On gene expression system and piggyBac transposon system. This piggyBac transposon system contains two plasmids: pB-TRE-EF1α-rtTA-2A-puroR-2A-EGFP and pBase. The SARS-CoV-2 N protein coding sequence (NCBI gene ID: 43740575) was inserted into the plasmid pB-TRE-EF1a-rtTA-2A-puroR-2A-EGFP and under the control of tetracycline-responsive promoter element (TRE). The validated construct was designated as pB-TRE-N-EF1a-rtTA-2A-puroR-2A-EGFP (Fig. 1A). In this plasmid, the coding sequences of RtTA, puromycin resistance and EGFP, each separated by a 2A sequence, were constitutive expressed under the control of EF1a promoter. Only in the presence of doxycycline will RtTA undergo conformational change, bind to the TRE and activate SARS-CoV-2 N protein expression. The integration of Tet-On system to the host cells was mediated by piggyBac transposase that expressed by pBase. Gene transfer was achieved by electroporation of the two plasmids into H1 cells. Selected puromycin resistant cells were distributed into 96-well plates for single cell

Table 1

Characterization and validation.

Classification	Test	Result	Data
Morphology	Photography	Normal	Fig. 1 panel B
Phenotype	Immunofluorescence	OCT4 and	Fig. 1 panel C
		NANOG positive	
	Flow cytometry	SSEA-4: 98.5%	Fig. 1 panel E
		TRA-1-60: 96%	
Genotype	Karyotype (G-banding)	46 XY,	Fig. 1 panel G
	and resolution	Resolution	
		450–500	
Identity	Microsatellite PCR (mPCR)	Not done	Not done
	STR analysis	20 alleles were tested and 100% matched	Submitted in archive with journal
Mutation analysis	Sequencing	Not done	Not done
(IF APPLICABLE)	Southern Blot OR WGS	Not done	Not done
Microbiology and virology	Mycoplasma	Negative	Fig. 1 panel H
Differentiation	Embryoid body	Express: SOX1,	Fig. 1 panel F
potential	formation	PAX6, SOX17,	
		CXCR4, MSX1	
		and TBX1	
Donor screening (OPTIONAL)	HIV 1 + 2 Hepatitis B, Hepatitis C	Not done	Not done
Genotype	Blood group	Not done	Not done
additional info	genotyping		
(OPTIONAL)	HLA tissue typing	No done	Not done

expansion. Only those single-cell derived clones with intense green fluorescence were expanded, and one of them, WAe001-A-58 was selected for further characterization, as SARS-CoV-2 N protein is inducible in a doxycycline dose-dependent manner (Fig. 1D).

WAe001-A-58 cells showed a typical human embryonic stem cell morphology (Fig. 1.B), normal karyotype (46, XY) (Fig. 1.G), and were free of mycoplasma (Fig. 1 H). Immunofluorescence staining analyses showed that pluripotent markers OCT4 and NANOG were normally expressed in WAe001-A-58 cells (Fig. 1.C). Flow cytometric analysis measured the expression level of stem cell surface markers SSEA4 and TRA-1-60, which were 98.7% and 96%, respectively (Fig. 1.E). Furthermore, the cell line retained its differentiation potential *in vitro* as determined by the mRNA expression of the three germlines layer markers (*SOX1, PAX6, SOX17, CXCR4, MSX1*, and *TBX1*) (Fig. 1F). Short Tandem Repeat (STR) analyses confirmed that the WAe001-A-58 cells were derived from the H1 cell line.

4. Materials and methods

4.1. Cell culture

WA01 (H1) and WAe001-A-58 cells were cultured on 1% Matrigelcoated plates in mTeSR1 medium (Stem cell) and maintained at 37 $^{\circ}$ C in humidified air with 5% CO₂. Cells were passaged with Accutase (Sigma) when 80% confluence was reached.

4.2. Plasmid construction and generation of WAe001-A-58

The pB-TRE-EF1 α -rtTA-2A-puroR-2A-EGFP and pBase plasmids were kept in our lab. The SARS-CoV-2 N protein encoding sequence (NCBI Gene ID: 43740575) was amplified from an expression vector of SARS-CoV-2 N protein (Constructed by Dr. Wang Pei-Hui from Shandong university) and cloned into pB-TRE-EF1 α -rtTA-2A-puroR-2A-EGFP using Clone Express II One Step Cloning Kit (Vazyme). The resultant plasmids were examined by sequencing (IGE Biotechnology).

 8×10^5 H1 cells were co-transfected with pB-TRE-N-EF1 α -rtTA-2A-puroR-2A-EGFP and pBase plasmids using Human Stem Cell Nucleofector® Kit (LONZA). The cells were plated in Matrigel-coated 24-well plates with 10 μ M Y-27632 (Selleck) in mTeSR1 for 24 h, followed by selection in mTeSR1 medium with 300 ng /ml puromycin for 48 h, remaining cells were re-plated into 96-well plates for single-cell culture.

4.3. Immunofluorescence staining

Cells were fixed with 4% paraformaldehyde at RT for 15 min, washed with PBS, permeabilized, blocked with 10% FBS for 1 h. Primary antibodies were incubated for overnight at 4 $^{\circ}$ C, followed by secondary antibodies incubation for 1 h in the dark. Images were captured with confocal microscope (Zeiss 710 NLO). Antibodies used in this study are listed in Table 2.

4.4. Induction of SARS-CoV-2 N protein with doxycycline

WAe001-A-58 cells were plated at a density of 1.5×10^4 /cm² on Matrigel-coated plates. 24 h after seeding, cells were treated with mTeSR1 medium supplemented with doxycycline for 48 h. The expression of SARS-CoV-2 N protein was verified by western blot. Antibodies used in this experiment are listed in Table 2.

4.5. Flow cytometry analysis

Cells were fixed in 4% paraformaldehyde for 15 min at RT, incubated with primary antibody for 30 min at 4 $^{\circ}$ C and followed by secondary antibody incubation for 30 min at 4 $^{\circ}$ C. The expression levels of cell surface markers were analyzed by Accuri C6 Plus flow cytometer (BD Biosciences). Antibodies used are listed in Table 2.



Fig. 1. Establishment and characterization of WAe001-A-58, an embryonic stem cell line with SARS-CoV-2 N protein doxycycline-inducible expression. (A) Schematic of the SARS-CoV-2 N protein doxycycline-inducible expression vector and the *piggyBac* system. (B) Phase contrast and green fluorescence images showed the morphology and GFP expression of WAe001-A-58 cells, scale bar 20 μm. (C) Immunofluorescence staining of pluripotent markers OCT4 (red) and NANOG (red), scale bar 20 μm. (D) Westernblot analysis showed SARS-CoV-2 N protein expression in different concentration of doxycycline treated WAe001-A-58 cells. (E) Flow cytometric analysis of SSEA4 and TRA-1-60. (F) qRT-PCR analysis of pluripotent and the three germ layers markers relative to WAe001-A-58-EB cells (Pluripotent: *OCT4* and *NANOG*; Ectoderm: *SOX1* and *PAX6*; Endoderm: *SOX17* and *CXCR4*; Mesoderm: *MSX1* and *TBX1*). (G) The karyotype analysis of WAe001-A-58 cells. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2

Reagents details.

Antibody Dilution Company Cat # and RRID Pluripotency Mouse anti-OCT4 1:200 Santa Cruz, Cat #: sc-5279 Pluripotency Mouse anti-NANOG 1:200 Santa Cruz, Cat #: sc-3293121 Pluripotency Mouse anti-NANOG 1:200 Santa Cruz, Cat #: sc-3293121 Marker Mouse anti-SSEA4 1:200 Abcam Marker Nucleo anti-TRA-1-60 1:200 Santa Cruz, Cat #: sc-3293121 Marker Nucleo.apsid antibody Santa Cruz Cat #: sc-3293121 Pluripotency Mouse anti-TRA-1-60 1:200 Santa Cruz Marker Incompary Cat #: sc-3293121 RRID: Santa Cruz Marker Nucleocapsid antibody Santa Cruz Cat #: ab16287 Structural Protein Nucleocapsid antibody Cat #: 40143- RID: Protein Donkey anti Mouse, APC- 1:1000 Sal 2827973 Secondary antibody Donkey anti Mouse, APC- 1:400 Thermo Fisher Alexa Fluor 56 RRID: AB 28233706 Cat #: A01037 Secondary antibody Cat #: A21006 RRID: AB 2090489 Secondary antibody	Antibodies for immun	ofluorescend	e, flow-cytometry	and western	n blot		
Pluripotency Marker Mouse anti-VET4 1:200 Santa Cruz, Cat #: sc-279 Pluripotency Marker Mouse anti-NANOG I:200 Santa Cruz Pluripotency Marker Mouse anti-SEA4 I:200 Santa Cruz Pluripotency Marker Mouse anti-TRA-1-60 I:200 Santa Cruz Marker RRD: Ab 778073 RRD: Ab 778073 Pluripotency Marker Rabbit anti-SARS-COV-2 I:1000 Sine Biological Inc SARS-COV-2 Rabbit anti-SARS-COV-2 I:1000 Sine Biological Inc Structural Protein Rabbit anti-J-Actin I:1000 Cat #: ab16287 Protein Rabbit anti-J-Actin I:1000 Cat #: A1037 Secondary antibody Donkey anti Mouse, APC- Alexa Fluor 56 I:400 Thermo Fisher Secondary antibody Donkey anti-Mouse, APC- Alexa Fluor 5-3 I:400 Thermo Fisher Secondary antibody Goat anti-Rabit IgG, HRP-linked Antibody I:400 Thermo Fisher Secondary antibody Goat anti-Rabit IgG, HRP-linked Antibody I:400 Thermo Fisher Secondary antibody Goat anti-Rabit IgG, HRP-linked Antibody I:400 Thermo Fisher Secondary antibod		Antibody		Dilution	Company Cat # and RRID		
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PrimersTargetForward/Reverse primer (5'-3')House-Keeping Gene (qPCR)β-ActinCTCCTCCTGAGCGCAAGTACTC/ Gene (qPCR)CCTCACTTCATGCAGTCACATCPluripotencyOC74CCTCACTTCACTGCAGCTAMarker (qPCR)CAGGTTTTCTTCCCTAGCTPluripotencyNANOGTGAACCTCAGGTAGAAGAGAAAAGMarker (qPCR)TGGTGGTAGGAAGGTAAAGEctoderm MarkerSOX1TTTCCCCTCGCTTTCTCA/(qPCR)TGCCGGTGAATCCGAGA/(qPCR)TGCCCGTTCAACATCCTTEndoderm MarkersSOX17GCATGACTCCGGTGTGAATCT/(qPCR)TCACACGTCAGGAAATGGGCT/(qPCR)CCCAAAAGCCAAGAGAAAAGAMesoderm MarkersMSX1TCCGCAAACAACAAGACGA/(qPCR)ACTGCTTCTGGCGGAACTTGMesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/(qPCR)TBX1ATGCTGCTCATGGACTTCG/(qPCR)TCGCGAAAGGGATTGCACTTMesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/(qPCR)TCGCGAAGGGATTGCACTTCG/Mesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/Mesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/Mesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/Mesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/Mesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/Mesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/Mesoderm MarkerTBX1ATGCTGCTATGGACTTCG/Mesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/Mesoderm MarkerTBX1ATGCTGCTATGGACTTCG/Mesoderm MarkerTBX1<	Secondary antibody	Goat anti-Rabbit IgG, HRP-linked Antibody		1:3000	Cell Signaling Technology Cat #: 7074S RRID: AB_2099233		
TargetForward/Reverse primer (5'-3')House-Keeping Gene (qPCR)β-ActinCTCCTCCTGAGCGCAAGTACTC/ CCTGCTTGCTGATCCACATCPluripotencyOCT4CCTCACTTCACTGCACTGTA/ Marker (qPCR)CAGGTTTCTTTCCCTAGGCPluripotencyNANOGTGAACCTCAGGTAGAAGAGTAAAGMarker (qPCR)TGGTGGTAGGAAGGTAAAGEctoderm MarkerSOX1TTTCCCCTCGCTTTCTCA/ (qPCR)Ectoderm MarkersPAX6TTGCTTGGGAAATCCGAG/ (qPCR)Endoderm MarkersSOX17GCATGACTCCGGTGTGAATCT/ (qPCR)Endoderm MarkersSOX17GCATGACTCCGGTGTGAATCT/ (qPCR)Endoderm MarkersSOX17CCCACACGTCAGGAAAGGGCT/ (qPCR)Endoderm MarkersSOX17CCCACAATGCCAGTAAGAGAMesoderm MarkersMSX1TCCGCAAACACAAGACGA/ (qPCR)Mesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/Mesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/ (qPCR)	Primers						
House-Keeping Gene (qPCR)β-ActinCTCCTCCTGAGCGCAAGTACTC/Gene (qPCR)TCCTGCTGCTGATCCACATCPluripotencyOCT4CCTCACTTCACTGCACTGTA/Marker (qPCR)CAGGTTTTCTTTCCCTAGCTPluripotencyNANOGTGAACCTCAGCTACAAACAG/Marker (qPCR)TGGTGGTAGGAAGAGTAAAGEctoderm MarkerSOX1TTTCCCCTCGCTTTCTCA/(qPCR)TGCAGGCTGAATTCGGTTEctoderm MarkerPAX6TTGCTTGGGAAATCCGAG/(qPCR)TGCCCGTTCAACATCCTTEndoderm MarkersSOX17GCATGACTCCGGTGTGAATCT/(qPCR)TCACACGTCAGGAAATGGCGT/(qPCR)CCCAAAAGCCAGAGAAAGAGAMesoderm MarkersMSX1TCCGCAAACACAAGACGA/(qPCR)ACTGCTTCTGGCGGAACTTMesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/(qPCR)TBX1ATGCTGCTCATGGACTTCG/(qPCR)TTCGCGAAAGGGATTGCT		Target	Forward/Revers	e primer (5'	-3′)		
Gene (qPCR)TCCTGGTTGCTGATCCACATCPluripotencyOCT4CCTCACTTCACTGCACTGTA/Marker (qPCR)CAGGTTTTCTTTCCCTAGCTPluripotencyNANOGTGAACCTCAGCTACAAACAG/Marker (qPCR)TGGTGGTAGGAAGAGAAAAGEctoderm MarkerSOX1TTTCCCCTGCTTTCTCA/(qPCR)TGCAGGCTGGAATCCGAG/Endoderm MarkersSOX17GCATGACTCCGGTGTGAATCT/(qPCR)TGCCCGTTCAACATCCTTEndoderm MarkersSOX17GCATGACTCCGGGTGGAATCT/(qPCR)TCACACGTCAGGAAATGGGCT/(qPCR)CCCACAATGCCAGTTAAGAAGAMesoderm MarkersMSX1TCCGCAAACACCAGAGACACTT(qPCR)ACTGCTTCTGGCGGAACTTMesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/(qPCR)TDCGCGAAGGGATTGCCTMesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/(qPCR)TTCGCGAAAGGGATTGCT	House-Keeping	β -Actin CTCCTCCTGAG		CGCAAGTA	CTC/		
PluripotencyNANOGCAGGTTTCTTTCCCTAGCTPluripotencyNANOGTGAACCTCAGCTACAAACAG/Marker (qPCR)TGGTGGTAGGAAGAGTAAAGEctoderm MarkerSOX1TTTCCCCTCGCTTTCTCA/(qPCR)TGCAGGCTGAATTCGGTTEctoderm MarkerPAX6TTGCTTGGGAAATCCGAG/(qPCR)TGCCCGTTCAACATCCTTEndoderm MarkersSOX17GCATGACTCCGGTGTGAATCT/(qPCR)TCACACGTCAGGATAGTTGCAGTEndoderm MarkersCXCR4ACTACACCGAGGAAATGGGCT/(qPCR)CCCACAATGCCAGTTAAGAAGAMesoderm MarkerMSX1TCCGCAAACACAAGACGA/(qPCR)ACTGCTTCTGGCGGAACTTMesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/(qPCR)TTCGCGAAAGGGATTGCT	Gene (qPCR)			GATCCACA1	GCACTCTA/		
Pluripotency NANOG TGAACCTCAGCTACAAACAG/ Marker (qPCR) TGGTGGTAGGAAGAGTAAAG Ectoderm Marker SOX1 TTTCCCCTCGCTTTCTCA/ (qPCR) TGCAGGCTGAATTCGGTT Ectoderm Marker PAX6 TTGCTTGGGAAATCCGAG/ (qPCR) TGCCCGTTCAACATCCTT Endoderm Markers SOX17 GCATGACTCCGGTGTGAATCT/ (qPCR) TCACACGTCAGGAAATGGGCT/ (qPCR) CCCAACATGCCAGTTAAGAAGA Mesoderm Markers MSX1 TCCGCAAACACAAGACGA/ (qPCR) ACTGCTTCTGGCGGAACTT Mesoderm Marker TBX1 ATGCTGCTCATGGACTTCG/ (qPCR) TTCGCGAAAGGGATTGCT	Marker (aPCR)	CAGGTTTTCTTT		FCCCTAGCI	1/		
Marker (qPCR)TGGTGGTAGGAAGAGATAAGEctoderm MarkerSOX1TTTCCCCTCGCTTTCTCA/(qPCR)TGCCAGGCTGAATTCGGTTEctoderm MarkerPAX6TTGCTTGGGAAATCCGAG/(qPCR)TGCCCGTTCAACATCCTTEndoderm MarkersSOX17GCATGACTCCGGTGTGAATCT/(qPCR)TCACACGTCAGGATAGTTGCAGTEndoderm MarkersCXCR4ACTACACCGAGAAATGGGCT/(qPCR)CCCACAATGCCAGTTAAGAAGAMesoderm MarkerMSX1TCCGCAAACAACAAGACGA/(qPCR)ACTGCTTCTGGCGGAACTTMesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/(qPCR)TTCGCGAAAGGGATTGCT	Pluripotency NAN		TGAACCTCAGCTACAAACAG/		G/		
Infected and the second sec	Marker (qPCR) Ectoderm Marker	TGGTGGTAGGA SOX1 TTTCCCCTCGCT		AGAGTAAA	AG		
Ectoderm Marker PAX6 TTGCTTGGGAAATCCGAG/ (qPCR) TGCCCGTTCAACATCCTT Endoderm Markers SOX17 GCATGACTCCGGTGTGAATCT/ (qPCR) TCACACGTCAGGATAGTTGCAGT Endoderm Markers CXCR4 ACTACACCGAGGAAATGGGCT/ (qPCR) CCCACAATGCCAGTTAAGAAGA Mesoderm Marker MSX1 TCCGCAAACACAAGACGA/ (qPCR) ACTGCTTCTGGCGGAACTT Mesoderm Marker TBX1 ATGCTGCTCATGGACTTCG/ (qPCR) TTCGCGAAAGGGATTGCT	(qPCR)	bom	TGCAGGCTGAAT				
Endoderm MarkersSOX17GCATGACTCCGGTGTGAATCT/ (qPCR)Endoderm MarkersSOX17GCATGACTCCGGTGTGAATCT/ TCACACGTCAGGATAGTTGCAGTEndoderm MarkersCXCR4ACTACACCGAGGAAATGGGCT/ (qPCR)Mesoderm MarkerMSX1TCCGCAAACACAAGACGA/ ACTGCTTCTGGCGGAACTTMesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/ TTCGCGAAGGGATTGCTMesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/ TTCGCGAAGGGATTGCT	Ectoderm Marker (aPCR)	PAX6	PAX6 TTGCTTGGGAA/ TGCCCGTTCAAC				
(qPCR) TCACACGTCAGGATAGTTGCAGT Endoderm Markers CXCR4 ACTACACCGAGGAAATGGGCT/ (qPCR) CCCACAATGCCAGTTAAGAAGA Mesoderm Marker MSX1 TCCGCAAACACCAAGACGA/ (qPCR) ACTGCTTCTGGCGGAACTT Mesoderm Marker TBX1 ATGCTGCTCATGGACTTCG/ (qPCR) TTCGCGAAAGGGATTGCT	Endoderm Markers	SOX17	GCATGACTCCG	GTGTGAAT	CT/		
(qPCR)CCCACAATGCCAGTTAAGAAGAMesoderm MarkerMSX1TCCGCAAACACAAGACGA/(qPCR)ACTGCTTCTGGCGGAACTTMesoderm MarkerTBX1ATGCTGCTCATGGACTTCG/(qPCR)TTCGCGAAGGGATTGCT	(qPCR) Endoderm Markers	CXCR4	TCACACGTCAGGATAGTTGCAGT ACTACACCGAGGAAATGGGCT/				
Mesoderm Marker MSA1 TCCGCAAACACAAGAGAGA/ (qPCR) ACTGCTTCTGGCGGAACTT Mesoderm Marker TBX1 ATGCTGCTCATGGACTTCG/ (qPCR) TTCGCGAAGGGATTGCT	(qPCR)	Mevi	CCCACAATGCC	AGTTAAGA	AGA		
Mesoderm Marker TBX1 ATGCTGCTCATGGACTTCG/ (qPCR) TTCGCGAAGGGATTGCT	(qPCR)	M5X1	ACTGCTTCTGG	AAGACGA/ CGGAACTT			
	Mesoderm Marker (qPCR)	TBX1	ATGCTGCTCAT	GGACTTCG, ATTGCT	/		

4.6. Karyotype analysis

Cells were incubated with colcemid for 130 min, dissociated, incubated in hypotonic solution for 20 min and fixed in methanol: acetic acid (3:1). Chromosomes of metaphase were then classified according to the standard G-banding technique.

4.7. Embryonic body (EB) formation and in vitro differentiation

Cells were dissociated with collagenase IV (Gibco) for 30 min at 37 $^{\circ}$ C, resuspended in EB medium (DMEM/F12 (Gibco) supplemented with

20% knockout serum replacement (Gibco), 1% L-GlutaMax (Gibco), 1% NEAA (Gibco) and 0.1% β -mercaptoethanol (Gibco)) and cultured for 14 days.

4.8. Real-time PCR analysis

Total RNA was extracted with TriZol reagent according to manufacturer's instructions (Invitrogen). Real-time PCR analysis was conducted in triplicate on a CFX96TM Real-Time System (Bio-Rad). Primers used are listed in table 2.

4.9. Mycoplasma detection

Mycoplasma detection was performed with MycoAlertTM PLUS Mycoplasma Detection Kit (Lonza) according to the manufacturer's instructions.

4.10. STR analysis

STR analysis was carried out by IGE Biotechnology LTD (Guangzhou, China)

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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