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Mesenchymal Stem Cell

Mesenchymal Stem Cell

2002 8

•



LifeCord &
LifeCord Biomedical Research Institute

가

가

가

- -

Mesenchymal Stem Cell

: (mesenchymal stem cell, MSCs)
 가
 (placenta)
 (umbilical cord blood) 가
 , (osteoblast) 가
 : ()
 ,
 가
 .
 : plastic adherent layer ,
 (fibroblastoid morphology)
 alkaline

phosphatase, Von Kossa

CD34

.
(transdifferentiation, differentiation plasticity)

.
:

(plasticity)

,

.

: , , , ,

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I.

(bone marrow) (stromal tissues)

, .

(hematopoietic cell), (endothelial cell),

(stromal cell) ,

(progenitor) .¹⁻²

,² ,³⁻⁵ ,⁶ ,¹ ,⁷ 1,8

9-10 (plasticity)^{7,11-13} 가

1974 Friedenstein¹⁴ “colony forming unit-fibroblast (CFU-F)” “marrow stromal fibroblast(MSF)” “

(bone marrow stromal stem cell) ,

, (mesenchymal stem cell, MSC)

.^{10-12, 15-17}

. 가¹⁷⁻¹⁸

가

, ,

가⁴ Muscular dystrophy

Osteogenesis imperfecta

19,20

가

(umbilical cord blood hematopoietic stem cell transplantation)²¹

(placenta)

(umbilical cord)

(hematopoietic stem cell)

가

가

(immature)

(antigen

expression)

(allogeneic

transplantation)

,²²

가

(fracture)

(bone defects)

(biodegradable scaffold)

(collagen)

II.

1.

38 , ()
 , 가
(contamination)
 . 24

2.

가 50 ml 10 ml 5 .
10 ml 30 ml PBS(phosphate buffered saline, Gibco BRL) 가
 , 20 ml 10 ml Ficoll-PlaqueTM plus(1.077 g/ml,
Amersham Pharmacia Biotech.) 2000 rpm
20 (density gradient centrifugation) .
PBS , Ficoll-PlaqueTM plus
1800 rpm 5
 .
1 × 10⁶ cells/cm² (75 T flask,
Nunc) 10% 20% (fetal bovine serum, FBS,
Gibco BRL) -MEM(alpha minimum essential medium, Gibco BRL)

trypan blue dye exclusion

3.

0.25% trypsin/0.02% EDTA 0.5×10^6 cells/ml
가 20 .
Negative control FITC, PE(BD Pharmingen) ,
anti-CD14, CD45(BD Pharmingen) , anti-CD3,
CD4, CD19, CD25 , anti-CD34 ,
anti-CD54 . 2
PBS flow buffer(1% paraformaldehyde, 0.1% sodium
azide, and 0.5% bovine serum albumin in PBS)
FACScan(Becton-Dickinson) .

4.

0.25% trypsin/0.02% EDTA(Gibco BRL)
 1×10^4 cells/cm² 6 well-plate .
10% DMEM(Dulbecco modified Eagle's medium,
high glucose, Gibco BRL) 10^{-8} M dexamethasone(Sigma), 10^{-4} M ascorbate-2-
phosphate(Sigma), 100 ng/ml -glycerophosphate(Sigma) 가 4
8 .

5.

2 ml 0.3% 1 (Nittagelatin) 12 well-plate

-20 (lyophilizer)

. vacuum oven 105 24

1×10^5 cells/ml

spinner flask(Belco)

(dynamic cell seeding)

6.

6-1. Alkaline phosphatase

alkaline phosphatase buffer 가

10 mg naphthol AS-TR phosphate/10 ml ALP buffer 2 mg Fast red violet/1 ml

ALP buffer 12 well plate well 1-1.5 ml 37

20-30

가 PBS 가 3 . 10

PBS 3 100% methyl

alcohol 1-1.5 ml 30

methyl alcohol 3 well-plate filter paper

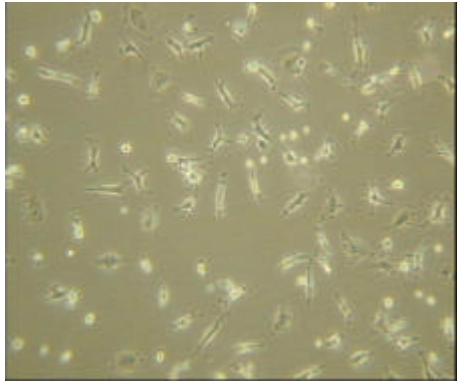
6-2. Von Kossa

	4% paraformaldehyde	10		PBS	3
	5% silver nitrate				
	60		3	5%	
sodium thiosulfate	2-3			silver	
		5		Nuclear fast	
red	5				

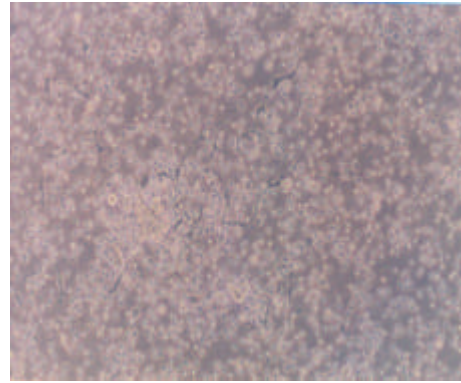
III.

1.

(mononuclear cell) 10% 20%
(fetal bovine serum, FBS) -MEM 7 ,
Figure 1 10% 가
가 . 가
가 .
7 14
, 10%
가 가 (Figure 2).
가



(A): 10% FBS containing media



(B): 20% FBS containing media

Figure 1. Photomicrograph of plastic-adherent cells in microscopic fields after 7 days in culture ($\times 100$).

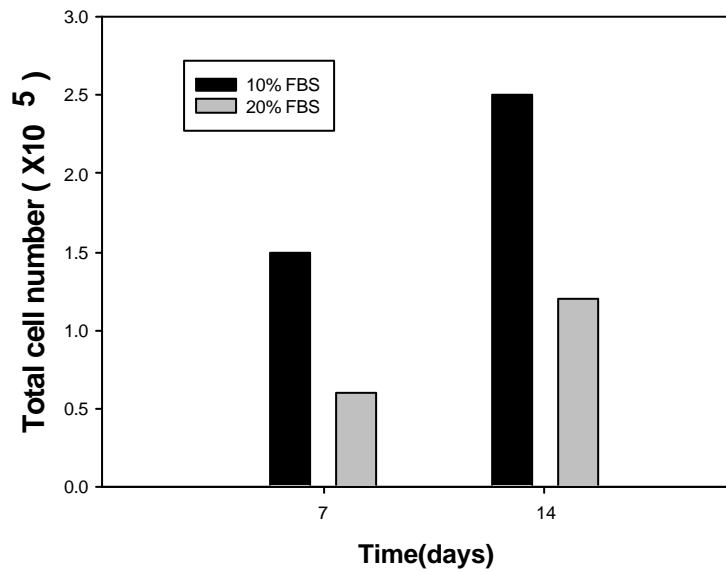


Figure 2. Cell proliferation according to serum concentration.
(Total initial inoculated MNC count ; 1×10^7 cells)

2.

가 ,
FACScan . Figure 3
(anti-CD14, CD45),
(anti-CD3, CD4, CD19, CD25), (anti-CD34)
(anti-CD54) 가 .
가

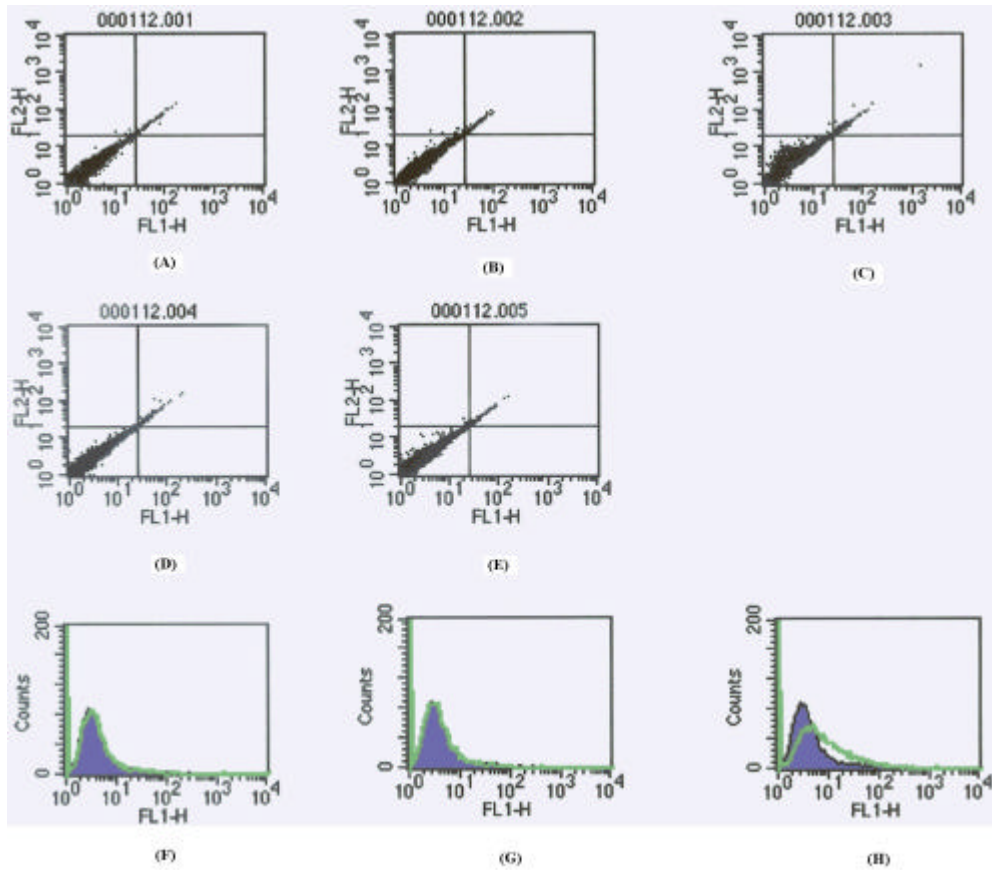


Figure 3. Immunocharacterization of cord blood-derived plastic-adherent cells.

Negative control, X (Axis): FITC, Y(Axis): PE, (B) X: CD45, Y: CD14, (C) X : CD3, Y: CD4, (D) X: CD3, Y : CD19, (E) X: CD3, Y : CD25, (F) CD11a, (G) CD34, (H) CD54

3. (osteoblast)

10^{-8} M

dexamethasone, 10^{-4} M ascorbate-2-phosphate, 100 ng/ml β -glycerophosphate

, Figure 4

alkaline phosphatase

, Von Kossa

Figure 5

(calcium deposits)

가 (bone)

1

Figure 6

alkaline

phosphatase

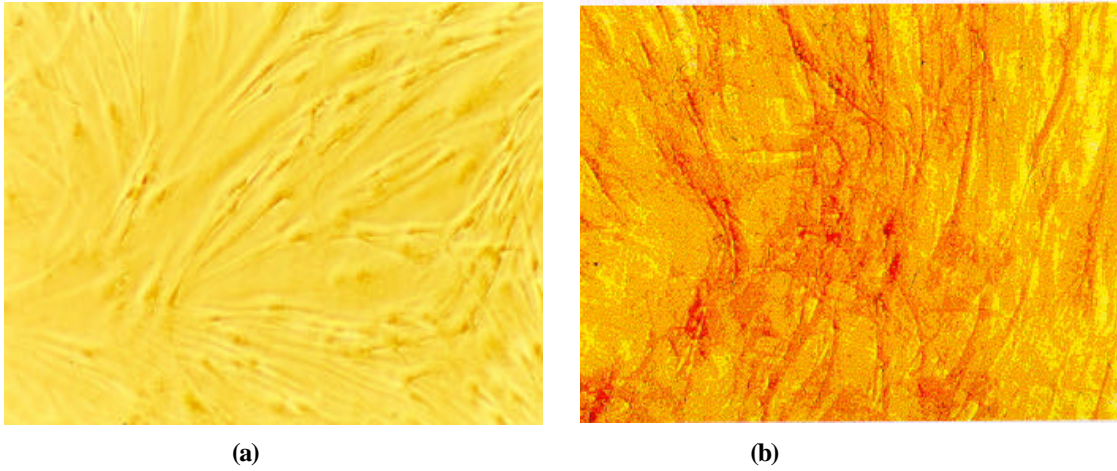


Figure 4. Alkaline phosphatase staining after osteogenic differentiation activity.

In comparison with negative controls(a), cells in the osteogenic differentiation group(b) show varying degrees of positive stain for alkaline phosphatase (X 100).

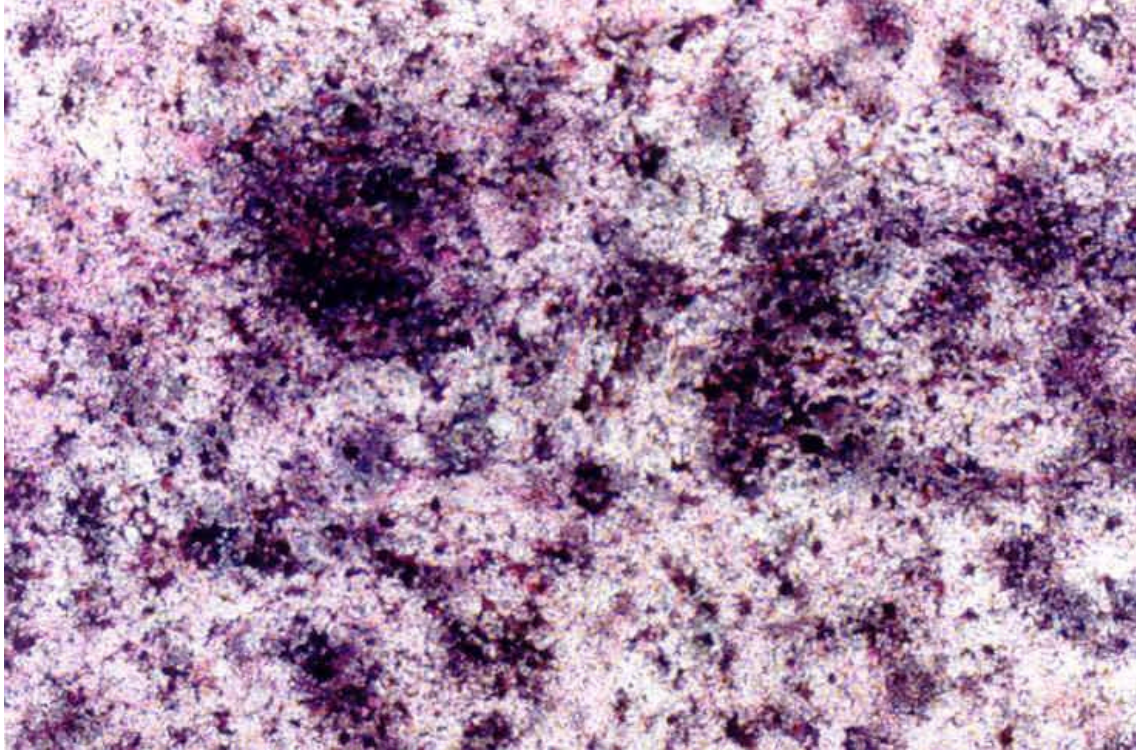


Figure 5. Von Kossa staining after osteogenic differentiation activity.

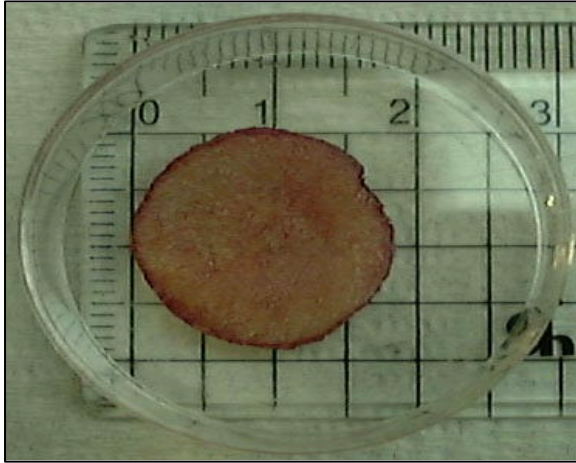


Figure 6. Alkaline phosphatase staining after osteogenic differentiation

activity by inoculating plastic-adherent cells into collagen scaffold.

IV.

가 ,

1988 Fanconi's anemia

,

.

,

가 (immature) (antigen expression)

.

4/6

(units)

.

(bone marrow engraftment) ,

(total cell count)가

가

, 가 (ex vivo expansion)

23

가 .

가

가 .²⁴

(non-hematopoietic cell components)

(stromal cell)

(mesoderm)

(ectoderm)

(embryonic stem cell)

가

1974

Friedenstein

가

,³

.²⁵ 21

가

.²⁶

가

,^{22, 27, 28}

(source)

가

,²⁹⁻³²

.³³

(plastic adherent layer)

가

plastic adherent layer

lot

lot 가

batch

가

³⁴

가

, Phinney

10-20%

³⁵

(osteoclast)

25% ~

75%

³⁶

(Pre-term < 36 weeks)

pool

75%

가

1974 Friedenstein plastic

(fibroblastoid cells)

,¹⁴

0.001%

0.01%

MSC ³ (10 cells/cm²)
 가 0.01-0.001%
 가
 "circulating"
 가
 가
 criteria
 (phenotypic
 marker) single set
 Flow cytometry Side Population(SP)
 Transdifferentiation potential
³⁷ MSCs가 SH-2, SH-3, SH-4, STRO-1,³⁸ MAB
 1470 , SH series가
³⁹
 STRO-1 in
 vitro

가

가

Simmons ⁴⁰

STRO-1

가 가

가

가

CD34, CD90 (Thy-1)

⁴¹

Hematopoietic marker CD34, CD 45

. Negative marker Positive marker

11

Negative staining for CD marker CD3, CD4, CD8, CD 11c, CD33, CD36,

CD 38, CD 45, CD117, glycoporin-A HLA-II(DR) ⁴²

CD marker(CD 3, CD 4, CD 19, CD 25, CD 34, CD45)

(Figure

3). , , heterogeneous

. Friedenstein , ,

, alkaline phosphatase ,

Pittenger

¹¹

Osteogenesis

가

alkaline phosphatase ,
 , osteocalcin mRNA .
 , hydroxyapatite mineralized nodule
 , organic inorganic phosphate
 가 , Von Kossa 가 . Osteoblast
 terminal phenotype identification marker cbfa-1, alkaline
 phosphatase, bone sialoprotein, osteopontin, osteocalcin, collagen type I
 . alkaline phosphatase activity Von Kossa
 2가 (Figure 4 & 5).

1

Figure 6 alkaline

phosphatase

scaffold

(tissue engineered bone)

spinner flask dynamic

95% (4)

Osteoblast modulator 1.25-

Dihydroxyvit D3, Prostaglandin E2, GH, IL-6, Leptin, TGF- 3, BMP-4

⁴³ bone morphogenic protein (BMP)

G-CSF, GM-CSF, IL-6 , IL-1

, TGF- , TNF

dexamethasone, TGF- , BMP-2, BMP-4, BMP-

7 (GH)

가 .^{20,43} dexamethasone

-glycerophosphate 가 mineralized

bone matrix

가

,⁵²⁻⁵³

.⁴⁴⁻⁴⁶

Chen Jieli⁵¹ rat stroke

, Sanchez-

Ramos retinoic acid(RA) nerve growth factor(NGF)

neural marker .⁴⁵

가

.^{47,49,50}

가 , 가

가 가

,
 , 24,27,48 , 54
 .
 .
 , ,
 , pre-term &
 term , (scaffold)
 가
 . 가
 (environmental signals)
 (gene expression) (plasticity)⁵⁵
 가 .
 () 가 ,
 (surface antigen)
 (phenotypic marker) .

V.

Transdifferentiation (adult
mesenchymal stem cell)

가 ..

가 .

, .
,

(osteoblast)

. 가 .

plastic adherent layer ,

(fibroblastoid morphology) .

alkaline phosphatase, Von

Kossa .

CD 34

(transdifferentiation, differentiation plasticity)

가 ,

(tissue engineering)

(regenerative medicine)

.

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가 .
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-Abstract-

Osteogenic Differentiation Activity by Cells Isolated from Umbilical Cord Blood

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(Supervised by Associate Professor Ho Yeong Lim)

Purpose: Bone marrow mesenchymal stem cells(MSCs) have the capacity for renewal and the potential to differentiate into multiple lineages of mesenchymal tissues. In the laboratory, MSCs have tendency to adhere to plastic culture flask and are characterized by fibroblastic morphology. I have cultured cord blood cells under osteogenic conditions with the aim of investigating the “trans-differentiation” potential like bone marrow MSCs.

Materials & Methods: Mononuclear cells and CD34+ cells were cultured in serum containing medium and osteogenic supplements. Media was changed at 24 hrs and then weekly with a 50% exchange. Cells were incubated at 37⁰ C in 5% CO₂ for at least 6 weeks. After 1 week, colonies of adherent fibroblastoid cells were apparent in the plastic flasks. Once 50-60% confluent, cells were passaged by trypsinization and replated in the culture media.

Results: Those plastic-adherent cells were strongly positive for alkaline phosphatase activity. Also, calcium(mineral) deposits were detected by Von Kossa staining. No cells with osteoblastic characteristics were detected when CD 34+ cord blood cells were plated in the same conditions.

Conclusion: These findings indicate the presence of osteogenic precursor cells in human umbilical cord blood which are much more potent in their differentiation plasticity as the so called MSCs observed in human bone marrow. These cord blood-derived MSCs appear to be candidates for the development of regenerative therapeutics.

Key Words: Umbilical Cord Blood, Mesenchymal Stem Cell, Osteoblast,
Transdifferentiation, Plasticity, Regenerative Therapeutics