Role of Mitochondria in Regenerative Medicine: Mitochondrial Biogenesis during Osteogenic Differentiation of Human Mesenchymal Stem Cells

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Taipei, Taiwan 112

CryoBanking and BioUtilization of Living Cells
Tainan, 12 March 2008
Stem cell research, a field with burning fire!

No federal funding for embryonic stem cell research except for the ES cell lines that are already in existence (August 10, 2001).


In 1995, Chris Reeve was paralyzed during an equestrian tournament and since then has been confined to a wheelchair for the remainder of his life.
Embryonic stem cells and somatic stem cells

Box 1 | **Adult stem-cell plasticity***

Adult stem cells are thought to be multipotent, but not pluripotent like embryonic stem cells (ESCs). However, in the past few years, more than 300 reports have indicated that adult stem cells might possess developmental capabilities that resemble those of more immature, pluripotent cells, similar to ESCs.

The main criticism regarding the claims of adult stem-cell plasticity is that most studies that describe such plasticity do not fulfill the criteria commonly used to describe stem cells: For instance, most studies published so far have not definitively proved that the greater potency of adult stem cells can be ascribed to a single cell that can differentiate into the tissue of origin and one or more additional tissues. Furthermore, most studies have equated differentiation with the acquisition of morphological and phenotypic characteristics of a novel cell type, but have not proven the functionality of the resulting cells. Similarly, few, if any, studies have shown that the adult stem cell can robustly repopulate not only the tissue from which it originates but also another tissue.
There are four plausible explanations for the observed plasticity of adult stem cells:

- The apparent differentiation of an adult stem cell to a cell lineage other than the tissue of origin could be due to contamination of the population by a stem cell or progenitor cell from the second tissue of origin.

- Fusion between donor and recipient cells, as occurs in heterokaryons, with silencing of the genetic programme of one of the two cells. There is evidence that fusion can occur in vitro and in vivo.

- Stem cells might dedifferentiate and then redifferentiate, or might be reprogrammed, in a manner similar to that found in other species (that is, blastema formation in amphibians), during metaplasia, or as occurs in somatic cell nuclear transplantation.

- Pluripotent stem cells generated before or after gastrulation might persist during development into adulthood.
<table>
<thead>
<tr>
<th>Tissue</th>
<th>Stem cell</th>
<th>Niche</th>
<th>Progeny</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Haematopoietic stem cell</td>
<td>Endosteal surface of bone marrow</td>
<td>All myeloid and lymphoid blood lineages</td>
<td>7–10,16–18,34–63, 86,90,91,99,100</td>
</tr>
<tr>
<td>Mesenchyme</td>
<td>Mesenchymal stem cell</td>
<td>Within bone marrow cavity</td>
<td>Bone, cartilage, tendon, smooth muscle, adipose tissue and stroma</td>
<td>116</td>
</tr>
<tr>
<td>Brain</td>
<td>Neural stem cell/ neurosphere</td>
<td>Subventricular zone and hippocampus</td>
<td>Neurons, glial cells and oligodendrocytes</td>
<td>8–10,57,64–70,88</td>
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<td>Gut</td>
<td>Crypt cell/gut epithelial progenitor</td>
<td>Gut crypt</td>
<td>Enterocytes, enteroendocrine cells, goblet cells and Paneth cells</td>
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<tr>
<td>Heart</td>
<td>Cardiac progenitor</td>
<td>Not determined</td>
<td>Cardiac myocytes</td>
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<td>Liver</td>
<td>Oval cell</td>
<td>Terminal biliary ductule</td>
<td>Hepatocytes and cholangiocytes</td>
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<tr>
<td>Pancreas</td>
<td>Pancreas-derived multipotent precursors</td>
<td>Not determined</td>
<td>Pancreatic endocrine and acinar cells</td>
<td>121,122</td>
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<tr>
<td>Skeletal muscle</td>
<td>Satellite cell</td>
<td>Between sarcolemma and basil lamina</td>
<td>Myocytes/myofibrils</td>
<td>123</td>
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<tr>
<td>Skin/hair</td>
<td>Bulge cell</td>
<td>Bulge in hair follicle</td>
<td>Epidermis, hair follicles and sebaceous glands</td>
<td>71–73</td>
</tr>
<tr>
<td>Male germ cells</td>
<td>$A_s$ spermatogonia</td>
<td>Basement membrane of seminiferous tubule</td>
<td>Sperm</td>
<td>124</td>
</tr>
</tbody>
</table>
The haematopoietic stem cells

**Genes/pathways associated with self-renewal**
- Self-renewal and multi-lineage differentiation potential
- Promiscuous gene expression of multiple lineage-specific transcripts

**Stem cell**
- HSC

**Progenitor cells**
- CLP
- CMP
- GMP
- MEP

**Mature cells**
- B cell
- T cell
- NK cell
- Erythrocyte
- Megakaryocyte
- Granulocyte
- Monocyte

**Genes/pathways associated with haematopoietic cell function**
- Globin genes
- Mpo
- Gata1
- Epor
- Mpl
Self-renewal of stem cells

- Microenvironment signal (niche)
- Asymmetrical division
- Stemness genes
- Telomerase
- Epigenetic control

The number and function of mitochondria are varied greatly in different tissue cells.

How is the variation of mitochondria regulated during cell differentiation?
Important features of mitochondria

- Each cell contains few hundreds to thousands of mitochondria
- Every mitochondrion has 2-10 copies of mitochondrial DNA
- Major site for the production of ATP in mammalian cells
- Major intracellular source of free radicals and reactive oxygen species (ROS)
- Ca\(^{2+}\) reservoir
- Act as the initiator, arbitrator and executioner of apoptosis
- Most proteins are synthesized in cytoplasm and translocated to mitochondria post-translationally
Overview of mitochondria

Cell
- 100 to 1000 mitochondria

Mitochondrion
- 2-10 copies of mtDNA
- Electron transport chain

Mitochondrial DNA
Mitochondria play a central role in energy metabolism of human cells
Multiple differentiation ability of mesenchymal stem cells

- MSC proliferation
  - Proliferation
    - Osteogenesis
    - Chondrogenesis
    - Myogenesis
    - Marrow stroma
    - Tendogenesis/ligamentogenesis
    - Other
  - Commitment
    - Transitory osteoblast
    - Transitory chondrocyte
    - Myoblast
    - Transitory stromal cell
    - Transitory fibroblast
  - Lineage progression
    - Osteoblast
    - Chondrocyte
    - Myoblast fusion
    - Unique micro-niche
    - T/L fibroblast
  - Differentiation
    - Bone
    - Cartilage
    - Muscle
    - Marrow
    - Tendon/ligament
  - Maturation
    - Osteocyte
    - Hypertrophic chondrocyte
    - Myotube
    - Stromal cell
    - Adipocytes, dermal and other cells
    - Connective tissue
Differentiation-Related Changes in Mitochondrial Properties as Indicators of Stem Cell Competence

THOMAS LONERGAN,* CAROL BRENNER, AND BARRY BAVISTER

Department of Biological Sciences, University of New Orleans,
New Orleans, Louisiana

Several methods may be used to assess stem cell competence, including the expression of cell surface markers and telomerase activity. We hypothesized that mitochondrial characteristics might be an additional and reliable way to verify stem cell competence. In a multipotent, adult monkey stromal stem cell line, previously shown to differentiate into adipocytes, chondrocytes, and osteocytes, we found that several mitochondrial properties change with increasing passage number in culture. Cells from the earliest passage (P11) versus those from a later passage (P17) are characterized by: (a) a much higher percentage of cells (85% vs. 18%) with a perinuclear arrangement of mitochondria; (b) a much lower percentage of cells (1% vs. 57%) with an aggregated mitochondrial arrangement, in which mitochondria appear to coalesce into large clumps; (c) a much lower percentage of cells with lipid droplets (1% vs. 36%), suggesting less differentiation into adipocytes; (d) a 5.6-fold lower ATP content per cell (0.45 vs. 2.51 pmoles ATP/cell); and (e) a 10-fold higher rate of oxygen consumption (37.8 vs. 3.8 nmoles O₂/min/10³ cells), indicating a higher metabolic activity. Collectively, these data indicate that the perinuclear arrangement of mitochondria, accompanied by a low ATP/cell content and a high rate of oxygen consumption, may be valid indicators of stem cell differentiation competence, while departures from this profile indicate that cells are differentiating or perhaps becoming senescent. These results represent the first characterization of mitochondrial properties reported for a primate stem cell line. J. Cell. Physiol. 208: 149–153, 2006.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Passage 11</th>
<th>Passage 14</th>
<th>Passage 17</th>
<th>Fibroblast control</th>
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<tr>
<td>Generation time, h</td>
<td>45.1</td>
<td>73.7</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>k (% change in population density/h)</td>
<td>1.5</td>
<td>1.1</td>
<td>(-) 1.7</td>
<td>N/A</td>
</tr>
<tr>
<td>% Adipose cells(^{a})</td>
<td>1.2(^{b})</td>
<td>11.6(^{c})</td>
<td>36.4</td>
<td>N/A</td>
</tr>
<tr>
<td>% Perinuclear</td>
<td>85(^{d})</td>
<td>46(^{e})</td>
<td>18</td>
<td>95</td>
</tr>
<tr>
<td>% Homogeneous</td>
<td>14</td>
<td>34</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>% Aggregated</td>
<td>2</td>
<td>20</td>
<td>57</td>
<td>0</td>
</tr>
<tr>
<td>pmoles ATP/cell(^{f})</td>
<td>0.45 ± 0.12(SEM)(^{g})</td>
<td>6.96 ± 2.14(SEM)(^{h})</td>
<td>2.51 ± 0.94(SEM)(^{i})</td>
<td>1.15 ± 0.29(SEM)(^{j})</td>
</tr>
<tr>
<td>nmoles O(_2) consumed/min/10(^3) cells(^{j})</td>
<td>37.8 ± 2.5(SEM)(^{k})</td>
<td>4.4 ± 0.4(SEM)(^{l})</td>
<td>3.7 ± 0.3 (SEM)(^{m})</td>
<td>33.8 ± 0.3 (SEM)(^{n})</td>
</tr>
</tbody>
</table>

\(^{a}\)The percentages of the cell populations scored as differentiated into adipocytes are based on a minimum of 250 cells at each passage.

\(^{b}\)P11 versus P14 P < 0.001.

\(^{c}\)P14 versus P17 P < 0.001.

\(^{d}\)P11 versus P14 P < 0.01.

\(^{e}\)P14 versus P17 P < 0.01.

\(^{f}\)Measurements repeated with three to six cell pellets with a minimum of four replicates per pellet.

\(^{g}\)P11 versus P14 P < 0.001.

\(^{h}\)P14 versus P17 P < 0.01.

\(^{i}\)P11 versus fibroblasts nsd.

\(^{j}\)Measurements repeated with three to six cell pellets with a minimum of four replicates per pellet. Values are corrected for CN-insensitive oxygen consumption.

\(^{k}\)P11 versus P14 P < 0.001.

\(^{l}\)P14 versus P17 nsd.

\(^{m}\)P11 versus fibroblasts nsd.
Images of adult Rhesus stromal stem cells
Lack of comprehensive understanding of the roles of mitochondria in stem cells biology

Differentiation-Related Changes in Mitochondrial Properties as Indicators of Stem Cell Competence


Dynamic changes in mitochondrial biogenesis and antioxidant enzymes during the spontaneous differentiation of human embryonic stem cells

1. Negative immunoselection

2. Limiting dilution

Using mesenchymal stem cells as a model to study the inter-genomic communication during differentiation

Nucleus: Let’s go differentiating, buddy~~

Mitochondrion: Cool !! But what should I do?
Hypothesis

The energy metabolic signature of stem cells is different from that of their differentiated progenies
Osteogenic stimuli

Nucleus

Mitochondrion

- Osteogenic genes
  - ALP
  - osteocalcin
  - osteonectin
  - osteopontin

- Bioenergetic genes
  - PGC-1α
  - mtTFA
  - Pol γ
  - OXPHOS

- Antioxidative genes
  - SOD
  - CAT, GPx

- mtDNA
  - OXPHOS

- ROS
  - ATP

Stem cell differentiation

I
II
III
IV
V
Mesenchymal stem cells (MSC)

- Capable of self-renewal
- Capable of differentiating into mesodermal cells
- Firstly isolated from bone marrow
- Fibroblast-like, adherent to plastic surface
- Surface phenotype: CD29(+), CD 44(+), CD 73(+), CD 105(+), CD 166(+), CD34(-), CD133(-) and Lin(-)


◆ Immuno-negative selection
◆ Limiting dilution
Osteogenic differentiation procedure

Maintenance of stem cells (30%-70% confluence) → IMDM medium
- Fetal bovine serum 10%
- L-glutamine 2 mM
- EGF 10 ng/ml
- bFGF 10 ng/ml

Seeding (5x10^3/cm²) → 60-70% confluence

Induction medium → dexamethasone 0.1 μM
- β-glycerol phosphate 10 mM
- Ascorbic acid 0.2 mM

Osteogenic differentiation

Investigation of mitochondrial changes
Osteogenic differentiation of hMSCs

dexamethasone 0.1 μM
β-glycerol phosphate 10 mM
Ascorbic acid 0.2 mM
Dynamic changes of mtDNA copy number and mitochondrial mass during osteogenic differentiation

![Graph showing mitochondrial content (% vs. Induction time (day)) with markers for Mass and mtDNA with error bars.](image)
Enhancement of aerobic respiration during osteogenic differentiation of stem cells

<table>
<thead>
<tr>
<th>Complex</th>
<th>Protein</th>
<th>msc</th>
<th>ost2w</th>
<th>Fold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex I</td>
<td>Fe-S protein 3</td>
<td><img src="image" alt="Complex I msc" /></td>
<td><img src="image" alt="Complex I ost2w" /></td>
<td>1.26 ± 0.44</td>
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<tr>
<td>Complex II</td>
<td>SDH subunit A</td>
<td><img src="image" alt="Complex II msc" /></td>
<td><img src="image" alt="Complex II ost2w" /></td>
<td>1.53 ± 0.39</td>
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<tr>
<td>Complex III</td>
<td>Core I subunit</td>
<td><img src="image" alt="Complex III msc" /></td>
<td><img src="image" alt="Complex III ost2w" /></td>
<td>3.14 ± 1.15</td>
</tr>
<tr>
<td>Complex IV</td>
<td>COX I</td>
<td><img src="image" alt="Complex IV msc" /></td>
<td><img src="image" alt="Complex IV ost2w" /></td>
<td>3.54 ± 1.16</td>
</tr>
<tr>
<td>Complex V</td>
<td>β subunit</td>
<td><img src="image" alt="Complex V msc" /></td>
<td><img src="image" alt="Complex V ost2w" /></td>
<td>1.70 ± 0.11</td>
</tr>
</tbody>
</table>

Actin | ![Actin msc](image) | ![Actin ost2w](image) | 1.00 |

O2 consumption rate (fold)

- msc
- ost2w

p < 0.01
Upregulation of mitochondrial biogenesis-associated genes during osteogenic differentiation

mtTFA: Mitochondrial transcription factor A
Polγ: DNA polymerase gamma
PGC-1α: PPARγ coactivator-1α
Perinuclear distribution of mitochondria during early osteogenic induction

<table>
<thead>
<tr>
<th>Control</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 28</th>
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<tr>
<td>α-tubulin</td>
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<td><img src="image3.png" alt="Image" /></td>
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<td>MitoTracker Red</td>
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<td>Merge</td>
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<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
</tr>
</tbody>
</table>
Anaerobic glycolysis

Glucose $\rightarrow$ glucose-6-phosphate $\rightarrow$ fructose-6-phosphate $\rightarrow$ fructose-1,6-bisphosphate $\rightarrow$ dihydroxyacetone phosphate $\rightarrow$ glyceraldehyde-3-phosphate $\rightarrow$ 1,3-bisphosphoglycerate $\rightarrow$ 3-phosphoglycerate $\rightarrow$ 2-phosphoglycerate $\rightarrow$ phosphoenolpyruvate $\rightarrow$ pyruvate $\rightarrow$ TCA cycle $\rightarrow$ respiratory chain (Complex I ~ V)

Glut: glucose transporter
HK: hexokinase
GPI: glucophosphate isomerase
PFK: phosphofructokinase
ALD: aldolase
TPI: triose phosphate isomerase
GAPDH: glyceraldehyde-3-phosphate dehydrogenase
PGK: phosphoglycerate kinase
PGM: phosphoglycerate mutase
ENO: enolase
PK: pyruvate kinase
LDH: lactate dehydrogenase
PDH: pyruvate dehydrogenase
PDK: PDH kinase

PDH: pyruvate dehydrogenase
PDK: PDH kinase

Glut: glucose transporter
HK: hexokinase
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PGM: phosphoglycerate mutase
ENO: enolase
PK: pyruvate kinase
LDH: lactate dehydrogenase
PDH: pyruvate dehydrogenase
PDK: PDH kinase
Downregulation of anaerobic glycolysis during osteogenic differentiation of stem cells

<table>
<thead>
<tr>
<th></th>
<th>msc</th>
<th>ost2w</th>
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<tbody>
<tr>
<td>GPI</td>
<td></td>
<td></td>
<td>0.59 ± 0.13</td>
</tr>
<tr>
<td>PFK</td>
<td></td>
<td></td>
<td>0.63 ± 0.20</td>
</tr>
<tr>
<td>LDH</td>
<td></td>
<td></td>
<td>1.07 ± 0.21</td>
</tr>
<tr>
<td>PDH</td>
<td></td>
<td></td>
<td>2.19 ± 1.31</td>
</tr>
<tr>
<td>PDK</td>
<td></td>
<td></td>
<td>&lt; 0.10</td>
</tr>
<tr>
<td>Actin</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Lactate** (ng/10⁴ cells/hr)

- msc: 1000 ± 140
- ost2w: 250 ± 40

*p < 0.01

**ATP (pmol/cell)**

- 0 → 7 days: Significant increase
- 7 → 28 days: Steady increase

**Fold change in gene expression**

- **GPI**: 0.59 ± 0.13
- **PFK**: 0.63 ± 0.20
- **LDH**: 1.07 ± 0.21
- **PDH**: 2.19 ± 1.31
- **PDK**: < 0.10
- **Actin**: 1.00

**Graphs**

- Lactate levels over time
- ATP levels over time

**Legend**

- msc: Green bars
- ost2w: Red bars

**Significance**

- *: p < 0.05
- **: p < 0.01
- ***: p < 0.001
The majority of intracellular ROS is derived from the mitochondrial respiratory chain.
Overproduction of ROS and free radicals may cause indiscriminative and cumulative damage to cells.
**Significant decrease of intracellular ROS during osteogenic differentiation of stem cells**

- **H$_2$O$_2$**
- **O$_2$.**

DCF: 2',7'- dichlorodihydrofluorescein diacetate

HE: hydroethidine
Induction of catalase and MnSOD during osteogenic differentiation of stem cells

Relative densitometry

Induction day 0 2 4 7 14 21 28

Relative densitometry

Induction time (day)

0 2 4 7 14 21 28

- catalase
- MnSOD
- Cu/ZnSOD
Dramatic decrease of intracellular ROS during osteogenic differentiation of stem cells
Dramatic upregulation of antioxidant enzymes in differentiated osteoblasts

**Catalase activity**

- msc
- ost2w

**Total SOD activity**

- msc
- ost2w

*p < 0.01*
No significant changes in the expression of other antioxidant enzymes during differentiation

<table>
<thead>
<tr>
<th>Induction day</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>7</th>
<th>14</th>
<th>21</th>
<th>28</th>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPx-1</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>GAPDH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prx-I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TrxR-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Trx-I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAPDH</td>
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<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

GR: Glutathione reductase
GPx-1: Glutathione peroxidase-1
Prx-1: Peroxiredoxin-I
TrxR-1: Thioredoxin reductase-1
Trx-I: Thioredoxin-I
The other side of ROS – important signaling messengers


Differentiated osteoblasts are more resistant to exogenous ROS as compared with hMSCs.
Differentiated osteoblasts are more sensitive to respiratory inhibitors.
Increased antioxidant enzyme activities confer to higher resistance to ROS of differentiated osteoblasts.
Inhibitory effects of $\text{H}_2\text{O}_2$ and oligomycin on upregulation of the ALP activity during differentiation of hMSCs.

ALP activity (arbitrary unit)

H$_2$O$_2$ (μM)

0 125 250 500

Oligomycin (μg/ml)

0 0.63 1.25 2.5

oligomycin: specific inhibitor to respiratory enzyme Complex V
Inhibitory effects of H$_2$O$_2$ and oligomycin on upregulation of the mRNA level of 

$Cbfa-1$ during hMSCs differentiation
Increase of MnSOD and decrease of lactate production during differentiation of hMSCs from different donors

(A) Donor 1 2 3 4 5
   m os m os m os m os m os

MnSOD

actin

(B) The decrease in lactate production of differentiated osteoblasts is caused by a metabolic shift from glycolysis to aerobic metabolism.
Osteogenic induction

Nucleus

PGC-1α

Respiratory genes

Antioxidative genes

Osteogenic genes

Glycolytic genes

ROS

SOD CAT

mtTFA

mtDNA

Pol γ

ATP

Chen CT et al. (2008) Stem Cells, in press.
Glycolysis is modulated by a wide-spectrum of signals leading to aging and diseases.

A preference for glycolysis as energy sources in stem cells

Characterization of Mitochondrial and Extra-mitochondrial Oxygen Consuming Reactions in Hematopoietic Stem Cells


Dynamic changes in mitochondrial biogenesis and antioxidant enzymes during spontaneous differentiation of human embryonic stem cells


A High Glycolytic Flux Supports the Proliferative Potential of Murine Embryonic Stem Cells


Mitochondrial oxidative metabolism is required for the cardiac differentiation of stem cells

Regulation of glycolysis and aerobic metabolism of glucose in human cells

Glycolysis

2 ATP / glucose

OXPHOS

36 ATP / glucose

Stem cell ageing: does it happen and can we intervene?

Ilaria Bellantuono\textsuperscript{1,*} and W. Nicol Keith\textsuperscript{2}

Adult stem cells have become the focus of intense research in recent years as a result of their role in the maintenance and repair of tissues. They exert this function through their extensive expansion (self-renewal) and multipotent differentiation capacity. Understanding whether adult stem cells retain this capacity throughout the lifespan of the individual, or undergo a process of ageing resulting in a decreased stem cell pool, is an important area of investigation. Progress in this area has been hampered by lack of suitable models and of appropriate markers and assays to identify stem cells. However, recent data suggest that an understanding of the mechanisms governing stem cell ageing can give insight into the mechanism of tissue ageing and, most importantly, advance our ability to use stem cells in cell and gene therapy strategies.
Proposed self-renewal and differentiation capacity in aging adult stem cells

Proposed self-renewal and differentiation capacity in ageing adult stem cells

Expert Reviews in Molecular Medicine 2007
© 2007 Cambridge University Press
Model of stem cell proliferation and aging

Model of stem cell proliferation and ageing

Expert Reviews in Molecular Medicine © 2007 Cambridge University Press
Concluding remarks

• To understand the fundamental biology of stem cells

• To choose high-quality mesenchymal stem cells from a suitable donor

• To produce well differentiated cells in high quality and quantity from mesenchymal stem cells

• To establish a good differentiation protocol to prepare mature and well-differentiated cells for clinical applications

• To study the transplantation of stem cells in regenerative medicine

• To study aging or pathology of disease from the stem cell point of view
Thank you for your attention!!