Stem Cells and Sport Medicine

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Overview

- Stem cell biology
- Potential applications of stem cells in musculoskeletal medicine
- Current research
- Medico-legal aspects

Stem Cells: Definition & Features

- Unspecialized cells that self renew indefinitely
- Can differentiate into mature cells with specialized functions
  - Locations: early embryo, fetal tissues, umbilical cord, placenta, adult organs
- Plasticity: Ability to differentiate into cell types beyond those of tissues where they normally reside
- Multipotent: Gives rise to multiple tissue types associated with different organs

Criteria for Ideal Stem Cells

- Produced in quantities ($10^7$ - $10^9$)
- Harvested by minimally invasive procedures
- Differentiates in reproducible manner
- Safely & effectively transplanted to either an autologous or an allogenic host
- Manufactured with Good Manufacturing Practice guidelines
- FDA regulation through Center for Devices and Radiological Health or Center for Biologics Evaluation and Research
- TRACK CELL MUTATION

Stem Cell Lineage

Stem Cell Types

- Embryonic (hESCs)
  - Pluripotent
  - Potential for tumor development (teratomas)
  - Ethically controversial
- Induced Pluripotent Stem Cells (iPS)
  - Derived from adult skin cells
- Mesenchymal Stem Cells (MSCs)
  - Progenitors of mesodermal cell types
  - Immunosuppressive, immuno-privileged
  - No reported tumor formation
  - High migration and motility
Mesenchymal Stem Cells (MSCs)

- Ability to differentiate into various tissue types
  - Musculoskeletal, Cardiac, Neural tissues
- Isolated from bone marrow, adipose tissue, skeletal muscle, tendon, peripheral blood
- Differentiation is environment dependent
  - Cytokines, growth factors, local stem cells

Minimal Criteria (ISCT 2006)

- Adhere to plastic under standard culture conditions
- Positively express CD73, CD90, CD105
- Negatively express CD34, CD45, CD14, CD11b, CD79a, HLA-DR
- Multipotency to differentiate into osteoblasts, adipocytes, and chondrocytes

Harvest:
- BMDSCs
- ADSCs
- SMDSCs

MSCs: Comparison

<table>
<thead>
<tr>
<th>Source: Animal</th>
<th>Surface antigens</th>
<th>Migration capacity</th>
<th>Proliferation</th>
<th>Morphology</th>
<th>Apoptosis tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat skeletal muscle</td>
<td>CD106, MEST, higher expression</td>
<td>high in placentaMSCs, low in UCFMSCs</td>
<td>highest</td>
<td>normal</td>
<td>high</td>
</tr>
<tr>
<td>Rat adipose tissue</td>
<td>CD49b, CD54, CD34; KIF67, CDCA8, CCNB2, higher expression</td>
<td>high</td>
<td>high</td>
<td>larger</td>
<td>not high</td>
</tr>
<tr>
<td>Rat bone marrow</td>
<td>CTGF, BMP antagonist, high expression</td>
<td>high</td>
<td>high</td>
<td>normal</td>
<td>not high</td>
</tr>
</tbody>
</table>

Orthopedic Applications

- Cartilage
- Ligament
- Tendon
- Muscle
- Peripheral Nerve
- Bone
- Limited regenerative capabilities
Musculoskeletal conditions are the most common causes of severe long-term pain and physical disability in the world.

- Prevalence increasing with increasing elderly populations.
- Musculoskeletal conditions are a leading cause of disability in the USA.
  - More than 130 million patient visits annually.
  - No. 1 reason people visit their physician.
  - Affects nearly ½ Americans over the age of 18.

**Cartilage Pathology**

- Traumatic cartilage defect
- Osteoarthritis
- Osteochondritis dissecans
- Osteonecrosis
- Polyarthritis

**In a Perfect Stem Cell World…**

**Stem Cells: Mechanisms**

- Direct:
  - Differentiation to specific tissues
- Indirect:
  - Promote vascularization, cell proliferation, tissue differentiation,
  - Modulate inflammatory process
  - ? Scaffold

**Challenges**

- Articular cartilage is avascular and aneural.
- Relies on diffusion of nutrients from adjacent bony tissues.
- Acidic environment, electrically negative polar environment, hypoxic environment, low glucose environment, catabolic environment (IL-1, TNF-α).
- Already harsh environment worsens with matrix degradation.

**Methods of Administration**

- Intra-operative versus non-operative
- Cultured versus non-cultured
- With or without PRP
- With or without a collagen scaffold
Why Does It Work?

- Improved Cell Migration
- Facilitates Inherent Cell Contraction
- Facilitates Cell → Tissue Organization

ADSCs and Knee OA

- Koh et al.; Knee 2012 – Case control study
- Study group: 25 patients with knee OA (8 men, 17 women), mean age 54 yrs.
  - ADSCs harvested from infrapatellar fat pad
  - Arthroscopic debridement, no microfracture done
  - 3 treatments: ADSCs + PRP intra-op, 3 cc PRP one and 2 weeks post op
- Matched control group: Debridement with PRP only
- Study group had worse ICRS and Kellgren-Lawrence grades than control group
- Clinical outcomes: VAS, Tegner scores, Lysholm scores
  - Measured at initial post-op, 3 months post-op, 12-18 months post-op

Findings

- No major complications in either group
- Pre-op Lysholm, Tegner and VAS significantly worse in study group versus control group (p=0.01)
- Both groups showed improvement (p<0.001)
- No difference in scores at final follow-up between groups (p=0.338)
- Degree of improvement from baseline better in study group than control

BMDSCs and Cartilage injury

- Kuroda et al.; Osteoarthritis and Cartilage 2007
- 31 yr old judo athlete injured right knee 1999 resulting in medial meniscectomy
- Reinjury in May 2004
- MRI– medial femoral condyle (MFC) defect with bone edema
- Initial arthroscopic findings– 20x30mm defect MFC, with medial meniscus tear– partial meniscectomy performed
- Harvested BMDSCs from iliac crest and cultured
- Reimplantation into defect 5 months later

Kuroda et al; Osteoarthritis and Cartilage 2007
Recent Legislature

- Celltex Therapeutics
  - Stem cell bank for ADSCs
  - Technology licensed through RNL Bio in Seoul for 800 million cells
  - Glenn McGee - Bioethics specialist recently resigned

- Not covered by insurance: out of pocket cost $7000/200 million cells

- Charging patients while conducting investigational studies
  - Unclear if studies were FDA approved
  - Nature; February 29, 2012

Texas Stem Cell Rules

- Doctors allowed to perform stem cell procedures as long as they are done for research and receive approval from a local institutional review board, which can be private and profit-making.

- Patients sign informed consent forms.

- Possible conflict with FDA regulations
  - Nature; February 29, 2012

Conclusions

- Promising treatment

- Work through cell differentiation and affecting cell environment

- Adult stem cells seem to be safe

- Randomized control studies need to be done