Neural Stem Cells for treatment of demyelinating diseases: Fantasy or Real Prospect

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What do we mean when we say stem cells

- Hematopoietic stem cell transplant: Myeloablative bone marrow replacement by autologous hematopoietic stem cells---For autoimmune diseases, the idea is to “reset” the immune system

- Mesenchymal stem cells: isolated from bone marrow or other sources. MSCs may exert immunomodulatory effects

- Neural stem cells: Cell replacement vs. Chaperone effect, endogenous vs. exogenous cells, immortalized vs. growth factor modified NSCs, survival of NSCs in a disease environment
Bone Marrow MSCs
• Represent ~ 0.001% to 0.01% of nucleated bone marrow cells
• Isolated by plastic adherence and culture
• Characteristic fibroblast-like morphology with spindle shapes
• Differentiate into mesenchymal cells:
  – chondrocytes
  – adipocytes
  – osteoblasts

Other MSC sources
• Umbilical cord blood
• Adipose tissue
• Muscle connective tissue
• Amniotic fluid and placenta
• Fetal tissues (bone marrow, lung, liver, spleen)
Reported Properties of MSCs

- Tissue cell replacement
- Immunosuppression
- Enhancement of hematopoietic engraftment
Natural Killer cells
- Inhibition of proliferation
- Partial inhibition of cytolysis
- Induction of cytokine secretion
- NK cells can lyse MSC

T cells
- Inhibition of proliferation
- Inhibition of cytokine production
- Impairment of their encephalitogenic potential
- Enhancement of MSC immunosuppressive activity by T cell-derived cytokines

Dendritic cells
- Inhibition of activation
- Inhibition of maturation

MSC

B cells
- Inhibition of proliferation
- Inhibition of differentiation to plasmacells
- Impairment of chemotaxis
- Activated B cells enhance the suppressive effect of MSC mediated by soluble factors
Potential Immune Indications

• Autoimmunity: Arthritis; M.S.; Diabetes
  Auto-HSCT + MSCs

• Organ allograft: With immune suppression
  Co-infusion with allo-HSCT for increasing mixed chimerism

• Blood and marrow transplantation:
  Non-ablative transplantation in older patients
  Single or double cord blood transplants in adults
Endogenous Neural Stem Cells

The adult mammalian CNS contains a population of immature, undifferentiated, multipotent cells, neural stem cells (NSCs), that may be called upon for repair in neurodegenerative and demyelinating diseases.

Remyelination and neuro-regeneration do not occur to a sufficient extent in MS or Experimental autoimmune encephalomyelitis (EAE; animal model of brain encephalitis; demyelinating disease).
Clinical Observations

- Most currently approved therapies suppress inflammation as evidenced by suppression of Gadolinium + lesions on MRI
- During the secondary progressive phase of MS there is less inflammation, but progression continues
- In spite of treatments that suppress inflammation, we continue to see progression of disability
Hypotheses to explain the lack of remyelination in MS

1) Failure of migration of OligoPCs to the lesions [Blakemore, 1999; Chari, 2002]

2) Differentiation arrest of OPCs [Chang, 2002; John, 2002]

3) Lack of trophic factors from destroyed axons [Chang, 2002; Viehover, 2001]

4) Non-permissive environment from reactive astrocytes [Hirsch, 1999]
We hypothesize that factors in the inflammatory microenvironment modulate the cardinal properties (self-renewing capacity and multipotentiality) of NSCs in vivo throughout the neuroaxis.
1st remission
Control
Relapse
Acute

Labeling index for Sox-2
(No washout)

Sox-2^BrdU^ (% of total Sox-2^ cells)

Control
Acute
1st remission
Late relapse
Late remission

Rasmussen et al. Brain 2007
What about stem cell transplantation?
Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis
Pluchino et al. Nature 2003
Timing of transplantation

Acute phase:
- Hemorrhage
- Destruction of BBB
- Infiltration of inflammatory cells
- Pro-inflammatory cytokine
- Free radical, NO
- Excitatory amino acid
- CNTF

Subacute~chronic phase:
- Anti-inflammatory cytokine
- Cystic cavity
- Glial scar formation

Optimal time for transplantation?

Inflammatory reaction

Glial scar formation

0 1 4 7 14 (post-injury day)
**CELL TRANSPLANTATION**

**Isolated glial progenitors**

**Infant/child**

**Hereditary Leukodystrophies**
- Congenital dysmyelination
  - Pelizaeus-Merzbacher Disease
- Lysosomal storage diseases
  - Tay-Sachs and Sandhoff’s gangliosidoses
  - Krabbe’s Disease
  - Metachromatic leukodystrophy
  - Mucopolysaccharidoses
  - Niemann-Pick A
- Non-lysosomal diseases
  - Adrenoleukodystrophy
  - Canavan’s disease
  - Vanishing White Matter Disease
  - Alexander Disease
- Cerebral Palsy
  - Periventricular leukomalacia
  - Spastic diplegias of prematurity

**Adult**

**Autoimmune Demyelination**
- Multiple Sclerosis
- Neuromyelitis optica
- Transverse myelitis
- Optic neuritis

**Vascular Leukoencephalopathies**
- Subcortical Stroke
- Diabetic leukoencephalopathy
- Hypertensive leukoencephalopathy
- Age-related white matter disease
- Spinal cord injury

**Inflammatory Demyelination**
- Radiation injury
Patients with neurodegenerative disorders

Reprogramming Oct4, Sox2, Klf4, c-Myc, etc.

Somatic cells → iPSCs

Differentiation

iPSCs derived neuronal cells

- Cell biological analysis of pathogenesis
- Drug discovery
- Diagnostic method
- Regenerative medicine
Risks

- Fetal calf serum response
- Non-specific immune suppression
- Cytokine and chemokine release from MSCs
- Cytogenetic instability of infused product
- Ectopic MSC differentiation (e.g., bone)
- Support of tumor growth*

*Demonstrated for human MSCs and B cell malignancies in vitro; demonstrated for murine MSCs and fibrosarcoma in vivo
General trial design issues/challenges

- Tissue source of MSCs (bone marrow; cord blood; other)
- Maximum passage number
- Donor source and matching requirements if any
- MSC treatment in vitro (eg. IFN\(\gamma\))
- MSC cell infusion number, frequency, duration
- Concurrent immune suppression
- Documentation of MSC engraftment
- Documentation of MSC specific suppression
- Homing of MSCs to appropriate environment
International experts in multiple sclerosis and stem cells, together with immunologists formed the “International Stem Cells Transplantation Study Group” (IMSCTSG) in order to achieve a consensus protocol on the use of MSCs for the treatment of multiple sclerosis, with protocols for cell cultivation and patient treatment.

Freedman et al. Mult Scler. 2010; 16(4): 503-10
• A systematic review and meta-analysis of the prospective clinical trials that used intravascular delivery of MSCs (intravenously or intra-arterially) in adult populations or mixed adult and pediatric populations (SafeCell) included 36 studies with a total of 1012 participants with clinical conditions of ischemic stroke, Crohn’s disease, cardiomyopathy, myocardial infarction, graft versus host disease, and healthy volunteers.

• The meta-analysis of the randomized clinical trials did not detect an association between acute infusion toxicity, organ system complications, infection, death or malignancy.

• There was a significant association between MSCs and transient fever.

• However, the results from the experimental studies raised some concerns regarding the tumorigenic potential.
• All trials reported safety and tolerability of MSCs and stabilization/mild improvement of the disease.
• There are still issues to be clarified about the migration potential and homing into the central nervous system of MSCs and also about the possibility of tracking the distribution of MSCs in humans.
• The small number of patients included in these trials and the differences between the trial designs consist of limitations in the interpretation of data and justify the necessity for further randomized multicenter controlled trials.

Harris VK et al. abstract ACTRIMS. 2014.
Standard of care or clinical trial?

Not a standard of care (no clinical evidence so far)

Only clinical trials can be realized
  • IRB approved research proposal
  • Informed consent for participation in clinical research
  • Patients should not pay