Stem Cells & Neurological Disorders

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Outline:

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Introduction
Benefits of stem cell research:

- **Treatment of complex diseases:**
  
  Chronic Disorders: Diabetes
  
  Neurological Disorders:
  
  *we focus on neurological disorders because neurons are not able to regenerate itself like other body parts*
  
  Alzheimer’s Parkinson’s Spinal Cord Injuries
  
  Heart disorders: MI

- **Regenerative medicine** (Spare parts!)
  
  Skin Cartilage
  Bone Cornea
  Heart Valves

*Stem cell will finish transplantation and immune rejection problem because we use the cells from the patient himself*

No one in the world could make full thickness functional skin

**Stem Cells and Neurological Disorders**
Definition:

- stem cells:
  - (i) renew itself indefinitely
  - (ii) differentiate to multiple tissue types

A stem cell is not committed to a specific function until it receives a signal to differentiate into a specialized cell.
Types & Potency
1. **Embryonic:**
   - Blastomere (4-5 day embryo)
   - Pluripotent

2. **Adult:**
   - Adult tissue
     - multi or uni potent

**Other:**

- **Fetal:**
  - Aborted embryos
  - Pluripotent

- **Umbilical:**
  - Umbilical cord blood
  - Multipotent

**Stem Cells and Neurological Disorders**

- The best time to take a stem cell from embryo
- From adult tissue not adult human
- In the last months of pregnancy when the embryo is fully developed the stem cell is considered adult

- If the abortion happened in the last trimester it is considered adult and it is not a good source for stem cell
- It is a good source and its considered adult but more potent than adult stem cells
Potency:

1. **Totipotent (Fertilized egg)** is the zygote
   - Generate: all embryonic cells and tissues
   - Generate: supporting tissue like placenta and umbilical cord

2. **Pluripotent**
   - Give rise to cells of all 3 germ layers (ecto-, meso-, and endoderm
   - Come from embryos and fetal tissue
   - Have active telomerase (maintain long telomers)

3. **Multipotent** hematopoietic stem cells
   - Give rise to multiple different cell types

4. **Unipotent** melanocyte stem cells
   - Cell differentiating along only one lineage

*the difference between the totipotent and pluripotent is that totipotent can make the supporting tissue (the placenta)*
Stem Cells and Neurological Disorders

Human Developmental Continuum

- Single-cell Embryo
- 3-day Embryo
- 5-7 day Embryo
- 4-week Embryo
- 6-week Embryo

Embryonic Stem (ES) cells
- Totipotent

Embryonic Germ (EG) cells
- (primordial germ cells)

Fetal Tissue Stem cells
- Pluripotent or Multipotent

"Adult" Stem cells
- Pluripotent or Multipotent

Cord Blood Stem cells
- Pluripotent or Multipotent

Placental Stem cells
- Pluripotent or Multipotent

- Infant
- Adult

Teratocarcinoma (germ cell tumor)

Embryonal Carcinoma (EC) cells
- Pluripotent
Stem Cells and Neurological Disorders

Hierarchy of Stem Cells

- Totipotent
  - Pluripotent
    - Blood Stem Cells
    - Other Stem Cells
      - Muscle
      - Nerve
      - Bone
      - Other Tissues

- Red Blood Cells
- White Blood Cells
Embryonic Stem Cell
The Embryonic Stem Cell

Source:

1. IVF embryos are the best source because we have a lot of spare embryos. The problem of IVF embryos is the immune rejection.

2. Aborted Fetus

3. Therapeutic cloning is to recreate the patient himself and stop the embryo at 4-5 days like Dolly the sheep.
Thousands of frozen embryos are routinely destroyed when couples finish their treatment.
Somatic Cell Nuclear Transfer

The nucleus of a donated egg is removed and replaced with the nucleus of a mature, "somatic cell" (a skin cell, for example).
Embryonic Stem Cell

- First isolated and cultured in 1998
- From inner cell mass of blastocyst (4-5 day embryo).
- Pluripotent with long-term self-renewal
- Capable of unlimited number of divisions without differentiation
- Can essentially live forever without forming tumors
- Maintain normal diploid complement of chromosomes (stable karyotype)
- Telomerase activity
- Clonogenic: give rise to genetically identical group of cells
- Expresses transcription factor Oct-4 (+ or – genes needed for proliferative state)
  
  *Oct 4 is a master transcription factor*

- Spend most of their time in S phase
  - *In-Vitro: 300 population doublings*
Human **Blastocyst** showing Inner Cell Mass

**Blastocyst**
- Outer cells - go on to form placenta
- Fluid
- Inner cell mass or inner cluster of cells - go on to become embryo then fetus
GROWING HESC IN VITRO:

Feeder cells is a mouse cells
**Advantages:**

- **Immortal:** supply endless amount of cells
- **Flexible:** can make any body cell
- **Available:** IVF clinics

**Disadvantages:**

- Hard to control their differentiation
- Ethics
- Immune rejection

Hard to control their differentiation like if we want to make a B cell from hematopoietic cell it is easy to reach B cell but if we have a embryonic cell the way is too long and its hard to control the process
Avoiding Immune rejection:

1. Genetically engineering stem cell to:
   a. Express MHC antigens of recipient
   b. produces stem cells with deleted MHC genes

2. Therapeutic Cloning:
   Clone somatic Cell nucleus of recipient into egg
devlop into blastocyst and isolate ES cells
   Such ES cells have recipient immunological profile

3. Co-transplantation with Hematopoietic Stem cells
Avoiding Immune rejection

Figure 3.3. Genetic Manipulation of Human Embryonic Stem Cells. (Reproduced with permission from Stem Cells, 2001)
Avoiding immune rejection

- **Nuclear reprogramming like in cloning the same mechanism so the body won’t reject it**

- **Genetic manipulation of MHC genes**

  *it is very hard to knock out MHC or to knock in MHC from the patient, the easy way is to make universal embryonic stem cell, we choose a baby with a low MHC molecules on the surface of his cells and knock them out so the cell now doesn’t have any MHC on the surface (universal) and we can use it with any patient without rejection*
Laboratory tests to identify ESC: to make sure that the stem cell is a stem cell and didn’t differentiate

1. **Immortality**: Sub-culturing stem cells for many months (long-term self-renewal) (*if it stayed alive for alooooong time → stem*)

2. **Morphology**: Inspecting culture by microscope (for undifferentiation)

3. **Surface markers & Stemness genes**: (e.g. Oct-4) (*if there is oct 4 → stem*)

4. **Karyotype stability**: Examining the state of chromosomes (*if their is no mutation and chromosomes number is stable → stem*)

5. **Telomerase Activity**: (*if their is a telomerase → stem*)

6. **Pluripotency**: testing differentiation potential into diff. cells types
Ethics and ESCs:

When is it OK....when is it NOT
Group of cells or Human life
Stem Cells and Neurological Disorders

I DIED WAITING FOR EMBRYONIC STEM CELL RESEARCH TO FIND A CURE. WHAT ABOUT YOU?

I WAS THE EMBRYO.
The Adult Stem Cell

- Undifferentiated cell found in a specialized tissue in adult.
- Capable of self-renewal
- Become specialized to cell types of the tissue from which it originated.

Properties:
- Somatic
- Long-term self-renewal
- Give rise to mature cell types
- Generate intermediate cell (progenitors) “committed”
- Can migrate whenever needed
- Uni- or Multipotent
Figure 4.1: Distinguishing Features of Progenitor/Precursor Cells and Stem Cells. A stem cell is an unspecialized cell that is capable of replicating or self-renewing itself and developing into specialized cells of a variety of cell types. The product of a stem cell undergoing division is at least one additional stem cell that has the same capabilities as the originating cell. Shown here is an example of a hematopoietic stem cell producing a second generation stem cell and a neuron. A progenitor cell (also known as a precursor cell) is unspecialized or has partial characteristics of a specialized cell that is capable of undergoing cell division and yielding two specialized cells. Shown here is an example of a myeloid progenitor/precursor undergoing cell division to yield two specialized cells (a neutrophil and a red blood cell).
Sources of adult stem cells:

- Bone marrow
- Blood stream
- Umbilical cord blood
- Dental pulp of the tooth *very good source*
- Cornea and retina
- Skeletal muscle
- Liver
- Skin (epithelia)
- Gastrointestinal tract
- Pancreas
- Brain & spinal cord

*All in red are easy to get*
Bone marrow
umbilical cord blood

Stem Cells and Neurological Disorders
Dental Pulp

Stem cells are in areas next to nerve and blood vessels within the pulp of the tooth. Companies that bank stem cells say cells that can be regenerated from dental stem cells will someday include:

- Nerve and spinal cord
- Brain
- Heart
- Liver
- Bone
- Ligaments and cartilage
- Muscle
- Skin
Could a baby tooth one day save your child’s life?
Adult stem cell plasticity

- **Plasticity**: stem cell from one adult tissue can generate the differentiated cell types of another tissue: “unorthodox differentiation” or “transdifferentiation”

- EX. Hematopoietic stem cell → Neurons

- Possible under specific conditions

Plasticity refers to the ability of cells to take on characteristics of cells elsewhere in the body. For example, bone marrow stem cells that are transplanted elsewhere can change into lung or liver cell.
Advantages:
1. No immune rejection
2. Available: eg HSC
3. Partly specialized: easier to control differentiation
4. Flexible: under the right conditions

Disadvantages:
1. Scarce (Rare): True for many Adult SCs
2. Unavailable: Some are difficult to isolate like Neural stem cells
3. Vanishing: Don’t live in culture as long as ES cells
4. Questionable quality: more prone to DNA abnormalities