STEM CELLS - BASIC CONCEPTS

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WHAT IS A STEM CELL?
A cell that can undergo self-renewing (expanding) proliferation and give rise to specialized differentiated cells

3 CONCEPTUAL CATEGORIES

Embryonic

Somatic

Tumor

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Found in blastocyst stage embryos, can generate all tissues of the body

Somatic

Tumor
3 CONCEPTUAL CATEGORIES

**Embryonic**
Found in blastocyst stage embryos, can generate all tissues of the body

**Somatic**
Found in fully-formed organs, can generate multiple cell types characteristic of organ of origin.

**Tumor**
Found in tumors, can reconstitute new tumors of same type, presumed source of metastases

THE CONCEPT OF STEM CELL POTENCY

**Totipotent**
(fertilized egg, entire body)

**Pluripotent**
(embryonic stem cells, most - all cell types)
embryonic germ cells
embryonal carcinoma cells

**Multipotent**
(somatic stem cells, several cell types)

HISTORICAL PERSPECTIVE

Fertilized egg + first few blastomeres are totipotent
Separated blastomere experiments of Driesch 1892

Embryonic stem cells first isolated from mouse blastocysts by Martin and Evans & Kaufman 1981
“inner cell mass”
established as expandable cell lines, are pluripotent
allowed for the generation of transgenic mice

Embryonic stem cells first isolated from human blastocysts by Thomson et al, Gearhart et al 1998
Established as expandable cell lines (first USA, now many countries including Sweden)
Requires use of human blastocysts, obtained in connection with *in vitro* fertilization for couples with fertility problems
**Embryonic Stem Cell Lines Derived from Human Blastocysts**

James A. Thomson,* Joseph Itskovitz-Eldor, Sander S. Shapiro, Michelle A. Waknitz, Jennifer J. Swiergiel, Vivienne S. Marshall, Jeffrey M. Jones

Human blastocyst-derived pluripotent cell lines are described that have normal karyotypes, express high levels of telomerase activity, and express cell-surface markers that characterize primitive embryonic stem cells but do not characterize other early lineages. After undifferentiated proliferation in vitro for 4 to 5 months, these cells still maintained the developmental potential to form trophoblast and derivatives of all three embryonic germ layers, including gut epithelium (endoderm), cartilage, bone, smooth muscle, and stratified squamous epithelium (ectoderm). These cell lines should be useful in human developmental biology, drug discovery, and transplantation medicine.

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Embryonic stem cells: example of a potential use


Fig. 1: Immuno-histochemical staining of a graft 16 weeks after transplantation of 100,000 cells into the substantia nigra of a 6-OHDA-lesioned rat. A-D: Immunostaining for the transcription factor Lmx1a in the substantia nigra of a 6-OHDA-lesioned rat. E: Immunostaining for the dopamine transporter in the substantia nigra of a 6-OHDA-lesioned rat. F: Immunostaining for the tyrosine hydroxylase in the substantia nigra of a 6-OHDA-lesioned rat. G: Immunostaining for the glial fibrillary acidic protein in the substantia nigra of a 6-OHDA-lesioned rat. H: Immunostaining for the vimentin in the substantia nigra of a 6-OHDA-lesioned rat.


Development/Plasticity/Repair

Human Embryonic Stem Cell-Derived Oligodendrocyte Progenitor Cell Transplants Remyelinate and Restore Locomotion after Spinal Cord Injury

Hana S. Kesterson, Gabriel Nato, Giovanni Beraldo, Minodora Tofani, Frank Genseler, Kelly Sharp, and Gerald Silverman

Department of Neurology and Neurosurgery, Neuroscience and Behavior, and Neuroscience, Stem Cell Research Center, College of Medicine, University of California at Irvine, Irvine, California 92697-452
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HISTORICAL PERSPECTIVE

Previously known to exist in organs with obvious self-renewal (bone marrow, skin, intestinal epithelium), and in organs with some capacity to regenerate after cell loss (liver, muscle)

Previously believed NOT to exist in organs with no obvious self-renewal (like brain)

More recently demonstrated in precisely such organs (like brain)


CONCEPT OF THE STEM CELL “NICHE”
Somatic stem cells: Remnants of embryogenesis?

“Stages” of development: proliferation versus differentiation

Stem cell ➔ Progenitor cell ➔ Precursor

- Pluripotent ➔ Unipotent (?)
- High proliferation ➔ Low proliferation
- Low differentiation ➔ High differentiation

Signals for proliferation ➔ Signals for differentiation

Role of the microenvironment

Proliferative kinetics: relationship to expansion in vitro (and to evolution?)

- Number of cells = \(2^n\)
- Number of cells = \(n + 1\)

AN IMPORTANT QUESTION REGARDING SOMATIC STEM CELLS

What is the differentiation potential of somatic stem cells?
- Organ-restricted (multipotent), or broader (pluripotent)?
- Much circumstantial evidence. Requirement for definitive studies proving full differentiation to specific cell types in vivo.

Somatic stem cells: examples of specific uses

Hematopoietic stem cells have been used for years in the treatment of bone marrow and blood disorders such as leukemia, aplastic anemia.

Skin transplants are de facto stem cell treatments.

More recent advances in regenerative medicine:
- Liver, connective tissue, etc...... (heterotypic, as for bone marrow transplants)

In the future: Tissues derived from heterotypic stem cell sources?
- (For example, nerve cells from hematopoietic stem cells or from fat stem cells)
Somatic stem cells: examples of specific uses

Make pluripotent stem cells!

Induced pluripotent stem cells (iPS cells): Pluripotent stem cells derived from somatic cells that have been reprogrammed to revert to a pluripotent state as in embryonic stem cells

Embryonic
Advantages: Clearly pluripotent, easy to expand and differentiate, platform for many model systems for studying normal and disease mechanisms
Disadvantages: Not autologous, may cause tumors, derived from embryos

Somatic
Advantages: Autologous, already programmed towards specific cell types, lower risk of tumorigenesis
Disadvantages: Restricted potential, some are hard to get, still carry genetic disease burden

Induced pluripotent
Advantages: Autologous, greater potential, platform for in vitro disease models
Disadvantages: Harder to generate and expand, require genetic/epigenetic “harassment”, may enter senescence sooner

The main message:

STEM CELL BIOLOGY STILL PRESENTS MANY CHALLENGES

What is needed is continued, integrated research into embryonic, somatic, and induced pluripotent stem cells