88 Stem Cell Biology

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Stem cell biology is a rapidly expanding field that explores the characteristics and possible clinical applications of a variety of stem cells that serve as the progenitors of more differentiated cell types. In addition to potential therapeutic applications (Chap. 90e), patient-derived stem cells can also be used as disease models and as a means of testing drug efficacy. Stem cells and their niche are a major focus of medical research because they play central roles in tissue and organ homeostasis and repair, which are important aspects of aging and disease.

IDENTIFICATION, ISOLATION, AND DERIVATION OF STEM CELLS

Resident Stem Cells The definition of stem cells remains elusive. Stem cells were originally postulated as *unspecified* or *undifferentiated* cells that provide a source of renewal of skin, intestine, and blood cells throughout life. These *resident stem cells* have been identified in a variety of organs (e.g., epithelia of the skin and digestive system, bone marrow, blood vessels, brain, skeletal muscle, liver, testis, and pancreas) based on their specific locations, morphology, and biochemical markers.

Isolated Stem Cells Unequivocal identification of stem cells requires their separation and purification, usually based on a combination of specific cell-surface markers. These *isolated stem cells* (e.g., hematopoietic stem [HS] cells) can be studied in detail and used in clinical applications, such as bone marrow transplantation (Chap. 89e). However, the lack of specific cell-surface markers for other types of stem cells has made it difficult to isolate them in large quantities. This challenge has been partially addressed in animal models by genetically marking different cell types with green-fluorescent protein driven by cell-specific promoters. Alternatively, putative stem cells have been isolated from a variety of tissues as side population (SP) cells using fluorescence-activated cell sorting after staining with the Hoechst 33342 dye.

Cultured Stem Cells It is desirable to culture and expand stem cells in vitro to obtain a sufficient quantity for analysis and potential therapeutic use. Although the derivation of stem cells in vitro has been a major obstacle in stem cell biology, the number and types of *cultured stem cells* have increased progressively (Table 88-1). Cultured stem cells derived from resident stem cells are often called *adult stem cells* or *somatic stem cells* to distinguish them from *embryonic stem* (ES) and *embryonic germ* (EG) *cells*. However, considering the existence of embryo-derived, tissue-specific stem cells (e.g., trophoblast stem [TS] cells) and the possible derivation of similar cells from an embryo/fetus (e.g., neural stem [NS] cells), it is more appropriate to use the term, *tissue stem cells*.

Successful derivation of cultured stem cells (both embryonic and tissue stem cells) often requires the identification of necessary growth factors and culture conditions, mimicking the microenvironment or *niche* of the resident stem cells. Recently, long-term maintenance of tissue stem cells in vitro is increasingly possible by growing them as three-dimensional (3D) organoids, which contain both stem cells and niche cells (Chap. 92e). For example, intestinal stem cells can now be cultured as "epithelial mini-guts" in the presence of R-spondin, epidermal growth factor (EGF), and noggin on Matrigel. Similarly, lung stem cells can be cultured as self-renewing "alveolospheres." A growing list of cultured stem cells, although not comprehensive, is shown in Table 88-1. Please note that the establishment of cultured stem cells is often under dispute due to the difficulties in assessing the characteristics of these cells.

SELF-RENEWAL AND PROLIFERATION OF STEM CELLS

Symmetric and Asymmetric Cell Division The most widely accepted stem cell definition is a cell with a unique capacity to produce unaltered daughter cells (*self-renewal*) and to generate specialized cell types (*potency*). Self-renewal can be achieved in two ways. *Asymmetric cell division* produces one daughter cell that is identical to the parental cell and one daughter cell that is different from the parental cell and is a progenitor or differentiated cell. Asymmetric cell division does not increase the number of stem cells. *Symmetric cell division* produces two

TABLE 88-1 EXAMPLES OF CULTURED STEM CELLS

Name	Source
Embryonic stem cells (ES, ESC)	Blastocysts or immunosurgically isolated inner cell mass (ICM) from blastocysts
Embryonic germ cells (EG, EGC)	Primordial germ cells (PGCs) from embryos at E8.5–E12.5 (m); gonadal tissues from 5–11 week postfertilization embryo/fetus (h)
Trophoblast stem cells (TS, TSC)	Trophectoderm of E3.5 blastocysts, extraembryonic ectoderm of E6.5 embryos, and chorionic ectoderm of E7.5 embryos (m)
Extraembryonic endoderm cells (XEN)	ICM from blastocysts (m)
Embryonal carcinoma cells (EC)	Teratocarcinoma—a type of cancer that develops in the testes and ovaries (m, h)
Mesenchymal stem cells (MS, MSC)	Bone marrow, muscle, adipose tissue, peripheral blood, and umbilical cord blood (m, h)
Multipotent adult stem cells (MAPC)	Bone marrow mononuclear cells (m, h); postnatal muscle and brain (m)
Spermatogonial stem cells (SS, SSC)	Newborn testis (m)
Germline stem cells (GS, GSC)	Neonatal testis (m)
Multipotent adult germline stem cells (maGSC)	Adult testis (m)
Neural stem cells (NS, NSC)	Fetal and adult brain (subventricular zone, ventricular zone, and hippocampus) (m, h)
Unrestricted somatic stem cells (USSC)	Mononuclear fraction of cord blood (h)
Epistem cells (EpiSC)	Early postimplantation epiblast (m)
Induced pluripotent stem cells (iPS, iPSC)	Variety of terminally differentiated cells and tissue stem cells (m, h)
Multilineage-differentiating stress-enduring (MUSE) cells	Adult human bone marrow stromal cells and dermal fibroblasts
Urine-derived stem cells (USC)	Urine (h)
Lung stem cells	Lung (m, h)
Amniotic fluid-derived stem (AFS) cells	Amniotic fluid (m, h)
Umbilical cord blood stem cells	Umbilical cord (h)
Adipose stem cells (AST)	Fat (m, h)
Cardiac stem cells	Heart (m, h)
Renal stem cells	Renal papilla (m, h)
Crypt stem cells	Intestine (m, h)
Colon stem cells (CoSC)	Colon (m, h)
Hepatic stem cells	Liver (m, h)
Dental pulp stem cells (DPSC)	Dental pulp (m, h)
Hair follicle stem cells	Hair (m, h)

Abbreviations: h, human; m, mouse.