# UNIT 2 TEACHER BACKGROUND INFORMATION

**Note: Terms that are bolded are defined in glossaries for teachers and students.**

## ADULT STEM CELLS' ROLE IN TISSUE HOMEOSTASIS

An adult stem cell is an **undifferentiated** cell found in tissues and organs that can **self-renew** and **differentiate** to become most or all of the **specialized** cell types within their specific tissue lineage. Adult stem cells, or **multipotent** cells, have been identified in many organs and tissues, including brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, liver, ovarian epithelium, and testis. They reside in a specific area of each tissue called the "stem cell niche" (*The Adult Stem Cell, 2009*).

The stem cell niche is the **microenvironment** in which the stem cells live, and interacts with stem cells to regulate **cell fate**. Several factors are important in the regulation of stem cell characteristics within the niche, including interactions between stem cells and neighboring cells, **adhesion molecules**, extracellular matrix (ECM) fibers, and signaling molecules such as hormones and proteins (*Stem Cell Niche, 2009*). (For more information on the microenvironment, see Unit 3, downloadable at: http://www.cirm.ca.gov/curriculum_unit-3.) Every major organ except the pancreas contains resident stem cells that are activated to divide and differentiate into new mature cells of that organ. (Some reports in 2012 suggest that adult stem cells may have been found in the pancreas as well.)

A major part of organ and tissue homeostasis is the constant or periodic generation of new cells to replace old, damaged, and dying cells. Thus, adult stem cells are the crucial effectors of the regeneration that underlies homeostasis. Adult stem cells normally remain quiescent (non-dividing) for relatively long periods of time until they are activated by signals to maintain tissues, from disease or from injury. Thus, they are important in maintaining homeostasis in the human body, multicellular animals, and plants. In plants, stem cells in the meristem give rise to new roots, shoots, and flowers. In animals, muscle contains stem cells that contribute to the formation of new muscle after exercise and injury. Red blood cells live for about 120 days, so **hematopoietic stem cells** in bone marrow continuously replace dying red blood cells (*Kadereit, 2005*).

Two specific areas of the brain contain neural stem cells that contribute to the formation of new neurons and supporting **glial cells** throughout life and, evidence suggests, also after traumatic brain injury. Without the action of adult stem cells, you could not heal or achieve cellular- and tissue-level homeostasis.

## Wound healing

Adult stem cells are also important in the process of wound healing, for example upon a cut to the skin. Immediately, a set of complex biochemical events takes place in a carefully orchestrated cascade to repair the damage. Wound healing occurs in a four phases: (1) hemostasis, (2) inflammation, (3) proliferation, and (4) remodeling. Within minutes post-injury, hemostasis begins. Platelets (thrombocytes) aggregate at the injury site to form a fibrin clot. This clot acts to control active bleeding, maintaining hemostasis. During the inflammation phase, neutrophils and macrophages degrade bacteria and debris, and damaged cells release factors that cause the migration and division of cells (**progenitor cells**, created by adult stem cells, which have important differences described below) involved in the next, proliferative phase. The proliferation phase is characterized by angiogenesis (capillary growth), collagen deposition, **granulation tissue** formation, **epithelialization**, and wound contraction.

In angiogenesis, new blood vessels are formed by vascular endothelial cells. In **fibroplasia** and granulation tissue formation, fibroblasts grow and form a new, provisional ECM by excreting collagen and fibronectin. Concurrently, re-epithelialization of the skin occurs, in which epithelial cells proliferate and "crawl" atop the wound bed, providing cover for the new tissue. During contraction, the wound is made smaller by the action of myofibroblasts, which establish a grip on the wound edges and contract using a mechanism similar to that in smooth muscle cells. In the remodeling phase, collagen is realigned along tension lines and cells that are no longer needed are removed by **apoptosis** (*Wound Healing, 2009*).

## Limb regeneration

Wound healing relies less on stem cell division and differentiation than on regeneration. An organism is said to regenerate a lost or damaged part if it regrows so that the original shape and function are restored. Regenerative capacity is inversely related to complexity: in general, a more complex animal part is less capable of regeneration. Whereas newts can regenerate severed limbs, mammals cannot. After a newt limb is amputated, the epidermis migrates to cover the stump in less than 12 hours, forming a structure called the apical epidermal cap. Over the next several days there are changes in the underlying stump tissues that result in the formation of a **blastema** (a mass of undifferentiated adult stem cells). As the blastema forms, pattern formation genes—such as HoxA and HoxD—are activated as they were when the limb was formed in the embryo. The distal tip of the limb (the autopod, which is the hand or foot) is formed first in the blastema. The intermediate portions of the pattern (the arm or leg) are filled in during growth of the blastema by the process of **intercalation**. Motor neurons, muscle, and blood vessels grow with the regenerating limb, and reestablish the connections present prior to amputation. The length

of this process varies according to the age of the animal, ranging from one to three months when the limb becomes fully functional.

In mammals, there is limited regeneration in the liver, kidney, ribs, and finger tips. However, there is a genetically-engineered mouse strain, called MRL mice, which exhibits remarkable regenerative abilities for a mammal: they can completely heal ear punctures, spinal cord injuries, and minor heart injuries (*Regeneration Biology, 2009*).

**CHARACTERISTICS OF ADULT STEM CELLS VERSUS EMBRYONIC STEM CELLS**

Adult stem cells exist in a very small amount in each tissue type, but have the ability to create the majority of the cell types in that tissue. They do this by differentiating. Differentiation is the process by which a less specialized cell becomes a more specialized cell type. A differentiating cell dramatically changes size, shape, membrane potential, metabolic activity, and responsiveness to signals (*Cellular Differentiation, 2009*). When an adult stem cell divides, it creates a copy of itself *and* a slightly more differentiated cell. This cell is called a progenitor cell. Progenitor cells usually are the direct precursors of the fully differentiated cell type (there are exceptions, such as in the blood system and the brain, where progenitor cells give rise to more specialized types of precursor cells, which eventually fully differentiate). In other words, a progenitor cell has little plasticity and will only become the cells along a certain lineage (*Adult Stem Cells, 2009*).

Before we continue, let's review the concept of plasticity. A cell that can differentiate into most types of body cells is known as **pluripotent**. Embryonic stem cells are pluripotent because they can become any cell in the developing embryo (excluding the placenta; cells that can become any tissue in the body *and* the placenta are called **totipotent**). Adult stem cells can turn into multiple cell types along a specific lineage; they are multipotent. Embryonic stem cells and adult stem cells have key differences including location, prevalence within tissues, plasticity/potency, and ultimate lifespan in culture.

Embryonic stem cells are only located in the inner cell mass of the blastocyst, which exists 5-14 days after fertilization in humans. Embryonic stem cells are easily isolated from the inner cell mass and can be grown in culture under certain conditions. Multipotent stem cells exist in small quantities in the tissue of the post-blastocyst embryo and onward and are very difficult to isolate. There are very few sources of easily extractable multipotent cells in the adult human body (one relatively easy source is the bone marrow) and those that are isolated have limited **plasticity** in comparison to embryonic stem cells.

Plasticity/potency in relation to stem cells refers to the differential property of stem cell types to alter their differentiation paths. Because of its limited plasticity as compared to a pluripotent embryonic stem cell, a multipotent *adult neural* stem cell, for example, could not eventually create a blood cell (like an embryonic stem cell could). However, recent studies suggest increased plasticity in certain types of adult stem cells, namely

Hematopoietic (blood) stem cells, which give rise to all types of mature blood cells. In comparison, embryonic stem cells are extremely plastic; they can turn into any cell type. In culture, embryonic stem cells have the ability to grow and divide indefinitely (as long as they are supplied with nutrient medium). Adult stem cells, however, are generally limited to around 30 divisions in culture before they become **senescent** (*The Adult Stem Cell, 2009*).

## DEVELOPMENTAL ORIGINS OF ADULT STEM CELLS

Gastrulation of the 14-day old embryo leads to three early germ layers: the **endoderm, mesoderm,** and **ectoderm**. At this stage, pluripotent embryonic stem cells begin migrating to these three areas and differentiating. These stem cells give rise to tissues specific to their germ layer. Later, reserves of stem cells that retain the abilities to self-renew and differentiate are used in tissue homeostasis.

### *Endoderm*

The endoderm is the innermost layer of embryonic tissue that is the precursor of the gut, digestive organs, and lungs.

### *Mesoderm*

The mesoderm is embryonic tissue that is the precursor to muscle, connective tissue, bone, kidneys, and other internal organs.

### *Ectoderm*

The ectoderm is the outermost layer of embryonic tissue that is the precursor of the epidermis (skin), nervous system, and sensory organs.

## ADULT STEM CELL TYPES

The best-characterized types of adult stem cells include hematopoietic stem cells, mesenchymal stem cells, neural stem cells, and epithelial stem cells.

***Hematopoietic stem cells*** give rise to all the blood cell types including the **myeloid** lineage (monocytes and macrophages, neutrophils, basophils, eosinophils, megakaryocytes/platelets, dendritic cells), the **lymphoid** lineage (T-cells, B-cells, NKcells), the **erythroid** lineage (erythrocytes, a.k.a. red blood cells), and possibly the cells that make bone (osteoblasts). They are found in the bone marrow from very early on in development, as well as in umbilical cord blood and placental tissue (*Hematopoietic Stem Cell, 2009*).

***Mesenchymal stem cells*** can differentiate into cartilage cells **(chondrocytes)**; muscle cells **(myocytes)**; fat cells **(adipocytes)**; tendons, ligaments, and connective tissue (including **osteoblasts**). Mesenchymal stem cells are located throughout the body and for this reason are difficult to isolate. A progenitor of the mesenchymal stem cell is a muscle stem cell.

The muscle stem cell resides as a satellite cell in the muscle tissue. Satellite cells are small mononuclear progenitor cells with virtually no cytoplasm. Quiescently, they are found

sandwiched between the basement membrane and sarcolemma (cell membrane) of individual muscle fibers. When an injury occurs to the muscle, the satellite cells are activated to proliferate and migrate to the damaged area. Once there, they begin differentiating into myoblasts, which then develop into single fibers which will fuse together to form a mature muscle fiber (*Mesenchymal Stem Cell, 2009*).

***Neural stem cells*** in adult mammals are located in the *subventricular zone* lining the lateral ventricles, where they give rise to newly-born neurons that migrate to the olfactory bulb via the rostral migratory stream, as well as the *subgranular zone* which is part of the dentate gyrus of the hippocampus. These regions are responsible for, among other things, smell and memory (respectively). Neural stem cells (also called neural precursor cells) directly give rise to progenitors of **neurons**, **oligodendrocytes**, and **astrocytes** through the process of **neurogenesis**. Newly-born neurons reach the olfactory bulb and mature into neurons that have specific chemical receptors that allow the detection and discrimination of a multitude of smells. These neurons are frequently damaged because of direct exposure to air and can be regenerated. Neurogenesis in the hippocampus is negatively affected by stressful experiences, while exercise and learning increase the number of new neurons in these areas (*Neurogenesis, 2009*).

***Epithelial stem cells*** give rise to **epithelial cells** which constitute 60 percent of the differentiated cells in the body (The *Adult Stem Cell, 2009*). They are responsible for covering the internal and external surfaces of the body, including the lining of vessels, glands, and other cavities. The epithelial cells in skin and the digestive tract are replaced constantly. Other epithelial cell populations—in the ducts of the liver or pancreas, for example—turn over more slowly.

The cell population that renews the epithelium of the small intestine occurs in the intestinal crypts, deep **invaginations** in the lining of the gut. The **crypt cells** are often regarded as stem cells. Epithelial stem cells of the skin are called **epidermal stem cells**. They are found in the bulge region of the outer root sheath of the hair follicle, the interfollicular epidermis, and the sebaceous gland. Further investigation shows that cells in the bulge region of the hair follicle are more primitive—giving rise to multiple skin cell types.

Epidermal stem cells undergo asymmetric cell division, where one daughter cell remains a stem cell and the other will differentiate into a transient amplifying cell that will divide several more times and generate larger quantities of specialized differentiated cells within the epidermis.

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**ADULT STEM CELL THERAPIES**

Adult stem cells are used in therapy. The most well known adult stem cell therapy is a bone

marrow transplant. Since its first successful use in 1968, bone marrow transplants have been used to treat patients diagnosed with **leukemia**, **aplastic anemia**, **lymphomas** such as **Hodgkin's disease**, **multiple myeloma**, **immune deficiency disorders** and some solid tumors such as breast and ovarian cancer. Importantly, a bone marrow transplant does not have a 100% cure rate, although it has saved many lives. Thus it usually represents a treatment, not an absolute cure, for these diseases. There are three kinds of bone marrow transplants:

***Autologous bone marrow transplant:*** *Auto* means *self*. Stem cells are taken from the patient before the patient gets chemotherapy or radiation treatment. When chemotherapy or radiation is done, the patient gets their stem cells back. This is called a "rescue" transplant.

***Allogeneic bone marrow transplant:*** *Allo-* means *other.* Stem cells come from another person, who is called a donor. Donor stem cells come from the donor's bone marrow or their blood. Most times, a donor must have the same **genetic typing** as the patient, so that their blood and tissue types "match" the patient's. Special blood tests will tell whether a possible donor is a good match for the patient. A patient's brothers and sisters have the highest chance of being a good match. Sometimes, parents and children of the patient and other relatives may be matches.

Donors who are not related to the patient may be found through national bone marrow registries—lists of people who have offered to be donors (*Johnson, 2008*). In the United States, there is a dire shortage of bone marrow and organ donors from people of mixed race. This decreases the likelihood of finding a good match for people needing bone marrow transplants from minority groups.

***Umbilical cord blood transplant***. Stem cells are taken from an umbilical cord right after delivery of an infant. Umbilical cord blood stem cell transplants are less prone to rejection than either bone marrow or peripheral blood stem cells. This is probably because the cells have not yet developed the features that can be recognized and attacked by the recipient's immune system. Also, because umbilical cord blood lacks well-developed immune cells, there is less chance that the transplanted cells will attack the recipient's body, a problem called graft versus host disease. The stem cells are tested, typed, counted, and frozen until they are needed for a transplant. This could be years later, if stored properly in a cord blood bank.

Most patients get high doses of chemotherapy, radiation, or both, before the bone marrow transplant. This is called **ablative** (or **myeloablative**) treatment. It kills any cancer cells that might remain, and it makes room in the bone marrow for the new stem cells to grow. Some patients receive less chemotherapy and radiation before their transplant. This is called a reduced intensity (non-myeloablative) or "mini" transplant. After the patient gets chemotherapy and, possibly, radiation, a doctor will do the stem cell transplant. The patient

gets the stem cells through a tube called a central venous catheter. The cells go right into the bloodstream. This delivery of cells is called an infusion. It may take up to several hours. It is not surgery; it is similar to a blood transfusion. The stem cells find their way into the bone marrow, where they may begin reproducing and making healthy new blood cells (*Chen, 2008*).

Adult stem cells have also been used to create a tissue specific organ. In November 2008, scientists in Spain carried out a trachea transplant for a woman whose windpipe had been damaged by tuberculosis. The doctors took adult stem cells and some other cells from the healthy right airway of the woman needing the trachea transplant, grafted those cells onto the stripped-down donated (cadaver) trachea, and marinated the trachea in chemicals in a lab to coax the trachea into rebuilding itself. When the trachea was ready, the doctors implanted it into the patient. The procedure worked—and since the trachea had been prepped by the patient's own stem cells before transplantation, her body accepted it without immune-suppressing drugs. Usually these are delivered along with **allogeneic** bone marrow transplants to decrease the likelihood of rejection and graft versus host disease, although often the patient is susceptible to opportunistic infections. (*Hitti, 2008*)

**U.S. ADULT STEM CELL CLINICAL TRIALS**

There also many adult stem cell therapies in clinical trial. The NIH website for clinical trials, http://www.clinicaltrials.gov, lists 2,000 such trials. The clinical trial process is long and complicated. Clinical trials and research are studies done to answer specific questions about novel vaccines and therapies, as well as new ways of using known treatments. The entire Food and Drug Administration (FDA) approval process can take up to nine years, depending on many factors.

Clinical trials are conducted in four phases. The trials at each phase have a different purpose and help answer different questions. In Phase I trials, researchers test an experimental drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects. In Phase II trials, the experimental study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety. In Phase III trials, the experimental study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely. In Phase IV trials, post marketing studies delineate additional information including the drug's risks, benefits, and optimal use (Understanding *Clinical Trials, 2007*).

All clinical trials must be conducted according to strict scientific and ethical principles. Every clinical trial must have a protocol, or action plan that describes what will be done in the study, how it will be conducted, and why each part of the study is necessary. This

includes details such as the criteria for patient participation, the schedule of tests, procedures, medications, and the length of the study. As a clinical trial progresses, researchers report the results of the trial at scientific meetings and in medical journals, as well as to various government agencies (*What is a Protocol?, 2008*).

Patient participation in a clinical trial is voluntary. Before joining a trial a patient will receive an informed consent document that includes details about the study, such as its purpose, duration, and required procedures. Risks and potential benefits are explained in the informed consent document. The participant then decides whether or not to sign the document and comply with the conditions. However, informed consent is not a binding contract, and the participant may withdraw from the trial at any time (*Understanding Clinical Trials, 2007*).

The ISSCR has released *Guidelines for the Clinical Translation of Stem Cells* that examine the scientific, clinical, regulatory, ethical and societal issues that must be addressed to ensure that basic stem cell research is responsibly transitioned into appropriate clinical applications. The guidelines present 40 recommendations to ensure the safety of patients, the ethical nature of the trials, and validity of the clinical results (*Guidelines for the Clinical Translation of Stem Cells, 2008)*. You can find all the guidelines at http://www.isscr.org/clinical_trans/index.cfm.

Here are a few of these recommendations (verbatim):

***Recommendation 3:*** In the case of donation for allogeneic use, the donor should give written informed consent that covers, where applicable, the following issues:

a) Cells and/or cell lines may be subject to storage. If possible, duration of storage should be specified.

b) The donor may (or may not) be approached in the future to seek additional consent for new uses, or to request additional material (blood or other clinical samples) or information.

c) The donor will be screened for infectious and possibly genetic diseases.

d) The donated cells may be subject to genetic modification by the investigator.

e) With the exception of directed altruistic donation, the donation is made without restrictions regarding the choice of the recipient of the transplanted cells.

f) Disclosure of medical and other relevant information that will be retained, and the specific steps that will be taken to protect donor privacy and confidentiality of retained information, including the date at which donor information will be destroyed, if applicable.

g) Explanation of what types of genomic analyses (if any) will be performed and how genomic information will be handled

h) Disclosure that any resulting cells, lines or other stem cell-derived products may have commercial potential, and whether any commercial and intellectual property rights will reside with the institution conducting the research

***Recommendation 20:*** Stem cell-based clinical researchers should:

a) Cooperate with and share scientific expertise to assist other investigators and human subjects research review committees in assessing:

i. The biological characteristics of the cells to be used in clinical trials

ii. Whether these cells have been developed with appropriate manufacturing standards

iii. Preclinical data on their use in animal and/or other models for evaluating their safety and efficacy, and

iv. Any early clinical data, if available, which address safety issues in the short and medium term and continued observation for long term effects

b) Address the risks of stem cell-based interventions including, for example, cell proliferation and/or tumor development, exposure to animal source materials, risks associated with viral vectors, and risks as yet unknown

c) Provide the utmost clarity regarding the potential benefits of participating in the trial with stem cells, since patients may have recourse to reasonable therapeutic alternatives; the informed consent process must emphasize the novel and experimental aspects of cell based interventions. It is important to minimize misconceptions patients may have about the potential for therapeutic efficacy

d) Disclose any financial and non-financial conflicts of interest among the investigators, sponsors, and institutions in which the stem cell research is being conducted

e) Monitor research subjects for long-term health effects and protection of the confidentiality of their health data

f) Provide a clear, timely, and effective plan for adverse event reporting

g) Offer a clinical plan to provide treatment for toxicity, including treatment of tumors that might arise. This plan might include compensation for research-related injuries, and

h) Ensure that insurance coverage or other appropriate financial or medical resources are available to patients to cover potential complications arising from their research participation.

**STEM CELL TOURISM**

It is important to know that stem cell-affecting drugs used in clinical trials are only available to participants in the trials, and they usually must stop all other treatments before beginning the trial. Those who wish to obtain the drug, yet are either not qualified for a clinical trial or are qualified but given a placebo, often take desperate measure to obtain these therapies. In what is called “stem cell tourism,” patients travel to other countries with

fewer restrictions to receive stem cell therapies. These therapies are sometimes experimental and can be dangerous, although there are many legitimate therapies going through the national regulatory processes in these countries. The number of patients who have traveled abroad for stem cell therapies is unknown, though experts say that anecdotally it appears to be thousands.

The proliferation of clinics marketing purportedly effective stem cell interventions online has many experts worried. A December 2008 study of stem cell clinic web sites found that they claimed to treat a range of diseases that go beyond the scope of the early evidence on stem cells' efficacy, while playing up the benefits and ignoring risks. The study, published in the journal *Stem Cells*, found that the average price tag for a stem cell treatment abroad, excluding travel and lodging costs, was $21,500 (*O'Reilly, 2009*). Recently, China and European countries have begun to crack down on stem cell tourism, releasing ethical guidelines aimed at discouraging doctors from offering patients unproven or sham (fake) treatments based on stem cells (*Coghlan, 2009*).

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**Links**

http://www.cirm.ca.gov/curriculum_unit-2 (Supplementary Adult Stem Cell PowerPoint and Appendix Materials)
http://www.cirm.ca.gov/curriculum_unit-3 (Materials on the microenvironment)

Marrow donors are rare for mixed-race patients: http://www.cbsnews.com/stories/2009/05/27/health/main5044251.shtml?source=RSSattr=Health_5044251