What do you mean when you say the words “stem cell”?

David W. Scharp, MD
Scharp Technologies
May 21, 2013

There are billions of cells in our bodies that are not stem cells, with the majority programmed to carry out very specific functions on their own and in concert with many other types of cells. These functional, non-stem cells are essential to complete all of the complex activities required for our bodies to function normally. A majority of these functional cells can undergo limited replication but many cannot duplicate after they are formed. With all of these different types of functional cells in the body, there are many different types of stem cells that can readily divide, reproduce themselves, and differentiate into the functional cell types. Once the stem cells differentiate into functional cells, they lose their stem cell status and become permanent, functional cells until their programmed lifetime is reached and they die. After a stem cell turns into a functional cell, it cannot go back to being a stem cell again. The majority of our body’s stem cells are restricted to making only one type of functional cell or a very limited number of different types of functional cells that are closely related. There are, however, a limited number of stem cells that can readily divide and produce many types of functional cells. Since the skin is the largest organ in our body, let’s look at the skin to give some examples of the stem cells that are limited in the types of functional cells they can produce.

The skin has two main parts: the thin outer coating, called the epidermis, and the deeper portion called the dermis. The outer epidermis only has three cell types: the actual skin cells, the skin stem cells that make the skin cells, and a few other cell types that complete the skin such as the melanin producing cells that provide the color of the skin and protect the skin cells from sun damage. These important melanin producing cells, melanocytes, are not produced in the epidermis. They are made in the dermis and migrate up to the epidermis. The skin stem cells called epidermal stem cells, divide and reproduce themselves in the lowest level of the epidermis, called the basal layer. These continuously replacing stem cells then differentiate into the skin cells, called keratinocytes. These new keratinocytes are able to divide a few times before they begin to differentiate as well. They can also produce anti-bacterial and inflammatory compounds. As more skin cells are produced below from the epidermal stem cells, these keratinocytes are pushed upward towards the surface and produce increasing amounts of keratins that will be used for skin protection. As they are moved upward, they undergo a number of differentiation changes that eventually reduce their cell components leading to their death. Only their cell membranes with the keratins are left that fuse together to make the outer, protective layer of the epidermis of our skin. This very strong outer layer has two critical functions: 1) it keeps the water within the body from passing directly through the tough outer skin layer keeping us from dehydrating and 2) it provides a formidable barrier to bacteria, fungus, and viruses in order to maintain our health. There are no blood vessels or capillaries, nerves, hair follicles, sweat glands or oil glands in the epidermis. These are all contained in the dermis layer below. All the nutrients needed for the epidermal cells diffuse up from the dermis through the basal layer to the epidermal stem cells and the keratinocytes. So the epidermis has a basal layer of skin stem cells that produce all of the skin cells that are moved to the surface and form its tough outer layer. This protective outer layer is continuously sloughed off the surface with the entire duration from newly formed keratinocyte to its appearance in the outer fused layer taking about 40 to 55 days. These epidermal skin stem cells are limited to only produce new skin stem cells that can only differentiate into the keratinocyte skin cells. This epidermal stem cell is not programmed to make any other types of cells. Whenever you have a blister on the skin, you are essentially seeing the epidermis lift off the basal stem cell layer on top of the dermis that also exposes the dermis nerve endings, causing the pain.

Moving to the much thicker, second layer of the skin, the dermis, we find that this is where the blood vessels and capillaries, nerves, nerve endings, hair follicles, sweat glands, and oil glands exist along with other cell types like fat and supporting and renewing cells like dermal fibroblasts. There are several specific types of stem cells located in the dermis. The most localized stem cells are in the hair follicle and are of several types: those that produce the hair shaft, those that produce oil or sebaceous glands, those that produce melanocytes that provide the color to the hair shaft and those that produce epidermal skin stem cells. While there are several stem cells involved, it is not yet certain whether some of these stem cells produce more than one type of functional cells. But if the skin is damaged, then the stem cells within the hair follicle are stimulated to produce epidermal skin stem cells and the skin cells themselves. These stem cells of the hair follicle may only produce a few types of cells under normal conditions. But, when they are stimulated, they may be able to produce multiple types of cells in response to injury. The important melanocytes containing the melanin pigment of the skin are also produced in the dermis by its own unique stem cell. The melanocytes migrate to the epidermal basal layer and form their own loose cell layer protecting the epidermal skin stem cells from ultraviolet light damage.

In the dermal portion of the skin, there are the blood vessels and blood capillaries, as well as motor and sensory nerves and specialized skin nerve endings. Under normal conditions, these cells are fairly stable with only basal numbers of mature cells being produced. There are also dermal skin fibroblasts that maintain the dermis by producing collagen as well as laminin, fibronectin and other substances to make the extracellular matrix that is critical to other cells functions. The dermal fibroblasts can also divide and replace themselves to an extent after being produced by a stem cell, but they do not differentiate into other cell types. All of these of mature cells of the dermis, except for the nerve cells, are produced from a single type of stem cell, called the mesenchymal stem cell or MSC. The MSC is located in all of our tissues and organs as well as migrating throughout the body in the blood. They are like a "mother ship" in a quiet state waiting for signals from damaged tissues or inflammation and remain in that resting state until stimulated by a sign of injury or damage. At that point, they readily start dividing rapidly and reproducing themselves in order to produce the many different types of cells required to help repair the damage from the injury. These new MSC's can differentiate into multiple different types of structural and supporting cells that may be needed at that site to replace the damaged cells. The MSC's also produce cell signaling molecules to recruit inflammatory and immune cells to the damaged site. Additional peptide signals also stimulate the dermal fibroblasts to begin the process of damage repair. The MSC is one of the most important stem cell types in the body since it is located everywhere and programmed to respond to a variety of damage or disease conditions. Whenever specifically programmed to do so, the Mesenchymal Stem Cell can differentiate into a variety of cell types including cartilage, bone, muscle, blood vessels, red blood cells, white blood cells, fat, and different types of fibroblasts that are the repair and maintenance cells of the body. Currently, the FDA has approved nearly 300 clinical trials of injecting human MSC's into the blood of patients with a variety of diseases and disorders to determine which can benefit from having more of these cells when the body is in a crisis. As we age, the number of MSC's in our bodies goes down significantly reducing our ability to respond to injury and disease.

The nervous system, including the brain, has its own specific stem cells that can reproduce multiple types of specific cells in the brain, spinal cord, and peripheral nerves including special organs like the eyes and ears. Yet, many of the nervous system tissues cannot be replaced once growth has been achieved as an adult. Each of the organs of the body have their own type of specific stem cells that produce only the liver, or kidneys, or pancreas, or intestine, or lungs. The intestinal stem cells are continuously producing the inner surface of the intestine that is responsible for absorbing the food nutrients in a similar way as described for the epidermal stem cells. All of these types of stem cells are active in childhood, but most lose their ability to function once adulthood is reached. Some of these stem cells like those that produce the liver become quiescent as an adult, but are able to become quite active and replace a portion of the liver if it is damaged. Others like those that produced the kidney or pancreas are not able to be stimulated to make more kidney parts or pancreas parts if they are damaged as an adult. Damage to these organs is permanent.

Some specialized stem cells are producing functional cells all of the time, like skin cells, hair, nails, intestinal cells, blood cells, immune cells, inflammatory cells, and fibroblast cells, each with its own specific type of stem cell. Other stem cells are normally very quiet, but can be primed to produce a variety of cells following injury or disease, like the MSC. The process of growing up from an infant to an adult requires almost every type of cell in our bodies to grow and expand by the specific types of stem cells. These efforts originate in stem cells and continue in many mature cells that have a limited ability to replace themselves. As adults, some stem cells continue to make cells that are needed all the time. Others, like the MSC wait for certain signals from injury or disease to make new cells. The MSC is also unique in that it makes a variety of important chemical signals when it is reacting to injury and expanding. It is these signal proteins, that are not currently identified, that are contained in the tissue culture fluid used to grow these stem cells in the laboratory. This conditioned fluid has become an important component for skin care and other similar types of new products. These products do not contain any stem cells, but do contain these important stem cell peptides that can assist the stimulation of the normal activities related to healing and rejuvenation.

So what are stem cells? They are the system of very specialized cells of the body that can replace themselves, as well as all of the rest of the cells in the body. This process is tightly controlled by having a few stem cells that can make multiple different types of cells in the body, coupled with those that can make a few or single type of cell. For example, there is a major type of stem cell that can make all of the organs in the body. From that stem cell, there are specific stem cells to make each organ. Each organ's stem cells can make specific stem cells required for each tissue type in that organ. If we consider the pancreas stem cell, from that organ stem cell, then there is a cascade of stem cells making more and more specific pancreatic cell types. Thus, a specific stem cell makes only the enzyme producing cells of the pancreas. Another stem cell makes only the duct cells of the pancreas. A third stem cell makes only the hormone producing cells of the pancreas, and a final stem cell only makes insulin producing cells of the pancreas. These are all coordinated to produce the number of cells that are required to make the entire, functioning organ. In the case of the adult human pancreas, it appears these productive stem cells no longer function. Yet, the rodent pancreas may be able to stimulate these stem cells again after damage. In some cases like the liver, its stem cells remain at rest so that the organ can be made again in part after it is damaged or destroyed by injury or disease even in humans. Yet, once that portion of the liver replacement has been completed, the stem cells go back to a resting state.

For the majority of human organs, only one is developed. If a portion of it is destroyed, it cannot be replaced. For example, the loss of pancreatic insulin producing cells causes diabetes. The loss of kidney filtering cells from glomerulonephritis or diabetes causes kidney failure. The loss of retinal cells causes blindness. The damage of the spinal cord causes paralysis. The interruption of blood flow to a portion of the brain causes stroke. Some stem cells are uniquely configured to produce ongoing specialized cells as required throughout our lives. Other stem cells are restricted in their production of specialized cells to children and youth but their function in adults is blocked. A major research question today is to understand how the stem cells become blocked as an adult and find a way to turn them back on again to reproduce lost functions. For potential diabetes treatment, this is currently a major focus of re-programming insulin producing cells to enable their direct growth and replication again to replace the damaged ones. Another diabetes approach is to find and stimulate the right stem cell that can have its adult replication block removed to enable it to replace the destroyed insulin producing cells. Regardless of the disease type, the disorder, or the results of aging on our bodies, stem cell research may lead to new answers that can enable new approaches to improve our lives. Understanding how all this coordinated stem cell system works together and maintains our health or begins to fail as we age, is an important challenge that is under extensive research.