Jonathan Slack

STEM CELLS

A Very Short Introduction

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What are stem cells?

It is an unpalatable fact that we all get old and we all die. We spend most of our lives trying not to think about this fact, and to help us in this regard most religions have created beliefs about survival of the self-conscious mind even after the body and brain have decayed. But while we tend to try not to think about death, all of us are very keen to avoid disability. We have a horror of congenital conditions such as cerebral palsy; of accidents that can cause serious injury such as blindness or paralysis; and of the loss of independence caused by many of the diseases that accompany old age, such as Alzheimer's disease, strokes, heart failure or cancer. This is especially the case if we have a close friend or family member who suffers from one of these conditions, or who cares for a sufferer. We yearn for some miracle cure that will end the suffering and restore the person we have known.

Our yearning is all the greater because of the success of public health in preventing, and of scientific medicine in curing, a large range of other afflictions of childhood and middle life. Most of us who live in rich countries can now expect to live to old age with only very mild medical problems on the way, and this makes all the more tragic those cases of serious disease that still do occur.

Most people value stem cell research because they believe it will generate new and effective cures for currently incurable conditions.

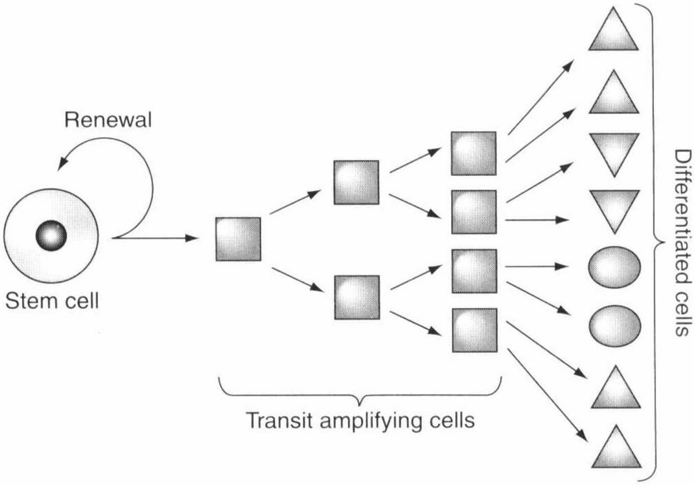
This is the main force behind the large sums of research money currently devoted to the area. Some scientists are also motivated by the desire to develop new cures, but often they have more limited objectives involving the understanding of particular biological phenomena. This is just one example of the different perceptions that different people have of stem cell research. When we consider that stem cell biology is also of interest to bioengineers, politicians, biotech investors, and desperate patients, and involves a bevy of ethical, legal and religious interests, we can see that this is a scientific area of more than usual fascination.

What is a stem cell?

A *stem cell* is a cell that can both reproduce itself and generate offspring of different functional cell types. To understand what this means we shall start by considering the nature of cells. Cells are the ultimate structural unit of an animal or plant body. Each has a *nucleus* containing the genetic material (*DNA*), and a *cytoplasm* containing a complex mixture of *proteins* and other sorts of molecule that perform particular biochemical or mechanical tasks. There are about 210 kinds of cell in a human body. Most of them are what we call *differentiated* cells, each type of which has a specific function and a particular appearance when viewed down the microscope. Cells of the liver (*hepatocytes*), of the heart muscle (*cardiomyocytes*), and of the brain (*neurons*), are well known types of differentiated cell. The differentiated type that a cell belongs to depends on which particular *genes* are active in its nucleus. Each gene encodes one specific protein and the repertoire of genes that are active, and thus of proteins that are produced defines the type of the cell. The term *gene expression* is used to describe the production of proteins from active genes. The complete set of genes present in the cell nucleus is called the *genome*, and to a first approximation the genome is the same for every cell in the body. An undifferentiated cell is one that does not have any obvious specialization of *gene expression* and has a bland generic appearance down the microscope. But just because you cannot see specialization this does not mean that it does not exist. Most undifferentiated cells are specialized in some way, especially in terms of restrictions into what other types of cell they can become. Undifferentiated cells are found in the *embryo*, where they develop into various types of differentiated cells in the course of time. They are also found in some cancers, where they tend to be bad news because of their capacity for unrestricted growth. Undifferentiated cells are sometimes, but by no means always, stem cells.

There is a fairly good consensus on the definition of stem cells given above. This comprises just two properties: they are cells that can reproduce themselves, and they can also generate daughter cells that become differentiated cells (Figure 1). Examples of differentiated cells arising from stem cells are those of the skin, the blood, and the lining of the intestine. Consider the skin as a familiar example. Its outer layer is called the epidermis and is composed of cells called keratinocytes. The top layer of cells of the epidermis are worn away every day, and our skin persists as a functional tissue because new cells are being created continuously in the lowest layer of cells. This basal layer contains the stem cells of the epidermis. When they divide, about 50 per cent of their progeny remain in the basal layer as stem cells and the others divide a few more times and then enter a programme of maturation to become keratinocytes. As they mature they move up through the layers of cells that comprise the epidermis. They start to activate new genes and to make proteins including large amounts of fibrous proteins called keratins which give the skin its desirable properties of flexibility, strength, and impermeability. Eventually the epidermal cells die and become flat discs largely composed of keratin. It is these dead cells that are constantly being rubbed away from the exterior of our skin.

The epidermis is an example of a *renewal tissue*, one whose cells are continuously being renewed by cell division throughout the life of the organism. Renewal tissues could not exist without stem cells, and the best characterized types of stem cell are those responsible



1. The concept of a stem cell. The stem cell renews itself and generates differentiated cell progeny. The immediate progeny of a typical tissue-specific stem cell will be transit amplifying, or progenitor, cells that divide a finite number of times before differentiating. Often, but not always, the stem cell generates more than one type of differentiated cell

for tissue renewal. They are often called *tissue-specific stem cells* to reflect the fact that each type of stem cell is responsible for making the cells of its own particular tissue and no other.

The structure of a renewal tissue always contains some form of microenvironment—called a *niche*—that is favourable for the persistence and function of the stem cells. For example, epidermal stem cells are associated with projections (papillae) from the base layer (dermis) in the skin; intestinal stem cells are associated with granule-containing Paneth cells at the base of tiny pits within the intestine (know as crypts); and blood-forming (*haematopoietic*) stem cells are located in the bone marrow, associated with bone cells or blood vessels.

Stem cells are by no means the only dividing cells in the body. Embryos, young organisms, and renewal tissues of adults all contain many other dividing cells that do not persist indefinitely and become some other cell type after a few cell divisions. These are called *progenitor* cells, or specifically in renewal tissues, *transit amplifying cells.*

The properties of the renewal tissues enabled the original definition of stem cell behaviour in terms of the ability to self-renew and to generate differentiated progeny. But the most famous stem cell of them all is now the *embryonic stem cell (ES cell).* In one sense, the ES cell is the iconic stem cell. It is the type of stem cell that has attracted all of the ethical controversy, and it is what lay people are thinking of when they refer to 'stem cell research'. But ironically, the embryonic stem cell does not exist in nature. It is a creature that has been created by mankind and exists only in the world of *tissue culture*: the growth of cells in flasks in the laboratory, kept in temperature-controlled incubators, exposed to controlled concentrations of oxygen and carbon dioxide, and nourished by complex artificial media. Cells grown in culture are often referred to by the Latin phrase *in vitro* (in glass, since the relevant containers used to be made of glass) and distinguished from *in vivo* (inside the living body).

ES cells do satisfy the basic definition offered above: they are undifferentiated cells that can divide without limit; and they can also produce functional differentiated cells, probably all the cell types that are normally found in the body. ES cells originate from cells that lie within the early embryo. The reason that their *in vivo* counterparts are not regarded as true stem cells is that in normal embryonic development they will soon develop into other cell types, so, unlike the basal layer epidermal stem cells mentioned above, they do not remain the same for more than a few days. But *in vitro*, in the culture flask, they really are stem cells because they can either remain the same for years, or can be caused to differentiate to a range of functional cell types. To avoid confusion it is useful always to distinguish clearly between the tissue-specific stem cells, such as those in the epidermis, and the *pluripotent* stem cells, which comprise the embryonic stem cells and also the *induced pluripotent stem cells* (*iPS cells*) which closely resemble them.

The term *pluripotent* will be used a lot in this book. It means the ability to form any of the cell types found in the normal body. Tissue-specific stem cells are not pluripotent as they are able to form only the cell types of one tissue. They are sometimes described as multipotent when the tissue contains many cell types (like the blood), or unipotent if there is only one (like the sperm-forming stem cells of the testis).

Another term that will frequently be encountered on websites and in ethical debates is *adult stem cell*. This is not so much a biological term as a political one. It refers to anything that might be considered a stem cell but is not an embryonic stem cell. So tissue-specific stem cells and iPS cells are both counted as adult stem cells although they are completely different in their properties, and in fact iPS cells closely resemble ES cells. In addition, various ill-defined cells in culture are referred to as 'adult stem cells' even though they may originate from parts of the placenta, the umbilical cord blood, or juveniles, as well as from adult human beings.

Philosophically inclined readers may have noticed that the definition of the stem cell I have introduced, which is generally accepted among biomedical scientists, involves defining a behaviour rather than an intrinsic state. In other words we cannot identify a stem cell as being a particular sort of 'thing', we can only identify it by observing what it does. This is a real practical issue and not just a philosophical one. Many scientists have attempted to find genes whose expression is characteristic of all types of stem cell, but so far this endeavour has proved unsuccessful, except in the trivial sense that the genes required for cell survival or cell division are necessarily active in stem cells. In particular, the genes known to be responsible for the pluripotent behaviour of

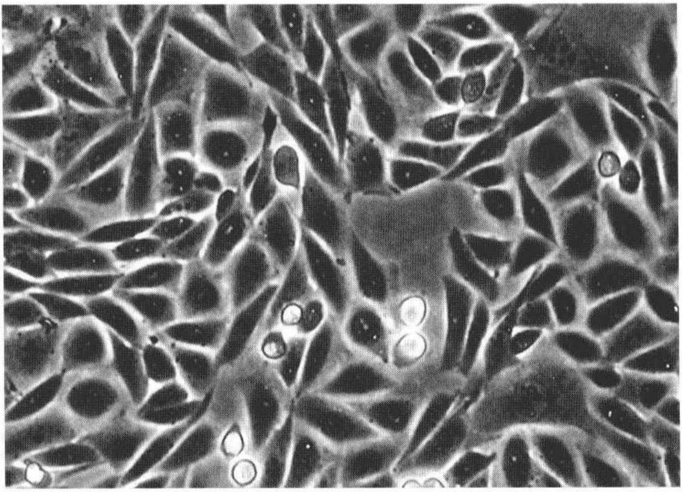
ES cells are not normally active in tissue-specific stem cells. So we are stuck with the fact that we can only define stem cells by their behaviour, and that the best known type of stem cell, the embryonic stem cell, is a human-created artefact rather than an entity belonging to nature.

Tissue culture

As implied above, the technology of tissue culture, also called cell culture, is absolutely central to stem cell biology and so its characteristics need to be introduced. Tissue culture means growing cells outside the body, in tubes, dishes, or flasks filled with artificial media.

The first crude methods for keeping animal cells alive *in vitro* were introduced by embryologists in the late nineteenth century and were refined particularly by Alexis Carrel, a French scientist who worked in the early twentieth century at the Rockefeller Institute for Medical Research in New York (later Rockefeller University). But tissue culture only became widely practiced from the 1950s, when it became possible to purchase the required complex media from biological suppliers, and it became easy to suppress microbial contamination using the newly available antibiotics.

Cells within the body are mostly not dividing and they exist within tissues, usually as communities of several different cell types in close proximity to each other and to blood vessels and nerves. When small pieces of tissue are placed into a tissue culture environment, certain cells will migrate out of the pieces and start to grow, but many others will not, so tissue culture is intrinsically a selective process. Tissue culture cells are normally grown on plastic surfaces where they increase in numbers to form a single layer (monolayer). Once the monolayer is continuous and fills up the whole dish, the cells will usually stop growing. In order to keep them growing they are subcultured by treating with an enzyme



2. Cells growing in tissue culture. These are chinese hamster ovary cells. Each dark shape is one cell

(trypsin) which degrades their attachments to the plastic and allows them to rise into the medium. As a suspension, the cells can be diluted into fresh medium and dispensed into fresh containers where they will reattach and the growth cycle can begin again. Each such subculture is called a *passage*. All manipulations of the cells need to be carried out in special safety cabinets which have a sterile air supply to prevent any bacteria or fungal spores from entering the vessels. Because the cell culture media are highly nutritive, microorganisms will thrive on them and if they manage to enter the culture they will outgrow the animal cells very easily. The culture vessels are usually kept in incubators at 37°C (mammalian body temperature) and 5 per cent carbon dioxide (a level approximating the normal tissue environment).

Tissue culture cells can also be stored frozen in liquid nitrogen (–196°C). Using careful freezing and thawing techniques, they can be stored at this temperature indefinitely and later revived for continued growth.