

What are stem cells?

Stem cells are frequently mentioned in the news. The 2012 Nobel prize for physiology or Medicine was awarded to two pioneers in this field (see the back page). So what are stem cells? Caroline Wood explains.

'Stem cells are cells which individually or as a population can produce differentiated progeny and reproduce themselves.'

Jonathan Slack, embryologist

Some animals such as newts and salamanders are capable of regenerating entire limbs. It was previously thought that these animals had large populations of dormant stem cells. Instead, it appears that cells near the injury site de-differentiate and multiply, forming a structure called the repair blastema. Cells of the **blastema** then redifferentiate to reform the lost limb. The blastema is key to the regeneration process – if it is

transplanted to a different site, the limb will form at the new position.

Animals that show regeneration can produce blastemas from mature tissue because they are able to switch off gene regulatory programs that keep cells in a differentiated state. When the equivalent pathways were silenced in mice (using a technique called RNA Interference), cells began to divide and proliferate. Greater understanding of the regeneration process may one day enable humans to regrow their own limbs or even heads!! ... Who knows? But for the time being, our understanding of the development and differentiation of cells, and how this knowledge may be used to treat medical problems, is advancing quickly.

Key words

stem cell
differentiation
regeneration
DNA

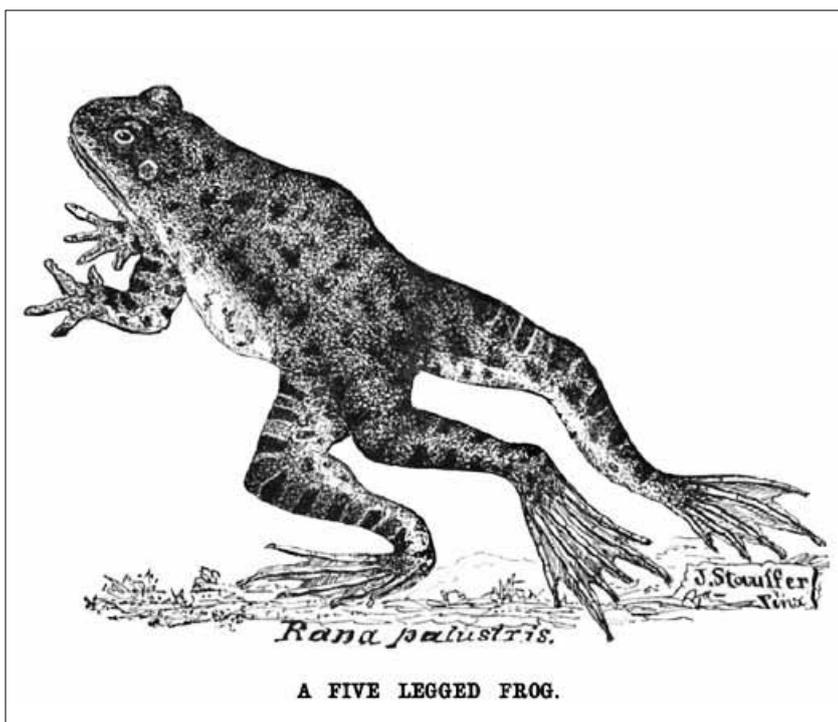
Definitions

Differentiation: the process in which a cell (or other unit) changes into a specialised kind.

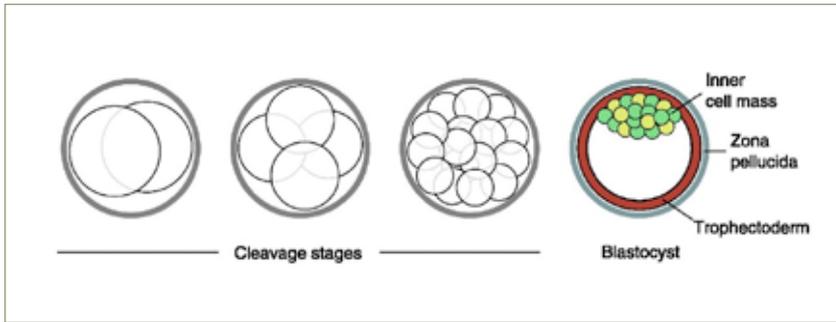
Potency: the range of developmental pathways in which a stem cell can differentiate.

Mesoderm: one of the three primary tissue layers which form in the embryo, whose derivatives include muscle, bone, cartilage and connective tissue. The other primary tissue layers are the ectoderm and the endoderm.

Antigen: any substance which binds to antibodies and causes an immune response.



A parasite sometimes forms cysts on a tadpole and this stimulates the 'regenerating limb tissues' to grow another leg. In this example, the extra foot has an extra toe. This illustration appeared in 1879, so it's nothing new.



Mammalian eggs are fertilised by sperm to produce a zygote. This divides symmetrically, producing 2 cells, then a 4-, 8- and 16-cell structure. Each of these divisions produces 2 new totipotent stem cells, causing an exponential increase in cell number. At the 32-cell stage, the blastocyst is formed. This is composed of the zona pellucida (a protective outer glycoprotein membrane), the trophoectoderm, which contributes to the placenta, and the inner cell mass, which forms the embryo proper. Embryonic stem cells can be harvested from the inner cell mass.

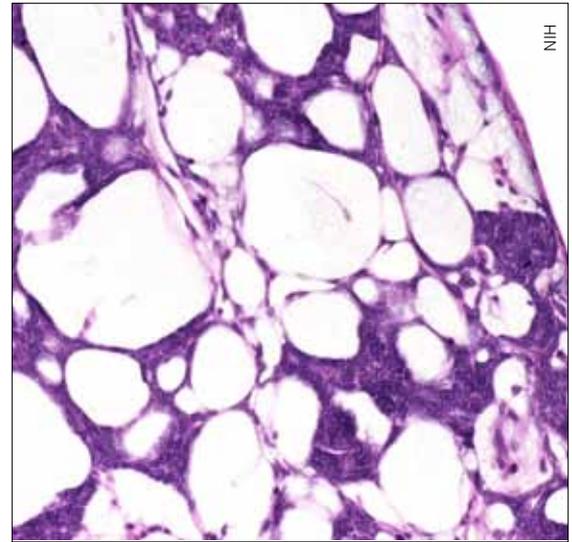
Stem cells

Stem cells can be classified into two main types: **adult stem cells** and **embryonic stem cells**. Adult stem cells include hematopoietic (blood cell making) stem cell precursors, which form all the cells of the blood, and populations that divide constantly to renew lost tissue such as the skin. These cells vary in their potency – their ability to form different cell types. Gastrointestinal cells, for example, are described as quadri-potent as they can form four different cell types: mucous, neuroendocrine, Paneth and absorptive. There are also reserve ‘satellite’ populations of stem cells, in the muscles for instance, which remain dormant until tissue damage occurs. These are unable to repair progressive damage, however, such as that which occurs in muscular dystrophy.

When adult stem cells divide, two daughter cells are formed. One of these remains a stem cell and the other loses potency to form a terminally differentiated cell. Therefore, the number of stem cells remains constant. It is currently unclear how one cell becomes committed to differentiating, although there are several competing theories.

Embryonic stem cells

The other class of stem cells are Embryonic Stem Cells (ES cells) which are described as totipotent; this means they can form any cell type in the body. ES cells form from the first divisions of the newly fertilised egg (zygote); each division forms two ES cells causing the number to increase exponentially – see the diagram. This forms a structure called the **blastocyst**; this is made up of the inner cell mass (ICM) which forms the embryo proper, and an outer layer, the trophoectoderm, which produces the placenta. During later divisions, ES cells begin to differentiate and lose potency, eventually forming terminally differentiated cells. ES cells are obtained from the inner cell mass; this is removed from the embryo and plated onto a feeder layer of cells, which supplies the physical scaffold and nutrients necessary for stem cell survival.

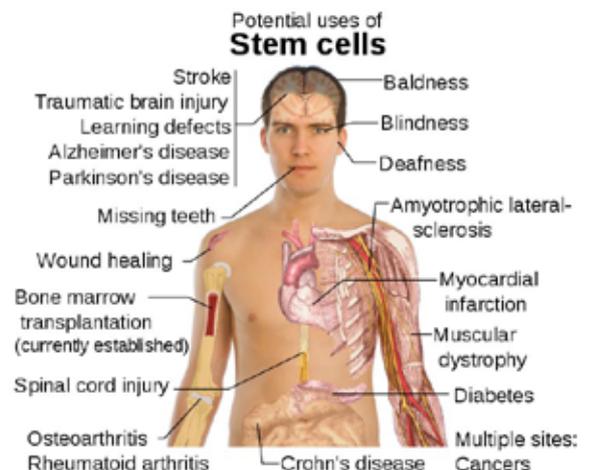


Blastema cells

Therapeutic applications

The ability of embryonic stem cells to form any other cell type gives them the potential to treat diseases caused by tissue loss or damage. During a heart attack (myocardial infarction), oxygen delivery to the heart via the bloodstream is cut off, causing death of cardiac tissue. Normally this damage is not repaired leading to scarring and loss of function. Many research groups are investigating whether new heart tissue could be generated by stem cells injected into the damaged site.

In one experiment, two groups of sheep were made to experience heart attacks, one of which then received an injection of 30 million mouse ES cells into the heart with the other group acting as a control. A month later, the hearts of the sheep who had received the injection were found to be 15% more efficient than the control group. Specific mouse cell markers indicated that the injected cells had themselves contributed to the new heart tissue. It is thought that injected ES cells respond to cues from the surrounding host environment, prompting them to differentiate into supporting tissue.



Medical problems which may find treatments using stem cells

However, simply injecting ES cells carries the risk that the undifferentiated cells may form tumours or differentiate into other cell types. For some treatments, researchers are investigating ways of manipulating ES cell differentiation in culture before injecting them, to ensure the correct cell types form.

An example is Type 1 Diabetes, an auto-immune disease which destroys insulin-producing beta cells of the pancreas. Current treatment involves daily insulin injections and/or a whole-organ pancreas transplant; if ES cells could be coaxed into forming insulin secreting cells, this may become unnecessary. In one method, mouse ES cells were treated with a solution containing a section of DNA that carried the gene for producing insulin linked to an antibiotic resistance gene. The cells were then exposed to the antibiotic to determine those which had successfully taken up the DNA. The cells were cultured under increasing concentrations of glucose; this allowed those which responded by producing more insulin to be selected. When these cells were injected into diabetic mice, their symptoms reduced significantly. Methods of directing human ES cells to differentiate into insulin-secreting precursors are now being investigated and offer hope for the estimated 2.6 million diabetes sufferers in the UK.



A typical newspaper headline introducing an article on trials of stem cell treatments

Mesenchymal stem cells

The use of human ES cells presents many ethical concerns because they are usually collected from spare embryos from IVF. Many people are undecided as to when life begins and are uneasy about using cells from embryos. Some people believe that life begins at the moment of conception, the point of fertilisation. For them, the destruction of an embryo to harvest stem cells could be equivalent to murder. A more practical consideration is that ES cells may form cells displaying antigens which prompt an immune response.

These problems may be avoided in future by using mesenchymal stem cells (MSCs): adult stem cells present in the bone marrow. These can form various cell types, such as bone, cartilage and fat cells. They have shown to be capable of replacing lost tissue in simple injection experiments, including bone tissue in rats whose femurs were removed. In humans, they have been able to reverse the symptoms of Systemic Osteopenia, a

debilitating disease caused by deformed Type 1 collagen. In one experiment, affected infants who received a transplant of MSCs showed increased bone mineral content and a significant reduction in fractures.



This X-ray shows the thin bone structure in the deformed hand of someone with Systemic Osteopenia, a disorder which may be diminished by stem cell therapy.

Scientists are also developing methods to form specific cell types from cultured MSCs. Grafting MSCs onto honeycomb structures made from ceramic material (mimicking the natural bone environment), causes them to form bone cells (osteocytes). This means that a person's own bone marrow could act as a supply of stem cells for growing certain tissues in case of damage. This also avoids the possibility of immune rejection, as the cells would be from the patient themselves. MSCs have already been used to construct windpipes after being cultured onto scaffolds made from donated tracheas or artificial material. These have been successfully transplanted into lung cancer patients. The future offers many exciting possibilities for treating disease using tissues and organs developed in this manner.

The future: induced pluripotent stem cells?

Recently, it was announced that adult differentiated cells could be de-differentiated into an embryonic-like state by forcing the cells to express certain genes. These cells were called induced pluripotent stem cells (iPSCs). They have been shown to be capable of differentiating into cells of all three primary tissue types yet their developmental capacity is currently unknown. It is hoped that they may be useful tools for developing drugs or for organ transplantation.

Caroline Wood is an undergraduate student currently studying Cell Biology at Durham University. She hopes to have a career in biological research.