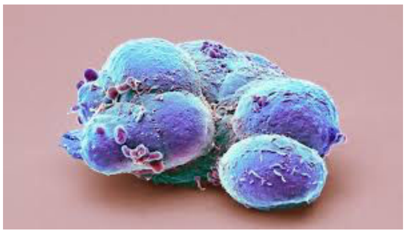

Stem Cells in Medical Technology
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Major ethical and scientific debates surround the potential of stem cells to radically alter therapies in health care. This article provides some basic background on the origins and functions of stem cells.

The stem-cell debate

I am writing this article as I wait for a flight at the George Bush International Airport in Houston, Texas. This in itself is not a remarkable event, but it comes just a few hours after attending a debate about the role of stem cells in regenerative medicine. The airport was named after George Bush the first, but of course it is George Bush the second who is having a significant effect on the general stem-cell debate with the uncompromising position that United States (US) federal funding should not be used for embryonic stem cell research. Many US scientists, including large numbers in Texas, are deeply unhappy about this situation because stem cells, and especially embryonic stem cells, have enormous potential for use in cell therapy and tissue engineering.

It is probably helpful at this point to deal with the ethical issues. There is no doubt that currently embryonic stem cells can only be derived from embryos that cannot survive the process by which the stem cells are gathered. In reality, the main source of embryos for this purpose will be the excess produced during in vitro fertilization treatments. Bioethics is concerned with the philosophical debate around issues of life and death where there are obvious, and often polarized, views, and where there is no clear right and wrong. The argument to ban stem-cell research is based on the premise that the gathering of embryonic stem cells involves the termination of life and that any individual has the right to believe that it is morally wrong to deprive life under any circumstances. If the person making the decisions is of that view, then a ban will prevail. However, any argument about ethics, as with life in general, should be taken to its logical conclusion and not stop half way through the analysis. If therapies involving stem cells have a realistic chance of saving many lives and increasing the quality of life for countless millions, is it right to save the lives of a few unwanted embryos and to deny the benefits of quality and quantity of life to potential recipients, who include sufferers of cystic fibrosis, Parkinson's Disease and many other conditions? As many US colleagues will appreciate, it would be morally reprehensible to allow US citizens to benefit from embryonic stem cell therapies that are based on research conducted by non-US citizens in other countries, or worse, to benefit from embryos that are derived in other countries.

What is obvious from so much of the debate is the lack of understanding of what stem cells are and what options we have concerning the sources and manipulation of stem cells. Some of the basic principles are set out in this article, with special reference to the potential use of stem cells in therapies that involve medical device technology.

The stem cell defined

Let us start at the beginning. A stem cell is a cell that has the ability to divide indefinitely (that is, to self-replicate) and, usually, the potential to differentiate into mature specialized cells. This point is worth emphasizing, because it implies that these cells can keep on self-replicating throughout the life of an organism and at any time, subject to receiving the right signals, can develop into mature cells that have their own characteristic shapes and functions, including those that are essential for critical physiological functions such as nerve cells and the cardiomyocytes that control heart function. This is the promise driving the research in this area. Bearing in mind that adult humans have largely lost the ability to repair themselves when diseased or injured by means of the regeneration of specialized tissues, these stem cells provide the glimmer of hope of functional self-repair.

Now let us move on to discuss where these stem cells reside, how we can influence their distribution and function, and then use them to our benefit. It was noted above that stem cells usually have self-replication and differentiation functions. Those that have this dual universal property are called pluripotential stem cells. There are a few stem cells, known as unipotent cells, that can only differentiate along one lineage; these are not discussed further here. Of particular importance in the concept of pluripotency is the fact that this type of cell can give rise to cells associated with all three embryonic germ layers: the mesoderm, endoderm and ectoderm. They can in theory regenerate tissues based on all of these highly different cell types, including those of the brain, skin, lung, pancreas and so on. It should be said in passing that it is not a straightforward matter to recognize a stem cell because it does not have any obvious distinguishing feature. To identify and classify these cells, cell biologists have had to develop a series of criteria, which are largely based on the molecular features of the cell membrane that are identifiable by their reaction with specific markers, and there are still some arguments about their precise features.

Embryonic stem cells

Although there are some other minor variations, we can divide stem cells into two essential types: embryonic and adult stem cells. Embryonic stem (ES) cells are derived from the inner cell mass of a developing blastocyst. A blastocyst is an early form of an embryo, which consists of approximately 150 cells that are produced by the cleavage of the fertilized egg (the zygote). It contains a fluid-filled cavity with this inner cell mass and an outer layer of cells (the trophectoderm), which goes on to become the placenta. Embryonic stem cells are best derived from a blastocyst that is approximately five days old (five days after fertilization); thus, for obvious reasons, these cannot be harvested directly in humans. Instead, they are obtained as a product of in vitro fertilization, in which a day-five embryo is treated by immunosurgery, which breaks down the trophectoderm and releases approximately 30-35 ES cells. Human ES cells are capable of long-term self-renewal and can be cultured for several years with hundreds of populationdoubling sequences. In vitro they also appear to be pluripotent and it is theoretically possible for the purposes of cell therapy and tissue engineering to direct these cells into any one of many different pathways to specific cell types. It is in this arena that the ethical issues arise and there have been significant restrictions on research into this use of human ES cells and on the optimal conditions under which they may be directed towards individual lineages. It should also be said that humans appear to be different from laboratory animals with respect to the manipulation of their ES cells and thus it is difficult to learn much from mice or rats.

Adult stem cells

As far as the technologies of regenerative medicine are concerned ES cells have considerable potential, but we still have a long way to go before they can be used routinely in clinical practice. A couple of biological hazards also remain. ES cells may have teratogenic potential and could give rise to tumors, and their immunological status is uncertain. Therefore, in spite of the considerable potential for ES cells, it is towards adult stem cells that most attention has been paid with respect to clinical developments. An adult stem cell is an undifferentiated, that is, an unspecialized cell, that is found in adult tissue. It can self-replicate to make identical copies of itself over long periods of time, which is why they survive until adult- hood. They also have the ability to mature into specialized functional cells, which provides limited capability of tissue repair. The problem is that adult stem cells are rare. Their most obvious source is bone marrow and even here they may only occur with a frequency of 1 in 10000. Fortunately, techniques such as flow cytometry are now available for cell separation and this scarcity is not a major limitation. It is now also clear that stem cells are found in, and can be harvested from, other tissues. Peripheral blood, which is obviously much easier to obtain than bone marrow, contains stem cells, although probably at only in concentrations of 1 in 100 000. Here, the patient can be given growth factors a few days before harvesting to significantly increase the number of stem cells. There is also a great deal of interest in obtaining stem cells from other tissue sources such as the adipose tissue, which is obtained from liposuction.

Adult stem cells are essentially of two types: hematopoietic, and stromal or mesenchymal. Hematopoietic stem cells are those that differentiate into mature blood cells. They are used following separation from the bone marrow in a number of cell therapy and gene therapy techniques for the treatment of various conditions, including cancer. Mesenchymal stem cells, also known as bone marrow stromal cells, gives rise to cells of other non-hemopoietic tissue such as neural cells, chondrocytes, cardiomyocytes and so on. It is the mesenchymal stem cells that attract so much interest in tissue engineering because they have the potential to cause the regeneration of a wide variety of tissues.

There are two other important basic facts about adult stem cells. The first is that when a stem cell is persuaded, by various signaling processes to differentiate down a line leading to a specialized tissue, it usually does so by generating an intermediate cell type that is committed to this pathway, but which can exist in this intermediate form for some time. These cells are called progenitor cells and they may be used in tissue-engineering processes aimed at specific specialized tissues. Second, adult stem cells appear to have the potential to readily change their appearance and characteristics so that adult stem cells derived from one type of specialized tissue can produce differentiated cells of another type. This process is referred to as transdifferentiation or plasticity, and leads to the possibility, for example, that the stem cells derived from the fatty wastes of liposuction could be manipulated into nerve cells.

Opportunities for stem cells

The great flurry of research activity in stem cells in recent years has raised many questions and offered much hope for new methods of treating serious illnesses. In many ways the ethical arguments over ES cells have overshadowed a number of other issues and to many people, especially in the media, stem cells have become synonymous with ES cells. Hopefully, the above discussion has shown that although ES cells are of extreme importance, the technology exists to harvest and manipulate adult stem cells as well and these are likely to be the front runners in the processes of cell therapy, gene therapy and tissue engineering, which are the three components of regenerative medicine. There are, of course, some significant challenges remaining, especially concerning the manner in which stem cells are signaled during any therapy to ensure they do what we want. Within tissue engineering, this implies a greater knowledge of how the technology of tissue-engineering processes, that is, the scaffolds and bioreactors, can influence these cells in the optimal way.