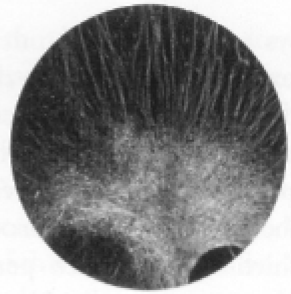

Introduction

WHAT IS A stem cell? We have a basic working definition, but the way we observe a stem cell function in a dish may not represent how it functions in a living organism. Only this is clear: Stem cells are the engine room of multicelluar organisms for both plants and animals. They live in cave-like "niches," surrounded by intricate signals that allow them to divide—either to make more of themselves (self-renew), or to produce a progeny that can go on to make a specific type of tissue. They can often be plucked from this environment and placed in a nutrient broth at body temperature and encouraged to divide, although the niche is generally lost and their characteristics often change.

Historically, the discovery of the microscope by Hans and Zacharias Janssen in 1590 paved the way toward modern stem cell biology. Before this time, the composition of animals and plants was a complete mystery. But with the microscope, cells were finally revealed by Robert Hook in 1655. He surely must have shouted "Eureka!" as he first stared at the strange, hollow, roomlike structures that made up cork! Interestingly, there was a long gap until animal cells were first described by Theodor Schwann in 1839. In 1855, Rudolph Virchow, a great German pathologist, explained the idea that all living things come from other living cells, and thus paved the way for our current definition of stem cells. Around this time, scientists started to take an interest in teratology, or as they described the field "the study of malformations or monstrosities." These were, in fact, the first descriptions of embryonic carcinoma cells, which are primitive stem cells that can make all types of body tissue (hair, bone, and brain along with others) within a single "monstrous" mass. This must have been both frightening and intriguing for 19th-century scientists. But it was E. D. Wilson in his classic textbook *The Cell in Development and Inheritance* who first coined the phrase *stem cell* in 1896 and this term stuck.

Fast forward to the 1950s and perhaps the biggest surge in stem cell science was initiated when bone marrow was first transplanted into irradiated mice and shown to reconstitute the stem cell population. The term *hematopoietic stem cell* was coined and this area of biology dominated the stem cell field for many years, and is still the only proven area of stem cell use in clinical trials. While stem cells were then found in the skin, gut, and other tissues, their characterization always lagged behind the hematopoeitic stem cells that expressed a range of convenient cell surface markers that could be used to sort them. Also, in other tissues, the stem cells were often buried very deep and difficult to remove and isolate. This led to the search for a "universal" type of stem cell, which was eventually isolated and characterized from mouse embryos by Martin Evans, who was awarded the Nobel Prize for Medicine in 2007. These embryonic stem cells from the mouse could divide endlessly in culture, while maintaining the potential to create every tissue in the body.

In 1998, Dr. James Thomson isolated similar cells from human embryos and opened up a Pandora's box of ethical issues along with a fascinating new source of human cells. A year before in 1997, Dr. Ian Wilmut had shown that adult mammalian cells retained all of the genes necessary to produce a whole animal by cloning Dolly the sheep from an adult mammary gland tissue. The adult cell had been reprogrammed back to an embryonic state in the egg. In 2007, Dr. James Thomson in the United States and Dr. Yamanaka in Japan simultaneously discovered that if you took adult human cells they too could be reprogrammed back to an embryonic state by overexpressing powerful stem cell genes. These so-called induced pluripotent stem (iPS) cells were not derived from live embryos and could be generated from any patient, thus removing both the ethical and immunological issues at one time. While some issues remain with iPS cells, they represent the future for cell therapy.

Today, stem cells have taken on an almost mystical quality. Perhaps this is because some stem cells are the master organizers of all living multicellular organisms, giving rise to every tissue in the body. Maybe it is because it is now possible to cure some diseases of the blood system through transplanting adult stem cells into the circulation. Maybe it is due to the fact that many different types of resident stem cell might one day be transplanted from carefully grown cultures or activated within the body to replace diseased tissues leading to cures for the incurable. The stem cell mystique may lie in simply gaining insights into the origins of human development and ailments such as cancer, or being able to model complex diseases of humans and screen novel drugs. Above and beyond the science, there remains an undercurrent of moral and ethical issues associated with creating cell lines through the destruction of living embryos, which perhaps may now be deflated due to iPS cells. However, controversies, breakthroughs, and frustration will continue to swirl in eternal storms through this rapidly moving area of research. But what does the average person make of all this, and how can an interested scholar probe this vast sea of information?

THE ENCYCLOPEDIA

In this wave of advances, and with extensive information available over the internet, you may ask why an *Encyclopedia of Stem Cell Research* is required. Surely, it will be out of date quickly! To this we reply that all of history requires punctuation points. This encyclopedia provides a source for experts to consider what is known and not known; a chance for the public, schools, colleges, and researchers to have access to a synthesis of this broad area in two volumes; for those in regions of the globe where widespread internet is still a distant dream, a chance to educate and enlighten; a chance to learn about who is doing the research and where it is being done; and finally, a chance to understand the basic concepts from A to Z in stem cell biology in simple, clear articles and learn about the politics, ethics, and challenges everyone in the field is currently facing. Of course, the encyclopedia cannot cover all aspects of stem cell biology, but we sincerely hope it will provide a stepping stone to more detailed investigation on a chosen topic.

For stem cell researchers, particularly the novice, the literature is scattered with a patchwork of terminology that clouds all efforts to characterize the stem cell world into neat descriptive words—"stem cell," "progenitor cell," and "precursor" are often used interchangeably. Further complexity comes when comparing embryonic and adult cells, cells in different tissues, and cells from different species. The combinations are endless. For this encyclopedia, the focus is on describing the different types of stem cell that have been reported so far and trying, where possible, to explain for each age, tissue and species what is know about the biology of the cells and their history. We do not attempt to come up with a new terminology, but simply explain what the different areas of this field consider to be stem cells and work from there.

We apologize in advance if your favorite researcher has not been included, or a country with interesting stem cell biology has been left out. This is simply a result of space and time. But we do hope to have captured at least a strong flavor of stem cell biology as it stands today and to have provided the reader with a reference manual to probe the mysteries of the field.

THE FUTURE

Many professionals are involved in stem cells. Engineers are developing new environments in which to grow stem cells; statisticians are producing new algorithms to detect genomic changes as stem cells divide and differentiate; chemists are designing new drugs to modulate stem cell biology; ethicists are debating the meaning of embryonic life; and politicians are working out how stem cells may get them more (or less) votes. While stem cells are exciting alone, they are also clearly fueling the traditional areas of developmental biology and emerging field of regenerative medicine.

It is good to be a stem cell biologist these days. California recently announced $3 billion over 10 years to fund stem cell research, and other states are also stepping up to the plate and funding this science. In some ways, this flow of private and state money has been enhanced by President George W. Bush's refusal to allow federal funding to be used to generate new embryonic stem cell lines from excess human embryos in IVF clinics.

However, there is also a bigger groundswell of support for stem cell research in general. The public feels that eventually stem cells will save lives, not destroy them. Whether this will happen remains to be seen. Stem cells are not miracle cells. Treatments will require robust clinical trials carried out under blinded conditions.

Many of us wait patiently for the first FDA-approved trials in the United States or other well-designed trials in the rest of the world. While seemingly very slow, they are coming. And then we will see.

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