Stem cells at the dawn of the 21st century

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It is rare that a field of scientific research can both have an enormous potential impact on human health and quality of life and be a font of new basic research discovery. Stem cell biology is surely one such field, offering hope for curing scourges like diabetes, Parkinson’s disease, neurological degeneration, and congenital heart disease, as well as bringing together many disciplines of cell and molecular biology. Five years ago, stem cell biology was an exciting but rather restricted area of science with growing basic science and clinical implications. Currently, the existence of stem cells is a matter of public discussion, with religious, ethical, political, and economic implications. A week does not go by without some new revelation, about either the politics or biology of stem cells in the general press. What has changed? Clearly we know more about the biology of these cells, but the public interest has been driven by their potential in the treatment of disease on the one hand and concerns for the ethical implications of their use on the other. Some of the arguments are semantic and can be resolved by making sure that everyone is using the same terms to discuss the topic. Other concerns are theoretical and religious, such as defining when human life begins, and reflect beliefs and philosophies rather than the facts and data that scientists are restricted to when formulating coherent models. Science relies on facts, and many of the extraordinary claims made about stem cells in the scientific and public domain need to pass the important test of independent verification.

Stem cells are loosely defined as self-renewing progenitor cells that can generate one or more specialized cell type. In vertebrates, stem cells have been traditionally subdivided into two groups. The first group consists only of embryonic stem (ES) cells, which are derived from the inner cell mass of the blastocyst and are capable of generating all differentiated cell types in the body (pluripotent stem cells). ES cells in turn generate the second group, which are called organ- or tissue-specific stem cells (multipotent). Such stem cells generate the cell types comprising a particular tissue in embryos and, in some cases, adults. The prototypic example of this second group is the hematopoietic stem cell, which generates all of the cell types of the blood and immune system. In addition to existing in the blood, there are stem cells that survive throughout life in many other organs of the mammalian body. In some tissues, like the intestine and skin, ongoing cellular turnover provides a rationale for the persistence of stem cells. In other organs, however, such as the brain and heart, stem cells are present, i.e., they can be isolated from these tissues, grown in culture, and then induced as the brain and heart, stem cells are present, i.e., they can be for the persistence of stem cells. In other organs, such as the intestine and skin, ongoing cellular turnover provides a rationale for the persistence of stem cells. In other organs, however, such as the brain and heart, stem cells are present, i.e., they can be isolated from these tissues, grown in culture, and then induced to differentiate, either in vitro or after transplantation in vivo. A flurry of studies have reported cell differentiations of blood-to-brain, mesenchyme-to-brain, blood-to-liver, skin-to-brain, brain-to-heart, etc. These findings suggest either that organ-specific stem cells can overcome their intrinsic restrictions upon exposure to a novel environment (“transdifferentiate”), perhaps via genomic reprogramming, or, alternatively, that the concept of developmental restriction in organ-specific stem cells is not firm. In the latter case, there would be essentially no intrinsic difference between organ-specific stem cells and ES cells.

These results have potentially important practical as well as theoretical implications: for example, if adult stem cells can transdifferentiate, the difficulty in expanding certain kinds of stem cells (e.g., hematopoietic stem cells) ex vivo to increase their number could be overcome by substituting stem cells from other tissues that are easier to grow, such as neural stem cells. Conversely, stem cells that are difficult to access for autologous grafting, such as neural stem cells, could be substituted by stem cells that are more easily accessible, such as hematopoietic stem cells. For these reasons, it is very important to determine the extent to which redirected differentiation of organ-specific stem cells to heterologous lineages is possible and applicable.

It remains possible that organ-specific adult stem cells cannot differentiate into functioning cells of another organ, but rather only take on the shape and express some of the proteins characteristic of “transdifferentiated cells.” In all cases to date, this latter alternative remains a viable interpretation. Especially given the recent results, some researchers report in this special issue that “cell fusion” might account for some of the previously reported transdifferentiation. There is no clear demonstration yet that stem cells derived from one organ can transdifferentiate into a cell of another organ and carry out its normal function. If this limitation is true, enormous amounts of effort remain to be applied to learn how to successfully and reliably induce multipotent, lineage-restricted stem cells to become mature, functioning, and appropriately useful cells of their own organ.

In addition to resolving the confusion around definition of terms and the lineage restriction of adult stem cells, many timely topics were covered at the Sackler Symposium. Several talks on human ES cell biology focused on the pluripotent cells of the inner cell mass that can give rise to all cell types of the body. At present, there are only limited numbers of human ES cell lines, and the similarities and differences among different cell lines...
have not been compared. Studies of these cells and of their properties and potentials, as well as comparisons to other mammalian stem cells, will lead to important biological and medical insights, adding to the bulk of information that has been gained and will continue to be gained not only from mouse ES cells but also from stem cells from other organisms.

A second related area of the Sackler Symposium was cloning by nuclear transfer (reproductive cloning). This term refers to the transfer of the genetic information in the nucleus of a somatic cell, like a skin cell, into an unfertilized egg, which can then be induced to give rise to a full organism with the genetic content of the donor of the somatic cells. To date, this process has been most successful in generating large animals like sheep and cows, but is being currently worked out in mice. Alternatively, somatic cell nuclear transfer (therapeutic cloning) refers to an experimental process conducted in a culture dish, where new ES cells are generated to study in culture. The distinction between these two procedures is that reproductive cloning refers to the generation of whole animals, whereas therapeutic cloning refers to the generation of cells entirely in a culture dish. The lack of understanding of the differences between the two is the root of the current confusion and debate around the world. Several presentations helped to provide a clear understanding of the problems and promise of these approaches.

In organizing the symposium, it was our intention to bring together scientists working on stem cells in different organisms to understand some common principles. We also hoped that discussions would lead to more realistic expectations of the fruits of this emerging field of biology. The 21st century, already heralded as the “century of the gene,” carries great promise for alleviating suffering from disease and improving human health. But new and highly experimental technologies have inherent risks and uncertainties. Scientists must find a balance between excitement and eagerness, problem and promise, hope and hype.

The reality is that the timeline of promises made is unpredictable, but the reaction to unfulfilled expectations is predictable.