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VIEW POINT

Neural Stem Cells: The End of the Beginning

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The study of adult stem cells, i.e., undifferentiated cells residing within an organ with the ability to either self-renew or differentiate, is undoubtedly one of the hottest topics in biology today, having captured not only the scientist's interest but also the public's imagination. The concept that cells persist in once considered postmitotic organs represents a paradigm shift that has raised hopes for applications to the fields of transplantation, repair of tissue-induced injury and cancer therapeutics. On the other hand, it has also raised a number of ethical, moral and political issues that have combined to create a very high profile atmosphere where it seems almost every new research finding makes its way into the lay press.

Unfortunately, the speed with which reports appear either claiming some new property of these cells or refuting earlier claims, makes keeping up with just the literature a full time job. Furthermore, the rhetoric surrounding these cells has advanced even faster than the science; thus, one finds political discussions over possible uses of these cells that in reality seem years away from even considering. Such an information explosion creates a need for frequent reviews of the increasing knowledge base so that the average scientist can keep up and help critically evaluate the progress. Such represents the rationale behind the following series of reviews on the neural stem cell.

First, some background. The hematopoietic system is the origin of the classic adult tissue-derived stem cell, and study of its biology can be traced back to the 1960s. It serves as the paradigm for a hierarchical system in which an undifferentiated stem cell gives rise to descendents with progressively narrower differentiation and replicative capacities. While this field matured, it remained unclear for many years whether such cells were also present in organs with much less replicative capacity, such as the brain.

Although it had been reported in the 1960s that proliferative cells persisted in adult mammalian brain, it wasn't until the early 1990s that several laboratories reported that undifferentiated cells with the capacity to become any type of neural cell, including neurons, were isolable from mammalian brain. Because of its implications for the important problems of neurodegeneration and CNS repair, this heralded the beginning of a revolution in mammalian neurobiology that is still ongoing.

So at this point, what can we say about these cells? It seems certain that mitotically active cells persist within the adult mammalian brain within distinct zones such as the subventricular area and hippocampus. It has also been convincingly demonstrated that such cells give rise to interneurons throughout life within the olfactory bulb and hippocampal area. Furthermore, activity within both these areas is sensitive to both environmental conditions and exposure to various cytokines. Finally, these cells can be isolated in vitro and maintained in either an undifferentiated state or induced to undergo differentiation into any of the neural cell types depending on environmental conditions. Thus, in vitro, such cells satisfy the necessary criteria to be called a stem cell.

Several other findings have been reported but remain controversial at this time, including whether birth of new neurons continues in areas other than those mentioned above and whether neuron formation can be induced to a significant enough degree to modify an injury. Another area that has generated quite a bit of controversy is whether the capacity for differentiation extends

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to cell types beyond neural, such as blood and muscle. Finally, the in situ mechanisms that underlie this process remain for the most part to be determined, exemplified by the fact that it is much easier to induce these cells to become neurons in vitro than in situ after transplantation.

The following six pieces were obtained in response to an invitation to write on some aspect of neural stem cells that the author(s) thought was of especial interest or potential. The six articles not surprisingly encompass a wide range of issues of relevance to the neural stem cell in particular, and stem cells in general and touch on a number of important and controversial issues that remain to be resolved in this field. Thus, three address aspects of neural stem cell physiology, relating to the identification of cycling cells in the CNS, how signaling pathways affect their behavior, and how the environment regulates their differentiation. Another article decided to focus on how current advances in neural stem cell biology might impact on our approach primary brain tumors.

Perhaps not surprisingly, two of the reviews address perhaps the most controversial aspect of the neural stem cell (and which is relevant to all adult stem cells): its ability to be induced to differentiate into cell types derived from organs other than which it arises. Such "transdifferentiation" or "somatic plasticity" is at the cutting edge, not only for addressing a number of methodologic and interpretive issues, but also for the sociopolitical ones that have arisen concerning these cells, especially whether this ability will obviate the need to use embryonic tissues clinically.

Generally, new discoveries in biology are greeted with an initial great enthusiasm as everyone rushes to apply them to their particular area of interest. All too frequently, however, this initial enthusiasm is followed by a report or reports that raise questions about the general applicability of the finding. This then results in an almost equally rapid appearance of disappointment and then skepticism about the finding's relevance. Once passions have cooled, however, it becomes apparent that something has in fact been discovered, but that more details and experiments are needed before its true importance can be evaluated. Once enthusiasts and detractors calm down, the field then enters a new more realistic plateau phase from which the true implications can be identified. The study of neural stem cells would seem to be at such a stage. We should expect in the near future that further studies will allow better understanding of their biology and applications to the clinic.