NEURAL CELL
SPECIFICATION

Molecular Mechanisms and Neurotherapeutic Implications
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NEURAL CELL SPECIFICATION

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FOREWORD

The last decades have witnessed a radical change in our views on central nervous system damage and repair. This change is not only due to the emergence of new powerful tools for the analysis of the brain and its reactions to insults, but it also reflects a conceptual change in the way we approach these problems. As an illustration to this development, it is instructive to go back to the proceedings of a meeting at the NIH in 1955 edited by William F. Windle, which summarizes the disillusioned and pessimistic view on CNS regeneration prevailing at the time. While this generation of researchers were well aware of the issues at stake, they felt they had reached the end of the road; the approaches they had pursued had got stuck and the tools available could not take them any further. I can very well imagine that the participants, most of them leaders in the field, left that conference feeling they had heard their field being sentenced to death.

In this perspective, the developments we have witnessed during the last few decades signal no less than rebirth. Research on neural development, damage, and repair is the aspect of neuroscience that has benefited most from the application of new tools and concepts generated by modern cell biology and molecular genetics. The recent revival can be traced back to the first descriptions of the modifiability of synaptic connectivity and of lesion-induced neuronal growth phenomena in the adult mammalian CNS, which emerged in the late sixties and early seventies (Raisman, 1969; Wall and Egger, 1971; Lynch et al., 1972; Tsukahara et al., 1974). This was followed by the demonstration that regeneration, growth, and functional recovery in the damaged CNS can be promoted by transplantation of neural tissue or cells derived from the central or peripheral nervous system (Björklund et al., 1976, 1979; Lund and Hauschka, 1976; Perlow et al., 1979; Richardson et al., 1980; Krieger et al., 1982), and by the discovery of new classes of molecules with potent neurotrophic and neurotropic actions, or growth inhibitory properties in the developing and adult nervous system (Edelman, 1986; Caroni and Schwab, 1986; Barde, 1990; Stöckli et al., 1989). These developments form the basis of some of the most active research strategies for CNS neuroprotection and repair pursued today.

Some of the most exciting future developments in this field will undoubtedly come from the interface between molecular genetics, developmental neurobiology, and neuroregeneration research. The editors of the present volume have been highly successful in capturing some of the central themes in this emerging new interdisciplinary research enterprise. Research on the detailed molecular mechanisms involved in early neural development, covered in some of the most interesting chapters in the book, has opened up exciting new possibilities. Much of the initial work on pattern formation and neuronal specification during early embryogenesis was carried out in Drosophila and other invertebrates. Most remarkably, however, work carried out during the last few years has shown that these families of regulatory genes, many of which code for proteins that act as transcription factors, are highly conserved throughout the animal kingdom. It is likely therefore, that essentially the same molecular mechanisms operate during early development of the nervous system in mammals, birds, fish, and flies. As a
consequence, new families of molecules that are critically involved in the regulation of neuronal diversity and phenotypic differentiation in mammals are currently being unraveled at an amazing pace. In the near future we may thus get at least partial answers to some essential questions, such as the mechanisms by which ectodermal cells decide to become neural precursors; the mechanisms by which early neural progenitors choose to become either neurons or glia; and the mechanisms of differentiation of neuronal progenitors into specific neuronal subtypes.

A second set of equally fundamental questions that are discussed in the book relate to the regulation of cell proliferation, cell death, migration, axonal growth, guidance and specification of neuronal connectivity. These are basic neurobiological phenomena that are critical for our understanding not only of how the nervous system is formed during development, but also for the understanding of degeneration, regeneration, and repair in the adult CNS.

The neurotherapeutic implications of all this (which is my own particular interest) are far-reaching. Indeed, the first applications of these emerging new technologies in clinical trials may not be so distant in the future. Intracerebral transplantation of fetal CNS tissue has already reached the clinical stage. Embryonic neurons and neuroblasts are powerful sources of cells for intracerebral transplantation. They have a remarkable capacity to grow, integrate, mature, and function after implantation into developing or adult injured brains. In particular, transplants of fetal dopamine neurons obtained from the developing midbrain have been shown to reverse many of the neurological deficits seen in animal models of Parkinson's disease, and this approach has been shown to be feasible also in patients suffering from this disease.

However, for the further development of the cell transplantation technique it is essential to find alternative sources of cells, and to find ways to increase the yield and growth capacity of progenitors or neuroblasts obtained from limited amounts of embryonic or fetal starting material. Deeper insights into the molecular mechanisms underlying cell specification, growth, and differentiation, which are leading themes in several chapters in this book, will greatly promote the development of rational cell transplantation and genetic engineering strategies that may ultimately form the basis for efficient new therapies, not only in neurodegenerative diseases but also in conditions of ischemic and traumatic insults to the CNS. According to the figures published by the U.S. Office of Technological Assessment in 1990, some 10-12 million Americans suffer from neurodegenerative diseases, stroke, or traumatic injury of the brain or spinal cord, with an estimated cost for the U.S. society of more than 100 billion dollars in medical expenses and lost income. Since current medicine has little to offer in the way of effective therapy, the search for new approaches to the treatment of CNS damage and repair is clearly of great importance.

The present volume is an excellent introduction to some of the most interesting current developments and the remarkable progress that is being made in this exciting field. For those readers who are about to explore the many interesting chapters in the book I can promise most stimulating reading. When you are finished, I may suggest you acquire a spare copy of Windle's 1955 book to be placed next to this one. Together they will tell you that 40 years of research can make a difference.

Anders Björklund
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