Paediatric brain tumours: an embryological perspective

Introduction

Primary tumours of the central nervous system are the most common type of solid tumour in childhood and constitute a significant cause of mortality and acquired neurological disability. The most common histological types are astrocytic and primitive neuroectodermal [21]. Among the primitive neuroectodermal tumours medulloblastomas are the most common type. This review will focus on medulloblastomas to illustrate the value of embryological studies as a source of ideas and molecular markers for the study of ‘embryonic’ tumours. Treatment strategies for such tumours include surgical excision, radiation therapy and chemotherapy. In the last two decades survival rates have been static [30]. There is significant late morbidity from treatment, and especially from radiation therapy, which can produce neuro-psychological deficits [10], neuroendocrine dysfunction [24] and second tumours [28]. A compounding problem is the difficulty of assessing the prognosis in any one case, as apparently identical tumours can behave in totally different ways. Conventional clinical, radiological and histological features are often unhelpful. Accordingly, many patients, especially those with primitive neuroectodermal tumours, receive dangerous and damaging therapies that may not be necessary. There is therefore a need to develop treatment strategies that are ‘brain-sparing’ if lifelong morbidity amongst survivors is to be reduced.

In order to improve the prognosis for these patients, we need to improve our understanding of the biology of these tumours so that we are better able to assign patients to high- or low-risk groups. If this were possible then it would be feasible to design less aggressive post-operative therapy regimens (with a concurrent decrease in the negative consequences of such treatments) for the former group of patients, whilst more aggressive or experimental strategies could be used on those patients for whom current treatments are known to be relatively ineffective. A better understanding of the tumours might also provide the basis for design of new therapeutic strategies.
The current lack of understanding of primitive neuroectodermal tumours (PNETs) is largely due to our poor knowledge of the normal cells from which they are derived. These tumours appear to arise from the most primitive neuronal precursors, which are normally only present in the brain as it develops up until the end of the 1st year of life. However, a variety of more differentiated cells are also often seen in these tumours [3]. Most analysis to date has focused on molecules normally found in the differentiated cells or those found in all primitive neuronal precursors. Few studies have developed molecular markers that allow the primitive neuronal precursors to be divided into groups with different behaviours. One argument for the lack of success in identifying useful markers is that the cells which underlie the outcome for these tumours are those which are still classified as primitive (the more differentiated cells which they produce being much less relevant to outcome). One must therefore identify variation within the primitive neuronal precursors to find the molecular changes which cause a tumour to be more or less aggressive. It is only recently that studies of normal neurogenesis in embryos have begun to determine stages in the development of neuronal precursors prior to the expression of markers of differentiation. Therefore, suitable molecular markers for the study of the primitive neuronal precursors within primitive neuroectodermal tumours are now becoming available.

In this paper we will discuss recent advances in understanding of the molecular events of normal neuronal development. Those molecules implicated in regulating key transitional events which are also likely to be of importance in the biology of tumours, such as initiation of migration, will be considered. Experimental approaches will be described which have demonstrated the potential usefulness of this wide range of molecules in understanding the biology and behaviour of medulloblastomas. Finally, we will consider some of the problems associated with carrying out molecular studies on this class of tumour.

### Normal neurogenesis

During prenatal and early postnatal life, neurons are continuously produced from proliferating precursors in the germinal regions of the central nervous system (CNS). No matter where in the nervous system this occurs, individual neurons appear as a result of a similar, but complex, set of molecular events (reviewed in [2, 4, 6, 23]). Many components of the regulatory machinery which control progress of neurons through these early steps of their development have been identified in recent years. (A simplified scheme of these events is described in Fig. 1.)

Initially the CNS is made up of a proliferating neuroepithelium. As development proceeds individual cells cease proliferation, migrate and differentiate. A key question in understanding CNS development is how this process is regulated so that, at any given time, some cells exit from the cell cycle, whilst cells continue to divide in sufficient numbers to generate enough neurons in the mature CNS. This appears to be controlled by a process termed ‘lateral inhibition’, whereby differentiating cells