Research Briefings
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Molecular mechanisms of brain development

Research in our lab is aimed at unraveling the molecular mechanisms that govern the development of the mammalian brain during embryogenesis. In particular, we are interested in how transcription factors and intercellular signaling molecules interact to regulate brain development. Our research may help us to understand how certain human birth defects arise and could shed light on the origins of certain paediatric tumours, such as medulloblastomas.

Development of the Forebrain
The mammalian brain is an extraordinarily complex structure, containing vast numbers of neurons, which must form precise patterns of connections for the brain to function correctly. The brain contains a number of different regions, such as the cerebral cortex or the cerebellum, each of which has a specific function. All of the different types of neurons and glia found in the adult brain are derived from a relatively simple sheet of cells in the early embryo. This simple structure must grow to give rise to precise numbers of neurons, of many different subtypes. Many newborn neurons must move considerable distances away from their birthplace to reach their correct destination. They must adopt appropriate fates and must make appropriate connections with neuronal partners, often over considerable distances. In the case of the mouse, all of these processes occur over just a few days, under the control of genetic pathways. In recent years, key members of these genetic pathways have been identified, and sophisticated technologies have been developed that allow us to investigate the normal functions of regulatory genes using genetically modified mice. Many of the important regulatory genes identified so far encode intercellular signalling molecules, which allow cells to communicate with each other; or transcription factors, proteins that bind DNA to regulate the expression of other genes.

Transcription Factors in Forebrain Development
Many transcription factors have been found to play crucial roles in regulating brain development. In our lab, we have concentrated on the activities of three such factors, Foxg1, Gli3 and Pax6. Mutant mice lacking

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Figure 1. Immunofluorescent staining of the ventral telencephalon of a Foxg1+/--Foxg1+/+ chimaera. Foxg1-- cells, marked by expression of a lacZ reporter (red) fail to express the ventral telencephalic marker gene Nkx2.1 (green). Nkx2.1 is expressed at normal levels by their wild type neighbours.
any of these genes have severely abnormal brain development. Studying such ‘null’ mutants can tell us a lot about the normal functions of the mutant genes. However, they often have very severe phenotypes, which arise as a result of both primary and secondary defects (secondary defects arise as a consequence of primary defects, rather than as a direct consequence of the loss of the mutated gene). To get around this issue, we use tissue-specific gene targeting (cre-loxP), which allows us to inactivate specific genes in a particular tissue and at a particular time.

**CHIMAERAS**

Chimaeric mice containing a mixture of wild type and mutant cells can be particularly useful to study the actions of transcription factors during brain development. For example, Foxg1<sup>−/−</sup> null mutants completely lack a ventral telencephalon and can therefore only yield a very limited amount of information about Foxg1’s normal role there. However, in Foxg1<sup>−/−</sup>↔Foxg1<sup>+/+</sup> chimaeras, the wild type cells are able to form a morphologically normal ventral telencephalon and by examining the behaviour of mutant cells in the chimaeric telencephalon, we can learn much more about Foxg1’s role there. In this way, we found that ventral telencephalic cells require Foxg1 for normal proliferation and to adopt correct fates. Human FOXG1 is implicated in some cases of the human neurodevelopmental disorder Rett Syndrome.

**CAN DISRUPTED DEVELOPMENT LEAD TO TUMOUR FORMATION?**

Some types of brain tumours found in children are thought to arise when signalling pathways involved in regulating brain development go awry. We are interested in how one such type of tumour, medulloblastoma, arises. Medulloblastomas arise in the cerebellum, and are the most common type of brain tumour in children. Loss of the tumour suppressor gene Adenomatous polyposis coli (Apc, a component of the Wnt signalling pathway) can contribute to the development of medulloblastoma. We are using tissue-specific gene targeting to explore the role of Apc in normal cerebellum development and medulloblastoma.