The cerebellum and autism

DR ALBERT BASSON

Dr Albert Basson of King's College London, UK, discusses his groundbreaking study which sheds light on the various regulatory mechanisms at play during the development of the mammalian cerebellum, and the relevance of this exciting research to autism and CHARGE syndrome

Firstly, could you outline the objectives and context of your research?

The broad aim of our research is to study the regulatory mechanisms that ensure that the expression of developmental genes and the activity of signalling pathways that control cell fate and organ development are maintained at appropriate levels. Deregulated gene expression and signalling can result in a range of birth defects. We use mouse models of human syndromes to investigate the causes of these defects in the hope that understanding the underlying mechanisms might help develop potential therapies in the future.

What are you currently investigating?

Over the last few years, we have been investigating the regulation of signalling pathways activated by a group of growth factors called the fibroblast growth factors (FGFs). FGFs are used repeatedly in many development contexts and also play important roles in the adult organism to control stem cell homeostasis and regeneration. Our work has shown that the level of FGF signalling has to be tightly regulated to ensure normal development and homeostasis; too much FGF signalling can be just as harmful as too little.

Many conditions that affect child behaviour and learning are neurodevelopmental in origin, ie. they result from abnormal brain development during gestation and the first few years after birth. A major objective of our current research is to understand how defects during development of the cerebellum are linked to the development of autism. We are particularly interested in the epigenetic mechanisms that control gene expression during different stages of cerebellar development, and our research is focused on a group of factors called chromodomain DNA helicase DNA-binding factors (CHDs) that fine-tune gene expression levels by altering chromatin structure. These factors have been implicated in autism, but the underlying mechanisms whereby mutations in CHD genes might cause autism are not known.

Could you explain CHARGE syndrome and the role of CHD7 in the occurrence of this genetic disorder?

CHARGE syndrome affects the development of many organs, including the eyes, ears, heart and cardiovascular system, genitourinary system and the brain. A significant proportion of children diagnosed with CHARGE syndrome shows signs of autistic behaviour. Around 60-70 per cent of CHARGE patients have mutations in the CHD7 gene. Our recent research has identified critical roles for CHD7 in the development of the cerebellum and we are actively exploring the possibility that these defects might predispose an individual to autism. We are in the process of identifying the genes that are deregulated in the absence of CHD7 to better understand how CHD7 deficiency results in brain defects, intellectual disability and autistic symptoms.

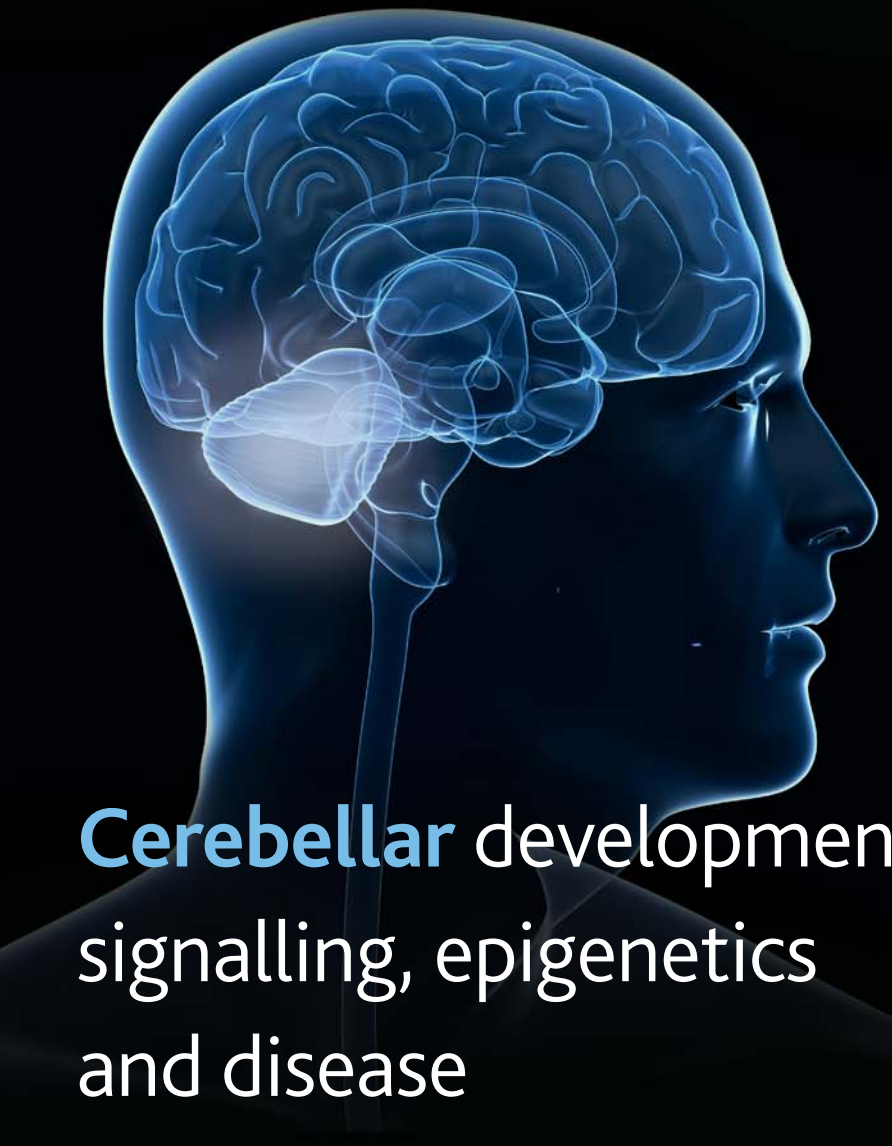
Is collaboration, both among members of the Basson Laboratory and specialists outside the lab, an important element of the development of your research?

Absolutely. Although different members of the lab have their own specific interests, collegiality is very important and we work together as a team; collaborations with experts outside the lab are key to our success, and also make science a lot more fun. My scientific career started in immunology, and with the help of numerous colleagues and experts who have selflessly given up their time to share their expertise, my transition to the field of developmental biology has been a thoroughly enjoyable one. Now that our research is moving into the areas of epigenetics and autism, we will rely again on the assistance of colleagues with expertise in those areas. Later this year, I hope to learn a lot during a six month sabbatical in the laboratory of Professor Danny Reinberg at New York University, who is a leader in the epigenetics field.

Are there any particular successes you would like to highlight from your research so far? Where do you see your work going in the future?

I am still very proud of the first paper on Sprouty1 we published from my post-doctoral work in Professor Jonathan Licht's laboratory at Mount Sinai School of Medicine. Not only was this our first foray into developmental biology, but it was the first paper describing a loss-of-function mouse model for investigating the many functions of these important signalling regulators. I think the work we are doing in collaboration with Dr Andrew Brack at Harvard University in the US on the role of Sprouty genes and FGF signalling in adult muscle stem cells is very exciting. We are now extending our interest in adult stem cell function by investigating the epigenetic mechanisms that control stem cell behaviour in the adult brain.

Finally, I am hopeful that we will be able to secure grant funding to take forward the many interesting leads we have on the role of CHD proteins in cerebellar development and autism. With an incidence currently estimated to be around one in 110, autism is one of the most prevalent genetic diseases, and understanding the developmental basis of the condition is a hugely important challenge.



By manipulating the levels of FGF signalling during brain development in mice, Basson's group has identified a specific region of the cerebellum, the vermis, which is particularly sensitive to reductions in FGF signalling

Cerebellar development: signalling, epigenetics and disease

A new project led by a team at **King's College London** is bringing greater understanding of the underlying causes behind a range of congenital conditions; an effort that may take researchers decades to complete

RECENT YEARS HAVE seen considerable advances in the area of biology known as epigenetics, the study of heritable changes in gene expression. Epigenetic processes, which, by definition, operate at a level over and above that of the genetic code contained in every specialised cell of the body, are at the heart of such phenomena as cellular differentiation during morphogenesis; embryonic stem cells have the potential to develop into any of the hundreds of different types of cell found in the adult human body, and this remarkable functional diversity is achieved and maintained by the epigenetic mechanisms which determine whether, and when, a gene is switched on or off.

Undifferentiated stem cells adapt to a specific fate through the timely activation or inhibition of different genes, in response to signals from the microenvironment, which often take the form of secreted proteins such as fibroblast growth factors (FGFs). These proteins have been found to play an important role in the development of many organs, including the cerebellum, as well as in vital processes like stem cell homeostasis and regeneration in the adult organism.

Located in the anterior hindbrain, the cerebellum is responsible for coordinating fine motor control and also plays a role in cognition. The development of the cerebellum has been the subject of much study over the past decade. Cerebellar defects can result in ataxia, and cerebellar hypoplasia is associated with many significant neurodevelopmental disorders, including autism. It has been shown that FGF ligands produced by the isthmic organiser coordinate the formation of the cerebellum and midbrain, and whilst observations indicate that midbrain and cerebellum development require different levels of FGF signalling, until recently, very little was known about the extent to which specific regions within these two parts of the brain differ in their signalling requirements during embryogenesis.

SPROUTY GENES

One of the main goals of researchers in the laboratory of Dr Albert Basson at King's College London is to understand how FGF signalling is regulated during the development of the mammalian cerebellum. By manipulating the levels of FGF signalling during brain development in mice, Basson's group has identified a specific region of the cerebellum, the vermis, which is particularly sensitive to reductions in FGF signalling.

Rather than focusing on genes that encode FGF ligands, much of the team's work in recent years has centred on Sprouty genes, which encode feedback antagonists of FGF signalling. Originally identified in fruit flies, these genes are critical intracellular regulators of receptor tyrosine kinase signalling, and the Basson laboratory team found that very tight control of FGF signalling levels is required for the normal development of the cerebellum.

By deleting Sprouty genes in different contexts during mouse embryo development, the group has shown that the removal of these genes can also have major impacts on the development of several other essential organs, including the kidney, thymus, parathyroid, sensory ganglia, and the cardiovascular system. Additionally, in collaboration with Dr Andrew Brack's group at Harvard University, it was found that Sprouty1 is essential for the normal function of muscle stem cells; its loss is strongly associated with defects in the maintenance of stem cells required for muscle repair after injury. More recently, the Basson and Brack research teams have identified abnormal levels of FGF2 as one of the critical alterations in ageing muscle that is associated with the depletion of muscle stem cells and reduced regenerative capacity of muscles in elderly individuals.

INVESTIGATING THE CEREBELLUM

The Basson group's work on FGF signalling and Sprouty genes led them towards more specific work on the development and function of the cerebellum, with particular emphasis on a chromatin remodelling factor called CHD7. The CHD7 gene is mutated in human CHARGE syndrome, a genetic pattern of birth defects occurring in about one in every 10,000 births worldwide. CHARGE is a complex syndrome, which can involve extensive medical and physical difficulties that differ from child to child. Life-threatening birth defects are common in babies born with CHARGE, who often undergo many surgeries and months of hospital treatment to ameliorate the effects of complex heart defects, breathing problems, and issues with hearing loss, balance and vision, which can pose serious challenges to the child's social development.

In collaboration with Professor Pete Scambler's group at the University College London (UCL) Institute of Child Health, Basson's lab has developed mouse models of this syndrome, allowing the study of the developmental causes of its associated brain defects. Their findings suggest that CHD7 functions as a kind of 'rheostat', responsible for fine tuning the expression levels of developmentally important genes. It is hoped that further study will elucidate the exact mechanisms whereby CHD7 controls brain development, not least because mutations in this gene, along with another related factor (CHD8), have also been implicated in autism in human patients.

Strictly speaking, the group is not investigating the epigenetics of autism, but their working hypothesis is that the loss of factors such as CHD7 results in the deregulated expression of genes and pathways essential for normal brain development. Although autism is considered to be a complex genetic disorder, it seems likely that such epigenetic approaches will yield important insights into its causes.

By allowing for the deletion of specific genes, in certain cell types and at particular developmental junctures, the powerful genetic techniques available in the study of mouse models constitute an approach which brings several advantages: it becomes possible to study the role of a gene in one particular context in isolation, whilst bypassing the early embryonic lethality associated with complete gene deletion. By observing the behaviour of mice in which Chd7 and Chd8 genes have only been deleted in the cerebellum, their roles and functions in psychiatric illnesses can be studied in depth. Basson and his collaborators believe that these studies will eventually help form a much better understanding of how epigenetic alterations such as methylation, and non-genetic changes such as external environmental factors, impact on the development of conditions like autism.

QUESTIONS STILL REMAIN

Many research groups have contributed to the current state of knowledge regarding the postnatal development of the cerebellum. However, many questions still remain, and new genes and signalling pathways are still being identified. In particular, the gene regulatory mechanisms that control the proliferation and differentiation of precursors of granule neurons, the most numerous neuronal cell type in the brain, are still poorly understood. Basson envisages that decades of further effort by many research groups will be required to fully unravel some of these mechanisms.

As far as molecular mechanisms are concerned, however, epigenetics is one of the fastest growing areas of research in this field. Novel techniques enabling the investigation of the three-dimensional conformation of the genome in the nucleus are seen as particularly significant in the quest to identify the many regulatory elements that cooperatively control the expression of developmentally-important genes.

FIGURE 1. PURKINJE NEURONS IN THE DEVELOPING CEREBELLUM

INTELLIGENCE

GENETIC AND EPIGENETIC MECHANISMS THAT CONTROL MAMMALIAN CEREBELLUM DEVELOPMENT

OBJECTIVES

The most recent focus of the lab involves the study of a chromatin-remodelling enzyme, CHD7, in development and disease. CHD7 is mutated in a devastating human syndrome called CHARGE, therefore the focus is on elucidating the various roles of CHD7 in brain development, with the aim of understanding the aetiology of the neurodevelopmental disorders associated with CHD7 deficiency.

KEY COLLABORATORS

Professor Peter Scambler, Molecular Medicine Unit, University College London Institute of Child Health, UK

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DR ALBERT BASSON obtained his PhD in Immunology from the University of Cambridge, which was followed by postdoctoral training at the National Institute for Medical Research (London), Mount Sinai School of Medicine (New York), King's College London and the University of California, San Francisco. Basson's research has contributed substantially to our knowledge of the functions of signalling antagonists of the Sprouty gene family during development, homeostasis and disease. More recently, the Basson Laboratory has been developing new mouse models to study the role of chromatin remodelling factors in the development of the cerebellum and their relation to autism.