Centre for Integrative Physiology

Research Briefings

Developmental neurobiology of axon guidance

THE MAMMALIAN BRAIN IS ARGUABLY THE MOST COMPLEX BIOLOGICAL ORGAN EVER TO HAVE EVOLVED. THE CORRECT FORMATION OF THE BILLIONS OF CONNECTIONS BETWEEN NERVE CELLS REQUIRED FOR BRAIN FUNCTION RELIES ON PRECISE NAVIGATION BY AXONS. THIS PROCESS IS LARGELY UNDER GENETIC CONTROL. WE USE MOLECULAR BIOLOGICAL APPROACHES TO UNDERSTAND HOW GENES DIRECT AXONAL GROWTH IN THE DEVELOPING BRAIN.

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It took several billion years for the human brain to evolve from the first life on earth. In contrast, the routine miracle of brain development starting from a fertilised egg takes a matter of weeks. Central to this self-assembly, much of which occurs before birth, is the ability of cells to communicate with one another.

RESEARCH

Heparan sulphate proteoglycans (HSPGs) are a class of cell surface and secreted glycoproteins which are a key component of the cell communication machinery driving cell production, movement, differentiation, axon guidance, and synaptic connections. The heparan sulphate (HS) carbohydrate component of HSPGs is a linear chain of sugars subjected to enzymatic modification by the addition (and removal) of sulphate groups to particular HS sugar coordinates. This generates an extremely large number of possible structures each of which could encode a distinct molecular instruction. HS binds to and modulates the function of a large number of signalling molecules including Slits, FGFs, BMPs, WNTs, Netrin, VEGF and many others.

The research addresses the fundamental biology of how axons navigate in complex environments and how the complex environments are themselves formed out of specialised cells, including glia, which guide navigating axons.

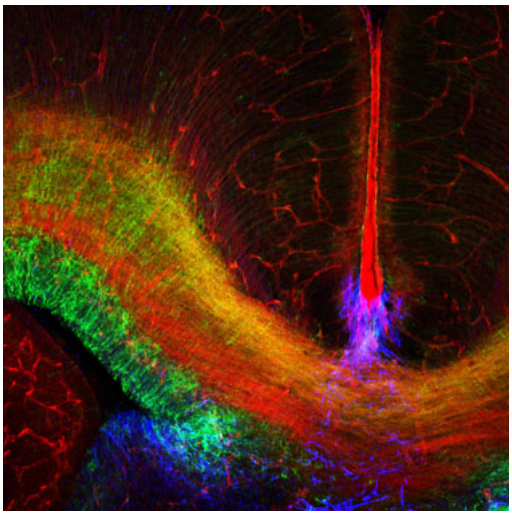

Figure 1. The corpus callosum illustrating the intimate association between axons (red) connecting the cerebral hemispheres and the glial cells (green or blue) which guide them.

We are using transgenic mice as a tool to understand HS function in the developing eye and brain, for example during the development of the optic pathway and the corpus callosum.

The emergence of ‘heparanopathies’, disorders which have their basis in genetic lesions to the HS biosynthetic machinery, adds a medical dimension to our research. Neurological heparanopathies including Kallmann

Syndrome and possibly Autism point to the importance of interactions between HS and signalling pathways suggesting future directions for research.

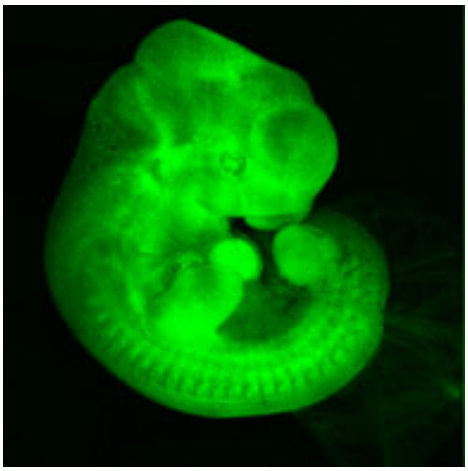

Figure 2: A transgenic mouse embryo engineered to express green fluorescent protein which is transported along axons. This is a valuable source of genetically marked cells and their axons for transplant and tissue culture experiments.

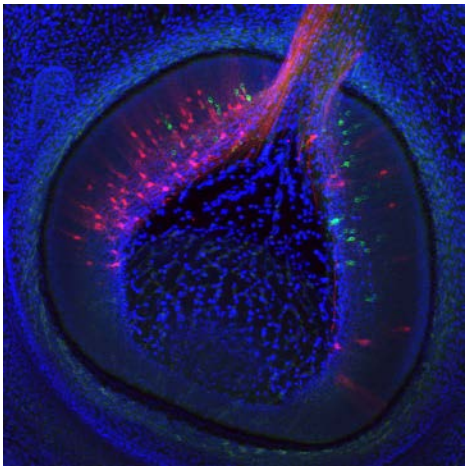

Figure 3: Ectopic retinal axon outgrowth (red) in the eye of a mutant embryo with abnormal HS structure illustrating the importance of normal HS structure for axon guidance.

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