Research Briefings

Thomas Pratt
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.

During development nerve cells project axons towards their targets. The axon is tipped by a highly motile structure, the growth cone. The direction the growth cone grows is determined by receptors on its surface which sense attractive and repulsive guidance molecules produced by cells along its route. The complement of receptors expressed by the growth cone and the axon guidance molecules expressed by the cells it encounters are controlled by transcription factors in the nucleus which regulate gene expression.

RESEARCH

Many Glycoproteins are expressed on the surface of the navigating growth cone and on the cells that guide it. Heparan sulphate proteoglycans (HSPGs) are a class of glycoproteins which are a key components of the axon guidance machinery. The heparan sulphate (HS) carbohydrate component of HSPGs is subjected to enzymatic modification by the addition (and removal) of sulphate groups to particular HS sugar coordinates producing an extremely large number of possible structures. This provides an attractive mechanism for generating functional diversity for navigating axons. We are using transgenic mice as a tool to understand how variations in HS structure are employed in the developing brain. For example, by using loss of function mutants for genes regulating specific modifications to HS structure we are uncovering specific functions for specific HS chemical structures in cell migration and axon guidance.

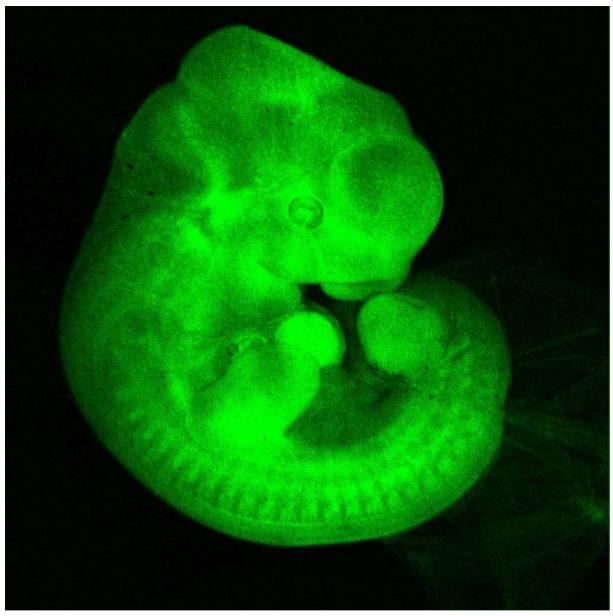

Figure 1: A transgenic mouse embryo engineered to express green fluorescent protein which is transported along axons. This is a valuable source of genetically marked cells and their axons for transplant and tissue culture experiments

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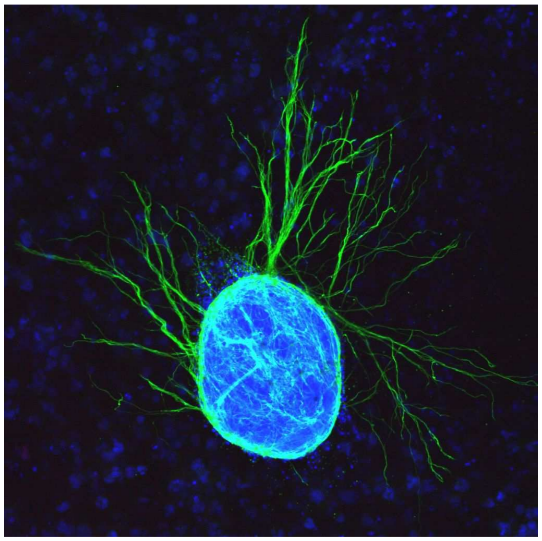

Figure 2
Tissue culture experiment. A small piece of retinal tissue projects axons (green) into a collagen gel. This type of experiment is used to study the responses of axons to factors added to the culture dish.

Other projects

The mechanisms by which the transcription factors Pax6 and Foxg1 guide axons from the eye into the brain and between the thalamus and the cerebral cortex.

The role played by mRNA transport and localised protein synthesis in axon guidance.

This research addresses the fundamental biology of how axons navigate in complex environments found in the developing brain and will have applications in the development of therapies to repair axonal connections damaged by disease or wounding.

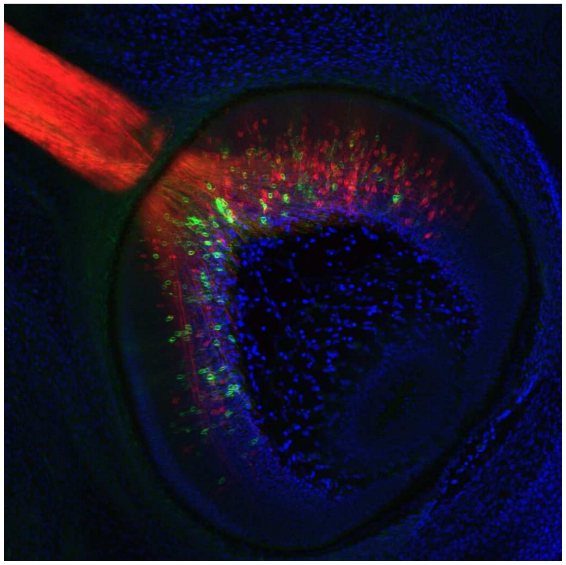

Figure 3
Retinal axons (red) misprojecting into the eye of a HS modifying enzyme mutant iembryo llustrating the importance of HS structure for narmal axon guidance

Selected references

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