Meeting report

When cell biology and neurobiology meet

Cristina Pelizon

Address: Journal of Biology, 34-42 Cleveland Street, London W1T 4LB, UK. E-mail: cristina.pelizon@jbiol.com

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A report on the British Society for Cell Biology (BSCB) meeting on 'Cell Biology and Neurobiology: A Meeting for Martin Raff', London, UK, 3-5 July 2002.

Martin Raff (University College London, UK) will retire from laboratory research this year. The special BSCB meeting entitled 'Cell Biology and Neurobiology: A Meeting for Martin Raff', which took place on 3-5 July this year, celebrated his many contributions to science and reflected his broad interests in cell biology, developmental biology, neurobiology of behavior, psychiatric disease, ethics and science education. This report highlights some of the talks on neurobiology and cell biology from the meeting. Other talks and discussions will be published in video form elsewhere [http://www.biomedcentral.com/meetings/2002/raff+bscb].

Neurodevelopment, wiring the brain and behavior

The nervous system is staggering in its complexity. The brain contains about 100 billion neurons forming thousands of interconnections. There are hundreds or even thousands of distinct neuronal subtypes, in addition to subtypes of glial cells (astrocytes and oligodendrocytes), which modulate neurons' functions.

A fundamental problem in neuronal development is understanding how the various classes of neurons and glia are generated from multipotent progenitor cells with input from both cell-extrinsic and cell-intrinsic factors. David Anderson (California Institute of Technology, Pasadena, USA) has started to address this problem using various experimental approaches, including *in vivo* transplantation and gene knockouts in mice. Anderson described the recent identification by his group of a subclass of neural basic helix-loop-helix transcription factors, the *Olig* genes; their products are called Olig1 and Olig2 in the mouse. Misexpression of Olig2 and Nx2.2, a proneuronal homeodomain transcription factor, is sufficient to cause ectopic differentiation of oligodendrocytes. Surprisingly, Olig2 also controls motoneuron fate determination at an earlier stage, before oligodendrogliogenesis. To study how *Olig* genes sequentially control motoneuron and oligodendrocyte differentiation, Anderson's group generated *Olig1/2* double-knockout mice. In the double mutants, progenitors that would normally express Olig2 generate V2 interneurons instead of motoneurons, and oligodendrocyte precursors that would express Olig2 are transformed into astrocytes. On the basis of these results, Anderson suggested a combinatorial code in which various combinations of Olig and proneural genes can determine neural, oligodendroglial or astroglial fates.

Neurons are the 'important' cells in the nervous system because they form synapses, but what do astrocytes, which constitute nearly half of the cells in our brains, do? This has long been a neurobiological mystery, discussed at the meeting by Ben Barres (Stanford University, USA). Barres isolated retinal ganglion cells from rat retinas by immunopanning and cultivated them with or without astrocytes. The astrocytes dramatically increased the synaptic activity of neurons by increasing the number of functional and mature synapses. They were also required for synaptic stability *in vitro*. As Barres pointed out, if the number of synapses on a neuron can be regulated by extrinsic factors, these findings have important implications for the possible role of astrocytes *in vivo* during normal embryonic development and possibly in adult neural plasticity. The molecular mechanisms underlying astrocytes' role in synapse formation and function are still unknown.

Regeneration of the peripheral branch of sensory neurons is a well-known example of neuronal plasticity in adult vertebrates. In contrast, the central process of sensory neurons does not usually regrow after a spinal cord injury. The studies presented by Marc Tessier-Lavigne (Stanford University, USA) showed that injection of the second messenger cAMP into adult sensory ganglia could cause significant regeneration of the injured central axon through a spinal

cord lesion site. Future important experiments will involve assessing the role of other signaling pathways (including stimulation of cGMP signaling) in helping regeneration. It is evident that these results could have enormous potential in the clinic, although, at this stage, injections of cAMP are far from being a therapeutic tool.

Of the talks on behavior, a particularly interesting one included a discussion of the genetic connection between sex, smell and behavior. Richard Axel (Columbia University, New York, USA) used mouse gene knockouts to study innate sexual and social behavior. Mice, which predominantly use their noses to 'sense' their environment, have two anatomically and functionally distinct 'noses', the main olfactory epithelium and the vomeronasal organ. Whereas the main olfactory epithelium senses odors at large, the vomeronasal organ recognizes pheromones, which provide social and sexual information on other individuals. To study the contribution of the vomeronasal organ to behavior, Axel's group generated mice in which the *trp2* gene was knocked out; *trp2* encodes a cation channel expressed in the vomeronasal organ. They then examined the sexual and social behavior of the mutants, which showed two striking features: high levels of intermale mounting, and a lack of aggressive behavior. Axel suggested that social and sexual behaviors are innate but there are external mediators (pheromones) as well as internal mediators (hormones) of behavior.

Cell biology and medicine

The talks in the cell biology sessions also covered a wide range of topics, from how cells normally grow and proliferate, to what goes wrong during abnormal proliferation leading to cancer. They also included a discussion of how best to translate basic research into diagnostic and therapeutic tools for the benefit of patients. Ron Laskey (Hutchison/MRC Cancer Cell Unit, Cambridge, UK) presented data on the role of cyclin A-Cdk2 in mammalian cells in both activating DNA replication at the beginning of S phase of the cell-division cycle and preventing it later, so that each piece of DNA is replicated exactly once, and only during S phase. Laskey also discussed a new model to explain the function of the minichromosome maintenance (MCM) protein complex in DNA replication. It has been suggested that the MCM proteins function as ATP-dependent helicases at the replication fork, but in fact they do not concentrate at the forks during replication. In the light of the structural similarity between the MCM complex and the F1-ATPase of mitochondria, Laskey suggested that the MCM complex might function as a 'DNA pump', causing the spooling and unwinding of DNA at a distance (other examples of this kind of protein are gp10, involved in phage packaging, and RuvB, found at the Holliday junction during recombination).

In an overview of the p53 pathway, David Lane (University of Dundee, UK) gave several examples of approaches to cancer therapy based on modulating the p53 response. Mutations of *p53* occur in half of all human cancers, and regulation of the *p53* pathway is defective in a variety of others. Lane stressed the importance of establishing to which class (*p53* wild-type versus *p53* mutated) cancer patients belong, in order to tailor treatment. The use of inhibitors of cyclin-dependent kinases may be an important step forward in the treatment of cancer. One of the molecules Lane described as the most promising, cyc202, has been obtained by a 'virtual screen' approach, through optimization of the existing structure of the cyclin-dependent kinase inhibitor roscovitine. This new molecule inhibits phosphorylation of the retinoblastoma protein *in vivo*, stabilizes p53 and activates p53 as a transcriptional regulator. The outcome of cyc202 administration is the induction of apoptosis in tumor cells; high therapeutic potential was shown when it was used in treating prostate cancer.

The focus of the meeting shifted briefly from animal cells to yeast, with a talk by Paul Nurse (Cancer Research UK, London, UK) who studies cell growth and morphology in the fission yeast *Schizosaccharomyces pombe*. Exploiting the fact that cells of this yeast grow 'in a straight line' and maintain the nucleus exactly in the center of the cell, the Nurse laboratory has identified several proteins important for generating positional information in the fission yeast cell. When mutated, the genes encoding Tea1, Tea2 and Tip1 produced striking morphology defects. In his talk, Nurse also addressed the fascinating question of how the cell knows how to divide right in the middle. This seems to be dependent on Cps1, as a temperature-sensitive *cps1* mutant was unable to maintain the actinomyosin ring in the cell's center.

Continuing with a related topic, Alan Hall (University College London, UK) described the signaling transduction pathway controlling the establishment of cell polarity in mammalian cells. By using rat astrocytes in an *in vitro* wound-healing assay as a model for cell migration, Hall found that, when following a scratch through the cells on the plate, cells at the edge of the scratch initiated movements accompanied by dramatic elongation and polarization. This is the result of activation of the Rho-family protein Cdc42, which in turn activates mPar6 and its associated protein PKCζ. Interestingly, by using the same kind of assay and time-lapse microscopy, Hall obtained data on how tumor cells migrate. Gliomas have different movement properties from non-tumor cells, and cells from poorly and highly invasive tumors migrate in different ways, with the latter showing a much more random and disorganized migration. Hall and colleagues are now working at understanding how cells switch their migration mode as a tumor becomes more invasive.

This meeting provided an excellent snapshot of work in progress in cell biology and neurobiology, breaking down barriers between these two fields of research and establishing myriad fruitful connections. To describe these synergies,

it is appropriate to include here a quote from Churchill used by Raff in a talk at the end of the 1970s: “This is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning”. More interdisciplinary meetings like this one can be expected in the future.