A cross-disciplinary approach to understanding neural stem cells in development and disease

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Summary
The Company of Biologists recently launched a new series of workshops aimed at bringing together scientists with different backgrounds to discuss cutting edge research in emerging and cross-disciplinary areas of biology. The first workshop was held at Wilton Park, Sussex, UK, and the chosen theme was ‘Neural Stem Cells in Development and Disease’, which is indeed a hot topic, not only because of the potential use of neural stem cells in cell replacement therapies to treat neurodegenerative diseases, but also because alterations in their behaviour can, in certain cases, lie at the origin of brain tumours and other diseases.

Key words: Drosophila, Brain tumours, Neural stem cells, Radial glia, Self-renewal

Introduction
In recent years, tumour cells with stem-like properties, called brain tumour stem cells (BTSCs), have been isolated from various adult and pediatric brain tumours, leading to the suggestion that cancer growth might be fuelled by a small population of such cells (Dirks, 2008). Studies of these cells have revealed that they share certain features with neural stem cells (NSCs), leading to the enticing hypothesis that tumour-initiating cells in the brain arise from the oncogenic transformation of endogenous NSCs, or from de-differentiated committed neural progenitors or mature glial cells (Dirks, 2008). If such BTSCs can be identified, they can be specifically targeted in the treatment of brain tumours, an exciting possibility with obvious clinical impact.

Given the proximity between NSCs and BTSCs, one of the goals of this inaugural Company of Biologists Workshop, which was organized by Kate Storey (University of Dundee, UK) and Silvia Marino (Barts and The London School of Medicine, London, UK), was to stimulate interactions between developmental biologists and neuro-oncologists, in the hope that their cross-disciplinary discussions and interactions could advance our understanding of the biology of NSCs and the mechanisms involved in brain tumour development. In the lovely setting of Wilton Park, in Sussex, UK, surrounded by the beautiful English countryside and served with excellent ‘gourmet’ food, there was ample opportunity to discuss in depth some of the most pressing questions concerning the biology of NSCs and BTSCs. We focus here on some of the key issues and perspectives that emerged during the meeting.

NSC pathways, self-renewal and differentiation

When discussing NSCs, a first hurdle is always to agree on a definition that encompasses the diverse nature of these cells, from neuroblasts in Drosophila to radial glial cells and adult NSCs in the mammalian brain. Formally, NSCs are defined as self-renewing cells that can differentiate into any of the three major neural cell lineages, namely neurons, astrocytes and oligodendrocytes (Temple and Alvarez-Buylla, 1999). However, the inference that progenitor cells of the nervous system have self-renewing capabilities arose mainly through the use of in vitro assays, such as the neurosphere assay (Reynolds and Weiss, 1992), and we are still missing formal evidence that truly self-renewing cells are actually present in brain tissues. For these reasons, we shall adopt here a more comprehensive definition of NSCs, as proposed by Kriegstein and Alvarez-Buylla (Kriegstein and Alvarez-Buylla, 2009), which defines NSCs as being all ‘primary progenitor cells at different developmental stages that initiate lineages leading to the formation of differentiated neurons or glial cells’. This definition has the additional advantage of exposing the pressing need to know in more detail the cellular hierarchies that govern neural development, in particular in vertebrates, and the molecular pathways regulating the successive transitions that progenitors undergo along their path to differentiation.

Role of FGF and retinoid signalling

Although in Drosophila we have abundant information on neuroblast lineages, we know relatively little about the cellular hierarchies that underlie vertebrate neural development. The first vertebrate neural progenitors are found in the embryonic neural plate, following neural induction, and their subsequent development is known to be regulated by the interplay between fibroblast growth factor (FGF) and retinoic acid (RA) signalling (Stavridis et al., 2010). Kate Storey presented a detailed analysis of the transcriptome alterations that occur in FGF-regulated neural progenitors in the forming chick spinal cord, as they come under the influence of retinoid signalling and commit to differentiation. Various molecules that might control this transition have been identified by her group, and of particular interest were the components of an alternative non-canonical RA pathway that might promote proliferation, rather than differentiation, in the neuroepithelium. Retinoids are also known to control the onset of neuronal differentiation in the cortex (Siegenthaler et al., 2009), and it will be interesting to compare which branches of the RA pathway are at work in these two distinct regions of the CNS.

The pro-differentiation effects of retinoids have been explored in various clinical settings, particularly in the treatment of acute promyelocytic leukaemias (Grimwade et al., 2009). Retinoids have also been used for the treatment of neuroblastomas, and the administration of 13-cis RA after chemotherapy is known to result in longer patient survival. A better knowledge of retinoid signalling might thus be important to target neuroblastomas more efficiently, and Chris Redfern (University of Newcastle, UK) described his work dissecting which retinoid receptors are involved in promoting the differentiation of neuroblastoma cells. His laboratory has also...
been searching for other signalling pathways that might interact with retinoids, and he reported that inhibition of arachidonic acid signalling sensitizes neuroblastoma cells to the pro-differentiation effects of retinoids, a finding that might lead to better therapeutic strategies.

**Sox and Notch**

Maintenance of vertebrate NSCs in the neural epithelium and their controlled differentiation is regulated by a conserved genetic network involving the Sox and proneural basic helix-loop-helix (bHLH) transcription factors, together with the Notch pathway. According to the current view, the Sox1 family proteins Sox1-3 function to maintain NSC identity and to suppress differentiation, while proneural bHLH proteins promote entry into differentiation (Guillemot, 2007). The connections between the various components of this circuitry are being actively studied, and Jonas Muhr (Karolinska Institute, Stockholm, Sweden) described his laboratory’s characterization of the genetic programmes elicited by different Sox1 proteins in NSCs and how they interact with other Sox proteins, such as Sox4 and Sox11, to regulate progenitor maintenance or differentiation. The interplay between Sox1 and proneural bHLH proteins seems also to be crucial in this decision, as entry into differentiation requires the absence of Sox1 activity. It is therefore not surprising that a Sox1 gene, Sox2, has been implicated in the generation of gliomas, being essential to sustain their stem-cell-like potential downstream of TGFβ signalling (Ikushima et al., 2009), in what constitutes another striking example of the molecular analogies between NSCs and BTSCs. An exception to the normal role of proneural bHLH factors in promoting NSC differentiation was described by François Guillemot (National Institute for Medical Research, London, UK), who showed that the proneural gene Ascl1 is transiently expressed, and maintains NSCs, in the adult subependymal zone (SEZ) and the subgranular zone (SGZ) in the adult dentate gyrus, probably by coordinating the transcriptional activation of various genes encoding positive regulators of the cell cycle. However, deletion of Ascl1 does not seem to cause a similar loss of NSC proliferation in the embryonic telencephalon, suggesting that NSCs in the embryonic and adult brain may be maintained by distinct genetic circuitries. It will thus be interesting to investigate whether Ascl1 expression is part of a genetic signature that is specific to BTSCs arising from the adult brain.

Notch signalling is also a well-established player in the molecular pathways regulating NSC maintenance, both in the embryo and during adult neurogenesis (Louvi and Artavanis-Tsakonas, 2006). Removal of Notch activity in cultures of NSCs derived from embryonic stem (ES) cells leads to their premature differentiation, and Domingos Henrique (Instituto Medicina Molecular, Lisbon, Portugal) reported the characterization of the Notch synexpression group active in these NSCs, through extensive transcriptome analysis. Various novel Notch targets have been identified in this analysis, and the challenge is to define which components of the pathway are active in NSCs and contribute to BTSC maintenance.

An interesting twist on the canonical view that Notch signalling serves to maintain proliferating NSCs in the CNS was provided by Laure Bally-Cuif (Institute of Neurobiology, Gif-sur-Yvette, France), whose laboratory obtained evidence that Notch is active in quiescent NSCs of the zebrafish adult brain and regulates the transition of these cells to a proliferative state, prior to neurogenesis. Similar data were recently obtained in the adult mouse SEZ, pointing to the likely conservation of this mechanism (Imayoshi et al., 2010). *Drosophila* neuroblasts also become quiescent in the period between embryonic and larval neurogenesis, and it will be interesting to identify conserved components of the Notch pathway that specifically mediate this pro-quiescent function in NSCs. Notch is part of a specific ‘niche’ that sustains adult neurogenesis in the SEZ, and Fiona Doetsch (Columbia University, NY, USA) discussed other aspects of this niche, in particular the vascular component, presenting a general view of the cellular architecture that underlies homeostatic neuronal production at the SEZ (Fig. 1) (Tavaezo et al., 2008). Despite an apparently uniform niche, there is significant heterogeneity in the adult NSC population, concerning their potential to generate different subtypes of neurons, a finding that poses a problem for defining a common NSC molecular signature that allows an unequivocal identification of these cells in the adult brain. To address the contribution of intrinsic mechanisms in generating this heterogeneity, Magdalena Götz’s laboratory (Institute of Stem Cell Research, Munich, Germany) developed a method to culture NSCs from the adult SEZ at the clonal level, without added growth factors, in which the lineages generated by each isolated NSC can be traced. Using this approach with live imaging, her laboratory could show for the first time that adult NSC asymmetric divisions generate transit-amplifying progenitors while self-renewing. As predicted from in vivo data (Brill et al., 2009),

**Fig. 1. Model of the SEZ cellular architecture in the adult mouse brain.** (A) Cross section of an adult mouse brain at the level of the subependymal zone (SEZ) of the lateral ventricle. Dorsal is uppermost. CC, corpus callosum. (B) High magnification of the SEZ area boxed in A. Ependymal cells (black) line the lateral ventricle. Neural stem cells (NSCs) correspond to type B astrocytes (B cell, blue) and possess apical processes that extend into the ventricle, while their basal end contacts blood vessels. NSCs generate transit-amplifying progenitors (TAPs) that divide and generate neurons. NSCs also generate oligodendrocyte progenitors (OPCs) that give rise to mature oligodendrocytes. The architecture of the SEZ is drawn from the results presented in Mirzadeh et al. (Mirzadeh et al., 2008) and Tavaezo et al. (Tavaezo et al., 2008).
most of the progeny in this culture system are neuronal and predominantly GABAergic. The recently discovered glutamatergic neuron lineage is also preserved in this system. Full transcriptome analysis of NSCs isolated from the SEZ without culturing showed that these cells are enriched for the expression of various neuronal-specific transcription factors, such as Sox4, Sox11, Dlx1, Ascl1 and Pax6, suggesting that adult SEZ NSCs are intrinsically primed to neuronal differentiation. The finding that ectopically transplanted SEZ NSCs do not produce neurons (Seidenfaden et al., 2006) is therefore likely to be due to the existence of restrictive environments that repress neuronal differentiation in most brain regions. These environmental restrictions also seem to influence oligodendrocyte maturation, as suggested by David Rovitch (University of California, San Francisco, CA, USA), who identified Wnt signalling as a restrictive factor that opposes the progression of Olig2-positive oligodendrocyte progenitors (OLPs) into myelin-generating oligodendrocytes. These ‘blocked’ OLPs are found in multiple sclerosis lesions and in periventricular leukomalacia, an ischemic brain injury in premature infants, indicating that these diseases are due to an inhibition of OLP differentiation (Fancy et al., 2009). These findings hint at the exciting possibility of targeting Wnt signalling to remove the blockade of OLP differentiation, a therapeutic approach that might lead to better clinical outcomes in these devastating diseases.

**Asymmetric division and NSC self-renewal**

Asymmetric division is a key mechanism that ensures stem cell self-renewal, but also tissue growth and homeostasis. Studies in *Drosophila* have been successful in unravelling the intrinsic mechanisms that regulate neuroblast asymmetric division in the embryonic and larval neuroepithelium (Chia et al., 2008). At mitosis, neuroblasts establish an apicobasal polarity, with two protein complexes (the PAR and the PINS complex) localizing apically and causing the basal segregation of certain polarity proteins, including the adaptor protein Miranda (Mira), the PTB-domain protein Numb, the translational repressor Brat and the homeodomain transcription factor Prospero (Pros). Upon neuroblast cytokinesis, and following the alignment of the spindle along the apicobasal axis, the apical and basal proteins are inherited differently by the two daughter cells, which then acquire different fates: the apical cell remains a neuroblast, while the basal cell becomes a ganglion mother cell (GMC) and undergoes terminal division before differentiation. When spindle orientation is irregular and partitioning of the apical and basal proteins abnormal, the ratio of apical versus basal activities inherited by each daughter cell determines their fate, as shown by Chris Doe’s laboratory (University of Oregon, Eugene, USA) in their analysis of *mutd* mutants. *Mutd* encodes a coiled-coil protein that links the spindle microtubules to the apical PINS complex and its absence spindle orientation is not perfectly aligned with the neuroblast apicobasal axis. Live imaging of dividing *mutd* mutant cells, induced by the MARCM technique (Wu and Luo, 2006), revealed that in cases in which the spindle becomes orthogonal, both daughter cells follow a neuroblast fate, irrespective of having also inherited basal components (Cabantard and Doe, 2009). This implies that the apical machinery is able to impose a neuroblast fate even when normal amounts of basal components are present, but little is known about how this machinery functions to promote the neuroblast fate. Nonetheless, unusually high levels of Pros can still impose a basal GMC fate even in the presence of apical complexes, in part by targeting cell cycle genes such as cyclins (A and E) and *string* (*cdc25*). Andrea Brand (Gurdon Institute, University of Cambridge, UK) reported that among the direct targets of Pros in the *Drosophila* embryonic CNS are genes like *asense*, *deadpan* and *snail*, which promote self-renewal and multipotency and are downregulated by Pros in GMCs. Strikingly, the transcription factors Asense, Deadpan and Snail bind to a very similar set of targets to Pros. However, whereas Pros represses neuroblast-related genes and activates differentiation genes, the other three factors have the opposite activities (Southall and Brand, 2009). Combined with expression profiling, such results are a step towards building the gene regulatory networks that govern the decision between self-renewal and differentiation in the neuroblast hierarchy.

These findings are also relevant to studies of NSCs in the vertebrate neuroepithelium, in which asymmetric divisions following a precise spindle orientation are also proposed to control cell fate and the timing of neurogenesis (Götz and Huttner, 2005). Charles ffrench-Constant (University of Edinburgh, UK) proposed that integrins participate in the spindle orientation machinery in mouse embryonic cortical NSCs. In a provocative set of experiments, he showed that in utero injection of integrin-blocking antibodies into the brain ventricle of E14-E15 mouse embryos led (among other phenotypes) to changes in the angle of progenitor cell divisions, which became more vertical. Because such divisions might lead to the asymmetric partitioning of the junctional components, these results raise the possibility that integrin signalling may control the transition from symmetrical to asymmetrical divisions in the mouse embryonic cortex.

**In search of the tumour-initiating cell**

Many brain tumour types can develop in humans, differing in their time of onset, the differentiated cell type involved (astrocytic, oligodendrocytic, immature), and their location (supra- or infratentorial, or spinal). This heterogeneity indicates that brain tumours have distinct cellular and molecular initiation mechanisms, raising several questions concerning the origin of the tumour-initiating cell and the molecular alterations that cause the emergence and progression of brain tumours. *Drosophila* offers an excellent model with which to address such questions, as malignant tumours can be conditionally induced in the larval nervous system during neurogenesis, and because direct imaging of cellular behaviour is feasible in ‘open brain’ preparations. Using this system, at least three distinct modes of tumour initiation from stem or progenitor cells have been recognized (Januschke and Gonzalez, 2008) and were further illustrated at the meeting (Fig. 2A). In the first mode, the neuroblast fails to divide asymmetrically, as in the *mutd* mutants reported by Chris Doe, and the two daughter cells inherit both apical and basal activities, behaving as neuroblasts and continuing to divide symmetrically to expand the neuroblast pool. However, normal neuroblasts do not expand uncontrollably, nor do they generate tumours after transplantation. So, what further alterations are needed to cause the uncontrollable proliferation of symmetrically dividing neuroblasts? A clue came from Chris Doe, who reported a novel mutant in which the formation of the apical PAR complex is defective. Neuroblasts from this mutant only become tumourigenic when they additionally lose PINS, unveiling a combination of events that contributes to neuroblast transformation.

A second mechanism that might lead to the generation of tumours within the *Drosophila* larval brain lobes involves a fate reversal from a GMC to a stem-like neuroblast state. Such reversions arise due to mutations in components of the basal machinery that promote GMC commitment and repression of self-renewal, like *pros*, *mira* and *lgl* (Neumuller and Knoblich, 2009). This is a classical example of how
errors in differentiation can lead to cancer (Harris, 2005): mutant cells are unable to implement the differentiated phenotype and proliferate abnormally, causing tumour formation.

In the third mode of tumour formation, the tumour-initiating cell seems to be a progenitor cell in the type II neuroblast lineage, a newly described set of neuroblasts that develop through a ‘transit-amplifying’ phase of intermediate, asymmetrically dividing progenitors (Fig. 2A) (Bello et al., 2008; Boone and Doe, 2008). These progenitors show apicobasal polarity and self-renew like a neuroblast, dividing asymmetrically to produce another progenitor and a GMC. Their intrinsic self-renewal capacity seems to make this lineage particularly susceptible to mutations in genes promoting commitment to differentiation, as is the case for mutations in brat and numb, which cause the developmental arrest of the progenitors in the self-renewal state and lead to their unrestrained proliferation (Bowman et al., 2008). This susceptibility was explored by Jurgen Knoblich (Institute of Molecular Biotechnology, Vienna, Austria) in a large-scale RNA interference (RNAi) screen aimed at identifying new tumourigenic loci that cause abnormal type II neuroblast proliferation. Several new mutants have been identified that might help to elucidate the molecular pathways that underlie neuroblast and progenitor self-renewal, and how alterations in these pathways can lead to tumour formation.

Comparable studies in mammalian systems are in progress that aim to elucidate which cells are competent to initiate tumour development and the molecular lesions involved (Fig. 2B). In a direct test of the hypothesis that oncogenic insults to NSCs might transform these cells into BTSCs, Sebastian Brandner [University College London (UCL), UK] reported on how mutations in known tumour suppressor genes, such as the retinoblastoma (Rb) gene, p53 and Pten, were tested for their capacity to transform NSCs in the mouse. All tested combinations (deletions in NSCs of Rb and p53, of p53 and Pten, or of all three genes) proved to be tumourogenic, leading to the formation of primitive neuroectodermal tumours (in the case of Rb:p53 or Rb:p53:Pten deletion) or gliomas (for the p53:Pten deletion). To exclude that transformed astrocytes contribute to these tumours, the same deletions were introduced into mature astrocytes, with no observed malignancy. Hence, it appears that NSCs in the SEZ are susceptible to human cancer-causing mutations. There are other examples of NSC-derived brain tumours, such as the Hedgehog-dependent medulloblastomas that originate from cerebellar granule cell precursors (Fults, 2005), and Richard Gilbertson (St Jude Children’s Research Hospital, Memphis, USA) described a new subgroup of human medulloblastomas characterized by mutations in the β-catenin gene (CTNNB1). He further showed that targeted expression of mutant (activated) β-catenin in the mouse embryonic hindbrain led to stalled cell migration and to hyperplasia, followed by medulloblastoma development in a manner very reminiscent to that of the human tumour. However, the fact that embryonic and adult NSCs can drive tumour growth does not mean that NSCs do so in the majority of cases in real life.

**Fig. 2.** A model of tumourigenic events in the *Drosophila* neuroblast and the mammalian neural stem cell lineages. **(A)** In *Drosophila*, neuroblasts (NBs) serve as stem cells and divide asymmetrically. The daughter cell that inherits apical determinants (blue) self-renews, while the daughter that inherits the basal components (brown) commits to neurogenesis following the nuclear localization of Prospero (pink). Neuroblasts of (a) type I and (b) type II differ in the absence or presence, respectively, of a transit-amplifying progenitor (TAP), which itself divides asymmetrically to self-renew and generate a ganglion mother cell (GMC). The different steps at which tumour initiation can occur (see text) are indicated by arrows, as are the affected cell-fate decisions. **(B)** A theoretical lineage for mammalian brain NSCs, based on the established mammalian SEZ paradigm. A self-renewing NSC (S) gives rise to TAPs that then generate neurons. By analogy with *Drosophila*, the steps at which cell fate can go awry with possible tumourigenic effects are indicated by arrows. The colour code indicates equivalent cell states in both organisms.
and major questions remain as to the origin of most types of brain tumours, including many forms of glioma (in particular those of late onset, when NSCs are scarce) and ependymomas. Most interestingly, as shown by the same group (Zhu et al., 2008), activation of Wnt signalling in cells expressing the NSC marker prominin (CD133) did not lead to neoplastic transformation in the mouse brain, indicating that Wnt activation in adult NSCs is not sufficient to drive tumour transformation. In line with these findings, Silvia Marino reported that when the expression of Bmi1, which encodes a polycomb group (PcG) protein known to regulate NSC self-renewal, is upregulated in the embryonic telencephalon, no brain tumours were formed, although the self-renewal potential of these cells is enhanced. It may therefore be possible to develop strategies to increase a NSC pool to enhance regeneration without triggering brain tumour formation.

More generally, understanding what makes a tumorigenic progenitor cell different to a normal progenitor cell is a crucial issue, and active efforts are underway to quantitatively and molecularly phenotype brain tumours. An extensive transcriptome analysis of human ependymomas by the Gilbertson laboratory, for example, has allowed them to classify these tumours into nine distinct subgroups. The profile of each subgroup reveals a regional signature (e.g. forebrain, spinal) that contains a particular set of overexpressed oncogenes. Most interestingly, the overexpression of site-specific oncogenes in appropriately matched neural progenitors recapitulated the development of ependymomas. The in-depth analysis of the functional interactions between the regional identity markers and oncogenes found in each tumour subtype will provide unique insight into the differential sensitivity of progenitor cells to tumorigenic transformation and the mechanisms involved. Such analyses in humans, however, are generally conducted long after a tumour has arisen, leaving time for extensive molecular changes to take place in cancerous cells. By taking advantage of the ability to induce the initial tumourigenic event in a timed manner in Drosophila, Cayetano Gonzalez (Institute for Research in Biomedicine, Barcelona, Spain) has analysed the early molecular signature of various induced tumours and has identified unique genetic programmes that are ectopically activated during the initial phases of tumour development and functionally required for tumour growth.

Towards identifying the epigenetic (versus genetic) alterations that might be associated with stem cell tumourigenicity, Steve Pollard (UCL, London, UK) focused on several human-derived glioblastoma NSC (GNS) lines that display different molecular signatures while all retaining tumour-initiating potential (Pollard et al., 2009). By challenging these cells through the forced activation of the pluripotency factors OCT4 and KLF4, he found that around one fifth of the GNS lines could be reprogrammed to the IPS (induced pluripotent stem) state. A comparison of the epigenetic status of the derived IPS lines with normal NSCs and the original GNS cells should now allow for the identification of epigenetic modifications associated with tumorigenic potential.

Such detailed information on NSC biology is of considerable therapeutic value. A recently characterized example, pointed out by Michael Weller (University Hospital Zurich, Switzerland), is the use of alkylation agent chemotherapy in the treatment of glioblastoma that is characterized by the methylation of the MGMT gene. MGMT (the DNA repair enzyme O-6-methylguanine-DNA-methyltransferase) antagonizes the genotoxic effects of alkylation agents, and epigenetic MGMT gene silencing in tumours is of good prognostic value for such treatments (Weller et al., 2010). A recurring finding at the meeting, however, was that there is an unforeseen variety of glioma (and other brain tumour) subtypes and, within each subtype, of molecular markers. Along these lines, Michael Weller reported on efforts to establish databases of patients with the aim of matching such molecular information and specific prognostic or predictive signatures, to help with selecting the best treatment option.

Conclusions

Advances in our knowledge of brain development are revealing surprising nuances in the molecular and functional features of NSCs, from Drosophila neuroblasts to glial progenitors in the adult mammalian brain. This NSC heterogeneity underlies the large cellular diversity of the nervous system, and much effort is being focused on dissecting the regionalization mechanisms that contribute to the establishment of specific NSC hierarchies in different brain regions. Genome-wide comparisons of the transcriptional and epigenetic signatures of different NSCs, at various stages of their progression to differentiation, are helping to build a detailed molecular roadmap of NSC specification. Similar analyses are also underway in several types and subtypes of brain tumours, in humans and in Drosophila, which will lead to a better definition of the molecular pathways recruited by tumour-initiating cells to promote malignant growth. This analysis, coupled with increasingly powerful functional studies in Drosophila and in mice, will lead to significant progress in our understanding of brain development and of how brain tumours can be treated with patient-specific therapeutic approaches.

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