Regulation of Self-renewal and Differentiation in the *Drosophila* Nervous System

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Stem cells can divide symmetrically to generate two similar daughter cells and expand the stem cell pool or asymmetrically to self-renew and generate differentiating daughter cells. The proper balance between symmetric and asymmetric division is critical for the generation and subsequent repair of tissues. Furthermore, unregulated stem cell division has been shown to result in tumorous overgrowth. The *Drosophila* nervous system has proved to be a fruitful model system for studying the biology of neural stem cell division and uncovering the molecular mechanisms that, when disrupted, can lead to tumor formation. We are using the *Drosophila* embryonic and larval nervous systems as models to study the regulation of symmetric and asymmetric stem cell division.

Stem cells have the capacity to renew themselves at each division while producing a continuous supply of differentiating daughters for the generation, and subsequent repair, of tissues (for review, see Weissman et al. 2001). These two aspects of stem cell biology must be carefully balanced during development to ensure that organs of the right size and tissue composition are formed. The spatially and temporally regulated differentiation of multipotent stem cells generates the enormous cellular diversity seen in the nervous system. A common strategy that stem cells use to generate cellular diversity is asymmetric cell division, where the unequal distribution of cell-fate determinants leads to the production of daughter cells with different fates (for review, see Morrison and Kimble 2006; Doe 2008; Gonczy 2008; Knoblich 2008). The *Drosophila* nervous system has proved to be a fertile ground not only for studying the asymmetric divisions of stem cells (Wu et al. 2008), but also, more recently, for understanding how unregulated division in a stem cell lineage can lead to tumorigenesis (Caussinus and Gonzalez 2005; Bello et al. 2006; Betschinger et al. 2006; Choksi et al. 2006; Lee et al. 2006a). Here, we focus on two key aspects of neural stem cell regulation: how the transition from proliferation to differentiation is achieved within a pool of stem cells and how the switch from self-renewal to differentiation is balanced within a single stem cell division.

SYMMETRIC VERSUS ASYMMETRIC DIVISION IN THE CENTRAL NERVOUS SYSTEM

Stem cells can proliferate through symmetric division, which leads to similar daughter cells, or they can divide asymmetrically to self-renew the mother cell and generate a differentiating daughter cell. The correct ratio between symmetric and asymmetric stem cell divisions is crucial for achieving the proper size of an organ and for the timely differentiation of a tissue. Failure to maintain this balance, or the incorrect activation of either division

mode, can lead to tumorous overgrowth or to premature differentiation (Morrison and Kimble 2006).

The importance of tight developmental controls over asymmetric division has been demonstrated in *Drosophila* by a number of studies showing that when the machinery that regulates asymmetric divisions is disrupted, neuroblasts proliferate aberrantly and form tumors (Albertson and Doe 2003; Caussinus and Gonzalez 2005; Bello et al. 2006; Betschinger et al. 2006; Choksi et al. 2006; Lee et al. 2006a,b). Less is known about the regulation of symmetric, proliferative stem cell division, which serves to increase a stem cell pool during normal development, nor how the transition from symmetric to asymmetric division is controlled. Such a transition can be seen in the developing mammalian cortex, where neuroepithelial cells initially proliferate symmetrically and then convert to radial glial cells (the main progenitor type) during neurogenesis (Gotz and Huttner 2005). The *Drosophila* larval optic lobe provides an elegant and tractable system for studying how the switch from one mode of division to another occurs.

The optic lobe generates the visual processing centers of the adult brain. It arises from two proliferative neuroepithelia in the larva, known as the inner and outer proliferation centers (IPC and OPC, respectively). During larval development, two morphologically and molecularly distinct cell populations can be identified in the OPC: lateral, symmetrically dividing neuroepithelial cells and medial, asymmetrically dividing medulla neuroblasts (Fig. 1) (White and Kankel 1978; Hofbauer and Campos-Ortega 1990; Ceron et al. 2001; Egger et al. 2007). Clonal analysis has shown that the symmetrically dividing neuroepithelial progenitors transform into asymmetrically dividing medulla neuroblasts at the medial edge of the OPC (Fig. 2) (Egger et al. 2007).

The transition from neuroepithelial cell to neuroblast occurs in a temporally regulated progression (Egger et al. 2007). The molecular mechanisms underlying this transition remain largely unknown, with the exception of one

Figure 1. Neural stem cells in the larval brain. The symmetrically dividing neuroepithelial cells and asymmetrically dividing neuroblasts of the optic lobe (OL, *white arrows*) can be seen on the right-hand side of the brain lobe, whereas, on the left, the large neuroblasts of the central brain (CB, *red arrows*) are evident. (Green) Dlg; (red) *l'sc-mRFP1*; (blue) DNA.

recent study (Yasugi et al. 2008). Yasugi and colleagues have shown that the transition from symmetrically dividing neuroepithelial cells to asymmetrically dividing neuroblasts coincides with expression of the proneural gene *lethal of scute* (*l'sc*) in the most medial epithelial cells. The transformation of neuroepithelial cells to neuroblasts is driven by a “proneural wave” of *l'sc* expression that sweeps across the neuroepithelium from medial to lateral. Progression of this proneural wave is negatively regulated by the Janus kinase–signal transducer and activator of transcription (JAK/STAT) pathway, whose ligand, Unpaired (Upd), signals from the most lateral neuroepithelial cells (Yasugi et al. 2008).

To identify potential regulators of the symmetric-to-asymmetric transition, we characterized the transcriptional

profiles of neuroepithelial cells and medulla neuroblasts. We devised a method by which to label and extract neuroepithelial cells and neuroblasts from the brains of live late third-instar larvae. Neuroepithelial and neuroblast cDNA samples were collected and directly compared on *Drosophila* whole transcriptome oligonucleotide microarrays. Statistical analysis of the data yielded nearly 200 genes that are significantly differentially expressed between neuroepithelial cells and neuroblasts. Several distinct classes of genes are strikingly enriched in the optic lobe neuroepithelium: the Delta/Notch and Hedgehog signaling pathways, proneural genes, and a number of genes with a role in retinal determination.

SELF-RENEWAL VERSUS DIFFERENTIATION IN THE CENTRAL NERVOUS SYSTEM

Drosophila neuroblasts divide in a regenerative fashion, producing a large daughter cell that self-renews and a smaller daughter cell (a ganglion mother cell [GMC]) that divides only once to give two postmitotic neurons or glial cells. This asymmetry in cell fate is achieved by the unequal partitioning of determinants (for review, see Morrison and Kimble 2006; Doe 2008; Gonczy 2008; Knoblich 2008; Zhong and Chia 2008). At each neuroblast division, cell-fate determinants, such as the phosphotyrosine-binding (PTB) domain protein Numb, the homeodomain transcription factor Prospero, and the NHL-domain protein Brain Tumour (Brat), are localized to the basal cortex by the adapter proteins Partner of Numb (Pon) and Miranda. When neuroblasts divide, only the basal daughter cell (the GMC) inherits Miranda, Pon, and their cargo.

We have been studying the role of Prospero in asymmetric division in regulating self-renewal and differentiation. Prospero is conserved in vertebrates, where the Prox (for Prospero-related homeobox) family of atypical homeodomain transcription factors appears to have a role in initiating the differentiation of progenitors in various

Figure 2. Neuroepithelial-to-neuroblast transition in the larval optic lobe. At the medial edge of the optic lobe, columnar neuroepithelial cells undergo a transition to neuroblasts. Neuroepithelial cells divide symmetrically, with horizontal spindle orientation, which results in the expansion of the progenitor pool. Medial neuroblasts divide asymmetrically, with vertical spindle orientation, and bud off smaller ganglion mother cells (GMCs) toward the medulla cortex. Most medial neuroepithelial cells (*green*) transiently express the proneural gene, *lethal of scute* (*l'sc*). This expression sweeps across the epithelium in the form of a proneural wave, from medial to lateral, as more neuroblasts are generated. (Adapted from Egger et al. 2007; Yasugi et al. 2008.)

tissues (Torii et al. 1999; Wigle et al. 2002; Dyer et al. 2003; Pistocchi et al. 2008). Prox1 is also associated with several reported cases of cancer progression (Versmold et al. 2007; Yoshimoto et al. 2007; Dudas et al. 2008; Petrova et al. 2008).

Prospero is transcribed in the neuroblast but not the GMC (Broadus et al. 1998). Prospero protein and its mRNA are anchored at the cortex of the neuroblast by the adapter protein Miranda (Ikeshima-Kataoka et al. 1997; Shen et al. 1997, 1998; Matsuzaki et al. 1998; Schuldt et al. 1998). Once segregated to the GMC by Miranda, Prospero is released from the cortex and enters the GMC nucleus. The nuclear localization of Prospero is one of the first molecular differences between a self-renewing neuroblast and a GMC (Hirata et al. 1995; Knoblich et al. 1995; Spana and Doe 1995). Therefore, identifying the genes regulated by Prospero should provide important insights into the genetic networks governing the switch from a stem cell to a differentiating cell.

To determine the sites to which Prospero binds throughout the genome, we used the *in vivo* chromatin

profiling technique DamID (van Steensel and Henikoff 2000; van Steensel et al. 2001). In brief, DamID involves fusing any DNA or chromatin-associated protein of interest to a bacterial DNA adenine methyltransferase (Dam). When the fusion protein binds to its native site in the genome, the methylase leaves a unique methylation tag on the sequence GATC. Genomic DNA is then extracted and digested with DpnI, which cuts specifically at methylated GATC sites. The tagged sequences can then be isolated and identified on DNA tiling microarrays.

We generated transgenic embryos expressing a Dam-Prospero fusion protein, or Dam alone to control for non-specific methylation, and collected genomic DNA material from stage-10–11 embryos. Following digestion with DpnI and ligation-mediated polymerase chain reaction (PCR) amplification of the methylated regions of DNA, the DNA was hybridized to full-genome tiling microarrays covering the whole euchromatic genome (Fig. 3A) (Choksi et al. 2006). The data from four biological replicates identified 1602 Prospero-binding sites. Of these, 1066 contain a previously published Prospero-consensus-binding site (Cook

Figure 3. Genome-wide mapping of Prospero-binding sites. (A) Schematic diagram of the DamID technique. (B) Prospero binding at the *CycE* locus. (Gray and black boxes) Genes; (brown boxes) *CycE* exons. Bar heights are proportional to the average of normalized log-transformed ratio of intensities from four replicate DamID *in vivo* binding-site-mapping experiments. (C) High-resolution gene expression profiling of cells from the ventral nerve cord of *prospero* mutants. (Red) Genes that are up-regulated; (green) genes that are down-regulated. (D) Model showing Prospero's segregation from the neuroblast to the GMC, where it enters the nucleus to repress neuroblast genes and activate differentiation genes.

et al. 2003), corresponding to 730 genes (Choksi et al. 2006). An example of Prospero binding to the intronic regions of *Cyclin E* (*CycE*) is shown in Figure 3B.

An unbiased gene ontology analysis of these genes using GTOolbox (Martin et al. 2004) highlighted cell-fate commitment, nervous system development, and regulation of transcription as the most enriched classes of biological function. This correlates with the known function and expression pattern of Prospero. Furthermore, Prospero binds to 41% of all annotated neuroblast genes and key regulators of the cell cycle, including *Cyclin E* (Fig. 3B), the *cdc25* homolog *string*, and *E2F*.

Expression of Prospero is maintained in glial cells but not in neurons, where the protein is absent (Spana and Doe 1995). Consistent with this, Prospero directly binds 45% of genes annotated to have a role in gliogenesis. However, to our surprise, we find that Prospero also binds to many genes involved in the terminal differentiation of neurons. These include 19% of all annotated neuronal differentiation genes, including the adhesion molecule FasciclinII (Lin et al. 1994) and the axon guidance molecule Netrin-B (Mitchell et al. 1996).

DamID provides information on whether a gene is bound by a transcription factor but not whether it is activated or repressed. To elucidate how Prospero regulates its target genes, we performed transcriptional profiling of neuroblasts and GMCs from wild-type and *prospero* mutant embryos. Approximately 100 cells were isolated from the ventral nerve cords of embryos using a glass capillary. The cells were expelled into lysis buffer, and cDNA was generated by reverse transcription and PCR amplification (Iscove et al. 2002; Choksi et al. 2006). These cDNA libraries were then compared on full-genome oligonucleotide microarrays.

We identified 91 genes that are directly bound by Prospero and show a significant change in transcription (Fig. 3C) (Choksi et al. 2006). Many genes involved in neuroblast cell-fate determination (*asense*, *deadpan*, *miranda*, *inscuteable*) and in cell cycle regulation (*Cyclin E* and *string*) show increased levels in a *prospero* mutant background, consistent with their being repressed by Prospero. Conversely, genes with a role in neuronal differentiation show decreased transcription in *prospero* mutants, indicating that Prospero is required for their transcription.

GMCs ARE TRANSFORMED INTO NEURAL STEM CELLS IN *PROSPERO* MUTANTS

If Prospero is key in promoting differentiation, then, in the absence of Prospero, neuroblasts should give rise to two self-renewing neuroblast-like cells. We followed the division pattern of individual neuroblasts in *prospero* mutant embryos by labeling with the lipophilic dye Dil (Choksi et al. 2006). Wild-type neuroblasts generate, on average, 16.2 cells that exhibit extensive axonal outgrowth (Fig. 4, left). However, *prospero* mutant neuroblasts produce an average of 31.8 cells with few, if any, projections (Fig. 4, right). Thus, *prospero* mutant neuroblasts produce much larger clones of cells with no axonal projections,

Figure 4. Neuroblasts overproliferate and fail to differentiate in *prospero* mutants. (Left) Wild-type clones, from a single S1 or S2 neuroblast labeled with Dil, extend axonal projections that often exit the central nervous system. (Right) *prospero* mutant clones give, on average, twice as many cells without axonal projections. (Left schematic diagram) Wild-type neuroblasts (white) divide in a self-renewing manner to produce a neuroblast and a GMC (gray). The GMC divides only once to produce two neurons or glial cells (black). (Right schematic diagram) In a *prospero* mutant, GMCs divide in a self-renewing manner.

suggesting that neural cells in *prospero* mutants undergo extra divisions and fail to differentiate. We followed the division pattern of individual GMCs in *prospero* mutant embryos by first labeling a single neuroblast with Dil. After the first cell division, we removed the neuroblast, leaving only a single labeled first-born GMC. Whereas wild-type GMCs give rise to just two daughter cells that extend axons, *prospero* mutant GMCs give up to seven cells that continue to express neuroblast markers and exhibit few, if any, signs of differentiation. We conclude that *prospero* mutant neuroblasts divide to give two stem-cell-like daughters. GMCs, which would normally terminate cell division and differentiate, are transformed into self-renewing neural stem cells that generate undifferentiated clones, or tumors. These results are similar to what has been observed in the larval brain, where clones of cells lacking Prospero or Brat undergo extensive cell division to generate undifferentiated tumors (Bello et al. 2006; Betschinger et al. 2006; Lee et al. 2006a).

Our data demonstrate that Prospero represses neural stem cell genes and is required for the activation of neuronal differentiation genes, suggesting that it acts as a binary switch between self-renewal and differentiation in neural stem cells. Consequently, when Prospero is absent, the daughter cell (to which Prospero is normally segregated) is no longer programmed to differentiate but continues to behave like a stem cell, undergoing further divisions and producing tumors.

Prospero is also present in the daughter cells of *Drosophila* midgut stem cells (Micchelli and Perrimon 2006; Ohlstein and Spradling 2006), suggesting that it may have a more universal role in regulating stem cell differentiation.

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