Chapter 2
Subplate and the Formation of the Earliest Cerebral Cortical Circuits

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The billions of cells and trillions of connections of the human brain are generated from the complex interactions between a developmental genetic programme and the environment. The resulting embryo is the ultimate readout of our genome; a combination of genetic susceptibility and environmental perturbations can lead to several devastating neurological and psychiatric conditions. The cerebral cortex constitutes half the volume of the human brain and is presumed to be responsible for the neuronal computations underlying such complex phenomena as perception, thought, language, attention, episodic memory and voluntary movements. These functions rely on elaborate cortical circuits, which are assembled during embryonic and early postnatal development. Understanding cortical circuit formation is a fundamental research underpinning all aspects of complex mammalian behaviour. Building the brain is like erecting a huge complex tower or bridge. The construction requires a dynamic scaffold, which is built and modified along with the final permanent structure. After the completion of the construction the scaffold must be dismantled at precisely the right places and time. The nervous system is particularly vulnerable at these stages. This is indicated by the high prevalence of cerebral cortical developmental disorders in the general population [schizophrenia (1:100); autism (1:166); attention deficit hyperactivity disorder (1:30); dyslexia (1:10); childhood epilepsy (1:200)]. In spite of recent progress, we are only beginning to understand basic neural developmental mechanisms and their involvement in the pathomechanisms of several debilitating diseases. In order to gain a more comprehensive understanding of the brain as a final product, we must thoroughly characterise neurodevelopmental processes contributing to its formation. In doing so, we will ascend to a platform from which we can critically analyse and perhaps treat the numerous disorders affecting the developing and mature brain.

Early cortical circuit formation in all regions of the mammalian cerebral cortex have a largely uniform structure with characteristic six layers. However, in the adult they show variations in cell numbers, the proportion of these layers and the cortical

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sheet can be divided into numerous well-defined areas (Brodmann, 1909). The slight differences in cytoarchitecture, connectivity and physiological properties reflect differences in the cortical circuits adopted for the performance of various computational functions. These differences emerge during embryonic and early postnatal life from circuits, which are drastically different from the adult. They involve transient neurons and they are substantially remodelled during perinatal stages. This remodelling is dependent on signals originating from the sensory periphery and from the immature brain itself (Katz and Shatz, 1996). An important aspect of developmental neurobiology is to understand the contributions from the environment on the unfolding genetic programme (see Rubenstein and Rakic, 1999; Shimogori and Grove, 2005; Price et al., 2006; O'Leary et al., 2007, Walsh 2007).

Thalamic projections arrive at the developing cerebral cortex at the peak of cortical neurogenesis while cell migration is ongoing and before the cortical cells differentiate or form their connectivity (Rakic 1976; Shatz and Luskin 1986); therefore, they are in a position to influence the area-specific development of the cerebral cortex (Dehay and Kennedy, 2007). The largely transient subplate neurons (SP) play an important role in thalamocortical axon pathfinding at the level of the initial areal targeting (Catalano and Shatz, 1998; Ghosh et al., 1990; Molnár and Blakemore, 1995; López-Bendito and Molnár, 2003) as well as the eventual innervation of cortical layer 4 by thalamic afferents and establishment of optical orientation columns (Kanold et al., 2003). They are also necessary for the maturation of inhibition in cortical layer 4 in areas innervated by the thalamus (Kanold and Shatz, 2006), and drive oscillations in the gap junction coupled early cortical syncytium (Dupont et al., 2006). Subplate cells were first described in primates (Kostovic and Rakic, 1980) and carnivores (Luskin and Shatz, 1985) as a substantial transient layer of cells below layer 6. In rodents, subplate is a thin band of cells separating the white matter from layer 6. Murine subplate (SP) cells, born around embryonic day (E)11, are among the earliest mature cortical neurones (Price et al., 1997), and begin extending axons towards the thalamus by E13 (DeCarlos and O'Leary, 1992; Molnár et al., 1998a,b). During development, SP neurons are electrically active and capable of firing action potentials (Hanganu et al., 2001) while incorporating (at least transiently) into the cortical and subcortical circuitry (Kanold et al., 2003; Friauf and Shatz, 1991; Higashi et al., 2002, 2005; Hoerder et al., 2006). The example for the subplate neuron in Fig. 2.1 only possesses intracortical projection, however, it is well known that subplate also develops subcortical projections (Allendoerfer and Shatz, 1994). Both electrophysiological properties and cell morphology point to a high degree of underlying diversity among subplate neurons (Hanganu et al., 2001; Antonini and Shatz, 1990; Hoerder, 2007). The diversity of subplate cells is further underscored by the heterogeneity of molecular markers of glutamatergic or GABAergic cells expressed in cells of the subplate (Allendoerfer and Shatz, 1994; Hevner and Zecevic, 2006). It is not yet clear whether the same types of subplate neurons possess intracortical or extracortical projections and how subplate neurons with different somatodendritic morphology relate to the diverse neurochemical properties and physiological fingerprints (Fig. 2.2).

The developing corticofugal circuit closer to the thalamus establishes an equally dynamic and puzzling transient circuit. It has been proposed that corticofugal

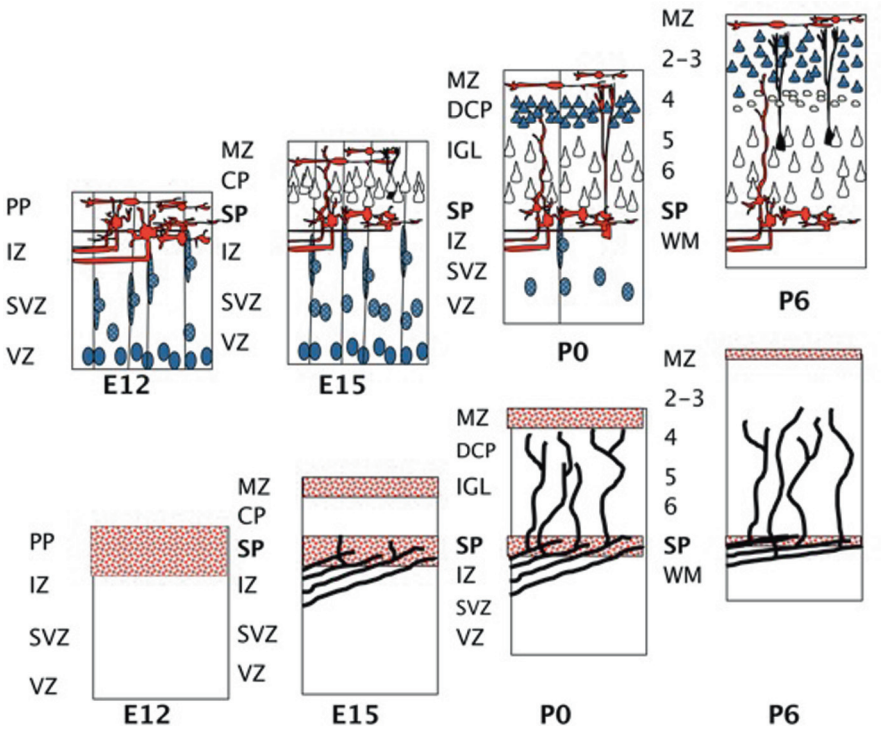

Fig. 2.1 Schematic summary of the early development of cortical lamination (*upper* row) with special attention to subplate, marginal zone and thalamocortical afferents (*lower* row) from E12 until P6 in the mouse. The *blue*, round cells at the *bottom* of the panel represent neural progenitors in ventricular and subventricular zones (VZ, SVZ) as well as radial glia along which immature neurons migrate (*black* bipolar cells). At E12 the earliest generated neurons form the preplate (PP). By E15 the cortical plate (CP) splits the preplate into subplate (SP) and marginal zone (MZ). By P0 the neurogenesis is completed, the cortex is comprised of infragranular layers (IGL, layers 5 and 6) and still migrating future cortical layers 2–4, the dense cortical plate (DCP). The lower, IGL cells are born at an earlier stage than the upper layers (4–2). By postnatal day 6 most neurons complete their migration and the cortical lamination is established. Thalamocortical axons (thick *black* lines in *lower* panels) arrive to the subplate around E15. Thalamocortical projections enter the cortex by birth and begin to establish characteristic periphery-related patterning in the barrel field of S1 by P3-6. Thalamocortical axons establish functional interactions in subplate as they arrive and accumulate in this layer before they enter the cortex and recognise their ultimate target cells in layer 4. Subplate neurons integrate into the overlying cortex and also develop various extracortical projections providing a stable platform for the establishment of cortical circuitry from early stages

projections accumulate outside the thalamus before they innervate their final target cells (Shatz and Rakic, 1981; Allendoerfer and Shatz, 1994; Molnár and Cordery, 1999, Price et al., 2006). The sequence of their development is not well understood in spite of their obvious links to cross-modal plasticity, early brain damage and some cognitive disorders. The better understanding of subplate molecular taxonomy and reporter gene expressing transgenic lines opened up new opportunities to readdress several of these issues (Table 2.1). Recently, our group identified several markers

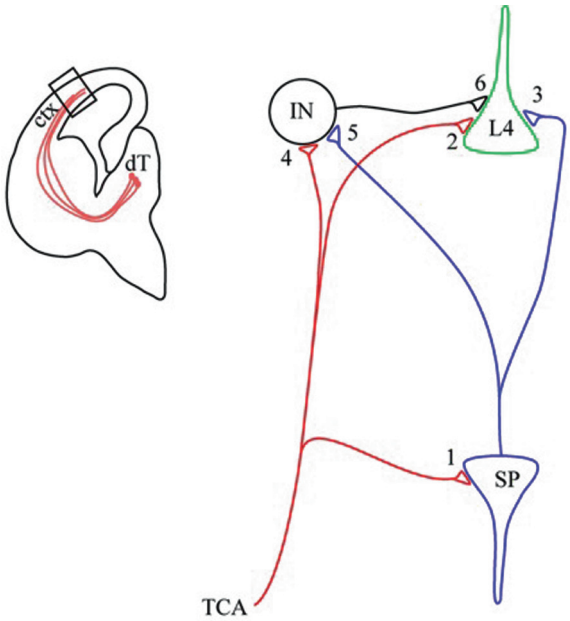

Fig. 2.2 Proposed transient minicircuit formed between thalamocortical axons and subplate and layer 4 neurons during cortical development. Thalamocortical axons (TCAs) navigate to the cortex and by E16 in mice project into the subplate (SP) before extending radial branches into the cortical plate from around E17 (*left* schematic panel of a coronal section). During this period TCAs form synaptic connections with SP cells (synapse #1) which they retain during their initial contact with the main target cells in layer 4 (L4, #2). The minicircuit is completed by SP axons also terminating on layer 4 neurons (#3). Some models of this interaction also include inhibitory interneurons (IN) that receive input from both TCAs and SP (#4 and# 5 respectively) and they themselves synapse with layer 4 excitatory neurons (#6). Activity in this circuit acts as a coincidence detecting mechanism and may act to guide and stabilise TCA – layer 4 connections. After Arber (2004)

for subplate (Hoerder-Suabedissen et al., 2009; Wang et al., 2009), which provided a unique opportunity to selectively monitor and modulate these cells using genetic approaches. The genetic models shall allow us to label a subgroup of these neurons with all their projections and follow their dynamic integration into local and long-range circuits, and to selectively control their synaptic input and output characteristics during development.

2.1 Clinical Importance of the Understanding of Early Cortical Circuits

The subplate layer is the foundation of the developing brain, and disruption of these cells may be the source of many developmental flaws, and therefore a fundamental topic to study (Kostovic and Rakic, 1990; Allendoerfer and Shatz, 1994; Kanold, 2004). Cerebral cortical developmental disorders (schizophrenia, autism, attention deficit/hyperactivity disorder, dyslexia) and perinatal hypoxic injuries such

Table 2.1 Questions surrounding early cortical circuit formation

When do the early subplate projections enter into the thalamus?
1. Do they wait outside the LGN (Shatz and Rakic, 1981)?
2. Do they wait in TRN (Molnár and Cordery, 1999)?
3. Do they wait in white matter or internal capsule (Clasca et al., 1995)?
4. Do subplate projections enter the dorsal thalamus (Allendoerfer and Shatz, 1994)?
Which cortical cells develop projections to the thalamus first?
1. Subplate cells (McConnell et al., 1989)?
2. Layer 5 cells (Clasca et al., 1995)?
3. Layer 6 cells?
What is the relationship between early corticofugal and thalamic projections?
1. Fasciculate with each other in IC and IZ (Molnar and Blakemore, 1995)?
2. Run in separate compartments (Miller et al., 1993, 1995)?
3. Interdigitate in a restricted portion (Bicknese et al., 1994)?
What is the mode of integration of subplate neurites into the cortical plate prior, during and after thalamic innervation?
1. Ocular dominance formation (Ghosh and Shatz, 1990)?
2. Orientation column formation (Kanold et al., 2003)?
3. Barrel formation (Jethwa et al., 2007; Pinon et al., 2009)?
4. Area-specificity (McConnell et al., 1989; Catalano and Shatz, 1998; Molnár and Blakemore 1995; Shimogori and Grove, 2005)?
5. Axonal and/or dendritic remodelling associated with thalamocortical ingrowth and periphery related patterning (Hoerder, 2007; Jethwa et al., 2007; Pinon et al., 2009)

as periventricular leucomalacia (PVL) involve cells of the subplate (McQuillen et al., 2003; Volpe, 2001). Some of these pathologies can be revealed by in utero imaging in human following the advent of novel image processing algorithms (Rutherford, 2002). We believe that it is impossible to understand pathological circuit formation without comprehending the transient structures contributing to its development, just as it is not possible to understand how a complex building or a bridge was constructed without the detailed knowledge of the actual scaffolding utilised during the time of the building.

Recent molecular markers provide handles to monitor and modulate very specific classes of neurons. Developmental neurobiologists have a long-standing interest in understanding cerebral cortical circuit formation and function, and investigate them using anatomical, genetic, physiological and molecular approaches (Thomson and Bannister, 2003; Nelson et al., 2006). Developments in cell separation and gene expression analysis enabled the field to identify molecular tags for the multitude of neuronal subtypes, which can be used as molecular handles to identify, modulate or eliminate very specific classes of neurons. Consequently, we are gaining greater insight into the regulation of the process of cortical neurogenesis and the classification of laminar specific sub-classes of cells (Markram, 2004; Nelson et al., 2006; Molyneaux et al., 2007; Molnár and Cheung 2006). These provide unparalleled opportunities to exploit genetics to monitor and modulate a selected group of neurons during development or adulthood (Luo et al., 2008; Miyoshi and Fishell, 2006).

2.2 Recent Microarray Screen of Murine Subplate Neurons

Most previous studies on the function of subplate cells have used carnivores and primates (Kostovic and Rakic, 1990; Allendoerfer and Shatz, 1994), which have a prominent subplate, but remain relatively unexplored as genetic models. Improving our understanding of the role of subplate cells in mice is thus particularly important, as they are increasingly used as a model organism for developmental neurobiology. We have recently identified novel subplate cell-specific gene expression by using a microarray-based approach (Hoerder, 2007; Hoerder-Suabedissen et al., 2009; Wang et al., 2009). By comparing gene expression between the subplate and the adjacent layer 6 we have identified moxd1, cplx3, ddc and tmem163 and confirmed ctgf and nurr1 (Heuer et al., 2003; Arimatsu et al., 2003) as highly expressed in the subplate but not in layer 6. MoxD1 and cplx3 gene expression is exclusive to the subplate in the P8 mouse cortex as assessed by in situ hybridisation, while tmem163 expression was also detected in layer 5 cells. DDC protein is localised to cells in the white matter, subplate and lower layer 6. The molecular data is currently being integrated with cellular and anatomical data. So far, co-localisation of Cplx3 and DDC with the known subplate marker Nurr1 as well as GABA to identify interneurons was assessed. Neither Cplx3 nor DDC expression co-localised with GABA. DDC did not co-localise with the known subplate marker Nurr1, but Cplx3 expression is present in approximately 50% of Nurr1+ glutamatergic projection neurons suggesting several subpopulations within the subplate. We have recently extended the identification of these markers by performing screens at additional developmental ages and adult. The identification of subplate-specific molecular markers will facilitate the characterisation of neurochemical, morphological and functional properties of these neurons.

2.3 Recent Studies of Subplate Neuron Integration into the Cortical and Extracortical Circuitry in Reporter Gene Expressing Mouse Models

Due to the lack of sensitive purely anterograde tracers and due to our inability to selectively label subplate neurons and their neurites, the exact timing and pattern of subcortical subplate projections is still controversial, although numerous functional suggestions have been based on their intimate association with thalamocortical projections and integration into layer 4 cortical circuitry. Moreover, the nature and the pattern of innervation of thalamic nuclei by various cortical projection neurons during development have not been resolved (Table 2.1). Recently, two transgenic mouse models were created with GFP expression restricted to a subset of SP and layer 6 neurons [Golli-tau-eGFP (GTE) mouse; Jacobs et al., 2007; Tbr1-driven GFP; Kolk et al., 2005]. Although neither of these two models is completely subplate specific, they both already help to answer some questions surrounding the integration of the subplate neurons into the intra- and extra-cortical circuitry (Molnár et al., 2007). Our studies on the GTE mouse, in collaboration with Campagnoni and Jacobs

(UCLA), suggest delayed and differential innervation of different nuclei of the dorsal thalamus by early GFP-positive corticofugal projections (Jacobs et al., 2007; Piñon et al., 2005; Piñon et al., 2009) and intimate association of early corticofugal projections with thalamic afferents (Piñon et al., 2005). At birth, GFP-positive neurites extending from the lower cortical layers into the overlying cortex are evenly distributed throughout the putative barrel field (Fig. 2.3). At P4, eGFP+ neurites aggregate within intra-barrels, a pattern becoming more defined by P6. By P10 the intra-barrel aggregation inverts to an inter-barrel pattern and remains so until P14 (Fig. 2.3).

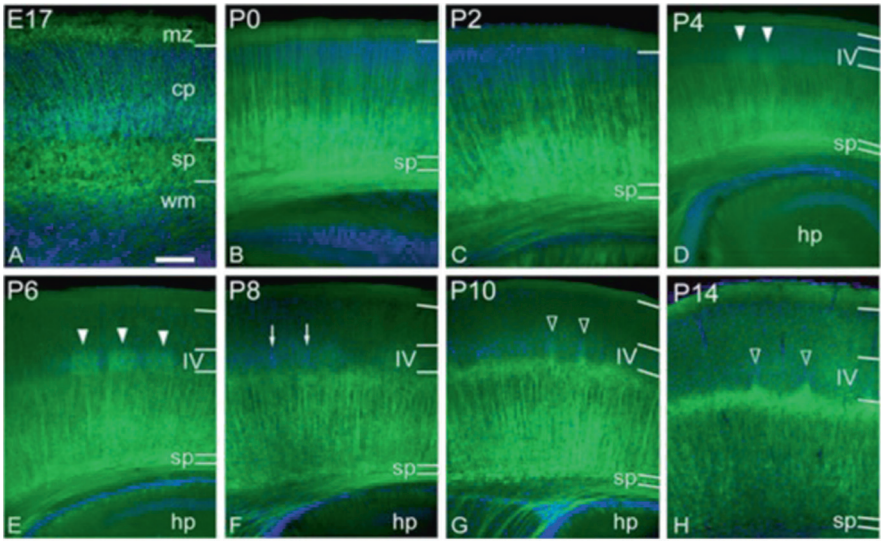

Fig. 2.3 Fluorescence micrographs of the barrel cortex in the coronal plane of the GTE mouse at ages E (embryonic day) 17 – P (postnatal day) 14. GFP neurites are shown in *green* and the bisbenzimide nuclear counterstain are shown in *blue*. Filled *arrowheads* indicate intra-barrel GFP densities; *arrows* indicate barrel septa; outlined *arrowheads* indicate inter-barrel GFP concentration. Abbreviations: mz marginal zone; cp, cortical plate; sp, subplate; wm, white matter; IV, layer IV; hp, hippocampus. Scale bar = 100 μm (**a**–**c**) and 200 μm (**d**–**h**) (Reproduced from Piñon et al., 2009)

2.4 Manipulation of the Sensory Periphery Alters Subplate Integration into the Barrel Field

Optical recording and current source density (CSD) analysis both demonstrated immature synapses between subplate and thalamocortical projections in both mouse and rat (Molnár et al., 2003; Higashi et al., 2002; 2005) as it was originally described in carnivores (Friauf et al., 1990; Kanold, 2004). The nature of these synaptic contacts is not fully understood, but it is likely that the combination of glutamatergic (mostly mediated through NMDA receptors) and depolarizing

GABAergic inputs plays a central role as in the development of other excitatory cortical synapses (Akerman and Cline, 2006; Iwasato et al., 2000). We examined whether changing the flow of sensory information from the whiskers can alter the transition from initial intra-barrel aggregation of GFP-positive neurites into inter-barrel pattern around P10. We found that the pattern inversion can be delayed until at least P10 by whisker removal at P0, suggesting that sensory input is modulating this rearrangement (Jethwa et al., 2007; Piñon et al., 2009). These experiments open up various possibilities to define cortical circuit formation by monitoring subplate neurite integration. Various paradigms (enucleation, infraorbital nerve cut, cross-modal plasticity, critical periods) become accessible with the use of reporter gene expressing lines from GENSAT (CTGF-GFP, Edg2-GFP, DDC-GFP in addition to the Golli-tau-eGFP). In these transgenic lines different populations of subplate neurons express the reporter gene; therefore, studying each line will give detailed information of that particular subplate population (e.g. Golli-tau-eGFP is expressed in broader population than CTGF-GFP, Aye et al., 2006, Hoerder-Suabedissen et al., 2010).

2.5 Subplate Cell Populations in Mutants with Cortical Migration Defects

Our new subplate markers (Hoerder-Suabedissen et al., 2009) opened up possibilities for further identification of subplate subpopulations in comparative and neuropathological studies. We have already tested six markers in the Reeler and p35KO mice, which have known defects in SP positioning (Hoerder-Suabedissen, 2009). MoxD1, cplx3, ctgf, nurr1 and tmem163 gene expression shifted to the outermost layer in Reeler and a thin band of cells in the middle of the p35-KO cortex. DDC+ cells on the other hand remained mostly in the white matter and lower half of cortex with few cells found in the outer layer in Reeler brains (Hoerder-Suabedissen et al., 2009). These findings confirm that the newly identified genes are specifically expressed in SP cells even in their altered position. Subplate has been implicated in the formation of numerous developmental malformations of the cerebral cortex such as epilepsy, schizophrenia and cerebral palsy (Eastwood and Harrison 2003; Volpe 2001). Clinical observations in preterm human suggest that neonatal hypoxia-ischemia causes selective injury in the subcortical white matter involving subplate cells, resulting in periventricular leucomalacia. The selective vulnerability of subplate cells is not understood. It is also not clear what is the causal relationship between the cellular pathologies and cognitive disorders. The combination of molecular genetics with anatomical approaches to selectively monitor and modulate subplate neurons during development could help in the understanding of causal relationships. We are currently utilising our subplate markers to investigate neuropathological changes of the subplate in animal models (hypothyroid and perinatal hypoxia-ischemia (HI) in rat) and in human histopathology (Oeschger et al., 2010).

In a neonatal rat model of HI, selective vulnerability of the subplate has been suggested using BrdU birthdating methods (McQuillen et al., 2003). We hypothesised that certain subplate subpopulations could be more susceptible than others and investigated the above subplate markers in a similar yet slightly milder HI model (Oeschger et al., 2008). After confirming the majority of the murine subplate markers in the postnatal rat, Franziska Oeschger started a study in collaboration with Vanessa Ginet and Anita Truttmann, University of Lausanne. To study hypoxia-ischemia, 2-day old male rat pups underwent permanent occlusion of the right common carotid artery followed by a period of hypoxia (6% O_2, 1.5 h or 2 h) and were analyzed 6 days later (Oeschger et al., 2010). We found some evidence of differential changes in the expression of individual subplate markers following HI. Most prominently, the number of Nurr1+ cells was increased in some mildly affected brains but decreased in the more severe cases while Cplx3+ subplate population was more generally decreased (Oeschger et al., 2010). In parallel, hypothyroid rat models are currently being examined in collaboration with Pere Berbel (Alicante) and with the help of G Slaters (FHS student). In this model, pregnant rats undergo thyroidectomy at E17 mimicking the situation in early preterm infants, which have to rely entirely on their own hormone production, and thus presenting a highly important clinical problem (Berbel et al., 2007)). Our preliminary data on P8 rats indicate that the subplate layer is enlarged and we observed an increase of 20% in the Nurr1+ population. We are currently extending our study to other subplate subpopulations (Cplx3+, CTGF+) and other cortical layers.

Subplate abnormalities have been described in several neuropathological disorders including schizophrenia, autism and periventricular leukomalacia (Eastwood and Harrison, 2003; McQuillen and Ferriero, 2005). We started to utilise our new subplate markers for human histopathological studies. Antibodies against our markers for murine subplate have been tested on human pathological specimen (CTFG, DDC, Nurr1), others are still being optimised for human tissue. For some of the markers, human in situ hybridisation probes have been generated and tested (Wang et al., 2010).

2.6 Summary

Our work in understanding the involvement of subplate cells in the establishment of earliest cortical circuits is benefiting from the recent advances of molecular and genetic approaches. However, there is a lot to be accomplished. The great challenge is now to understand the combinatorial effect of lineage- and area-specific gene expression profiles during area-specific cortical circuit formation. The discovery of molecular markers will allow distinct subclassification of cells and functional dissection of early cortical circuits.

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