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Molecular Guidance and Cell-to-Cell Interactions in Intrauterine Brain Construction during Typical and Atypical Development

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Abstract

Our understanding of the etiology of axon guidance disorders as well as our ability to correct axon guidance defects or treat neuronal network dysfunction is limited. Surgical methods currently employed to improve some forms of strabismus cannot, for example, be readily applied to more complex disorders, although experimental neurosurgery for neuropsychiatric disorders can now successfully target thalamocortical networks. Should aberrant projections be silenced or should the growth of new connections be promoted? This chapter examines the role of axon guidance molecules in the regulation of cell–cell interactions during normative and atypical development. It discusses how this affects the formation of neural circuit connections (normal and pathological) and posits what types of experiments and novel tools are needed to explore these processes. It is recommended that these observations be expanded to derive general rules of network construction and developmental sequences.

Introduction

In vertebrate embryos, developing organs undergo dramatic changes in size, shape, and cellular constitution. This is particularly striking in the central nervous system (CNS) where glial and neuronal cells are born at a distance from their final location. After undergoing their final division, postmitotic neurons migrate through a highly complex and changing cellular and molecular environment. Concomitantly, most neurons extend an axon that will have to find

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its appropriate target cells among the billions of neurons that constitute the CNS. This is a particularly daunting task for axons which form point-to-point connections on specific compartments (e.g., cell bodies, dendrites, spines) of one or a few distant target cell(s). Specificity is lower for aminergic axons that extend and branch throughout the CNS, although with variable density between brain regions (Chédotal and Richards 2010). The task appears easier for most interneurons which synapse with partner neurons located in their vicinity (Ascoli et al. 2008).

Since the end of the nineteenth century, studies have shown that the processes of neuronal migration and axonal elongation are not random but precisely orchestrated by cells and molecules distributed in the developing CNS (Dickson 2002; Valiente and Marín 2010). In this chapter, I address the role of axon guidance molecules in the development of neuronal networks and their possible involvement in neurological diseases.

A Brief History of Axon Guidance Molecules

The existence of axon guidance cues in the developing CNS was postulated by Ramón y Cajal at the end of the nineteenth century. This hypothesis was based on the observation of a polarized growth of dorsal spinal cord axons toward the ventral midline or floor plate (Ramón y Cajal 1892). It was later shown that in all species with bilateral symmetry, one of the first decisions that newborn neurons make is to project their axons to target cells located either on the ipsilateral side or on the opposite (or contralateral) side (Chédotal and Richards 2010; Chédotal 2014). Axons crossing the midline are called commissurals; they represent a paradigm for the analysis of axon guidance mechanisms. Over the last 25 years, genetic and biochemical studies have identified a variety of axon guidance molecules in multiple families of secreted or membrane-bound proteins. These guidance cues either promote or inhibit/repel axon outgrowth by acting on the stabilization of the growth cone, the motile structure found at their distal tip (Tessier-Lavigne and Goodman 1996; Dickson 2002).

The most studied axon guidance proteins belong to four protein families whose structure and function have been reviewed extensively. *Semaphorins* (with more than 20 members in mammals), secreted or membrane bound, bind to neuropilin and plexin receptors, respectively. *Slits* are secreted and bind to Roundabout (Robo) receptors and some proteoglycans. *Ephrins* are membrane-bound ligands of Eph receptor tyrosine kinases, but signaling is bidirectional: Ephs can act as receptors (or co-receptors) for ephrins and vice versa. *Netrins* comprise soluble and membrane-bound proteins related to laminins. The founding member, netrin-1, has diverse receptors such as deleted in colorectal carcinoma (DCC) and Unc5s (Unc5a–Unc5d). Semaphorins, Slits and ephrins/Ephs are primarily repulsive for axons unlike

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netrins, which can be either attractive or repulsive depending on axon types or developmental stages.

Importantly, many unrelated proteins can also guide axons in addition to the "canonical" ones. Many are immunoglobulin superfamily members, such as Down syndrome cell adhesion molecules (Yamagata and Sanes 2008; Dascenco et al. 2015; Alavi et al. 2016), draxin (Islam et al. 2009; Shinmyo et al. 2015), and L1-related IgCAMs (Castellani et al. 2000; Ango et al. 2004; Chauvet et al. 2007; Huang et al. 2007). They can also be morphogens, such as Sonic hedgehog (Charron et al. 2003; Okada et al. 2006), members of the Wnts/planar cell polarity pathway (Lyuksyutova et al. 2003; Liu et al. 2005; Zhou et al. 2008; Shafer et al. 2011; Chai et al. 2014), and bone morphogenetic proteins (Butler and Dodd 2003). Other notable ones are the repulsive guidance molecules (Monnier et al. 2002; Rajagopalan et al. 2004), some neurotrophins (Lumsden and Davies 1983; O'Connor and Tessier-Lavigne 1999; Park and Poo 2012), homeobox-containing proteins (Brunet et al. 2005; Sugiyama et al. 2008), chemokines (Zhu et al. 2009), and even lipids (Guy et al. 2015).

This is a non-exhaustive list and new molecules are still to be found. Importantly, recent studies indicated that posttranslational modifications, such as glycosylation (with potential sugar codes), modify the activity of axon guidance proteins (Conway et al. 2011; Blockus and Chédotal 2012; Wright et al. 2012). Axon guidance gene splicing has also been described and increases their structural diversity (Chen et al. 2008; Colak et al. 2013). Along this line, up to more than 350,000 combinations of clustered protocadherin ectodomain isoforms might exist (Zipursky and and Sanes 2010; Rubinstein et al. 2015). These proteins, which exhibit isoform-specific homophilic binding, were shown to play a role in neuronal self and nonself recognition (Lefebvre et al. 2012). Protocadherins also control axon guidance (Uemura et al. 2007; Leung et al. 2013; Hayashi et al. 2016) and some have been associated with neurological diseases such as epilepsy (Nabbout et al. 2011; Aran et al. 2016).

Recent studies show that growth cones integrate multiple guidance signals and that this combinatorial action might have a synergistic or antagonistic outcome (Bielle et al. 2011b; Lokmane et al. 2013; Poliak et al. 2015; Sloan et al. 2015; Morales and Kania 2016). A plethora of *in vitro* and *in vivo* data show that axon guidance molecules control the targeting of axons from long projection neurons (including aminergic ones) and interneurons throughout the nervous system. There is also evidence in the neocortex that clonally related excitatory pyramidal neurons within a column are preferentially interconnected, but the underlying guidance mechanism (if any) is unknown (Li et al. 2012). Whether this lineage-driven connectivity pattern applies to cortical interneurons is still under debate (Harwell et al. 2015; He et al. 2015; Mayer et al. 2016; Sultan et al. 2016).

Notably, axon guidance molecules are pleiotropic and control cell–cell interactions during tangential and radial neuronal migration, angiogenesis, and

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immune response, among others. Therefore, it would be simplistic to expect that axon guidance disorders result only from mutations or risk variants in axon guidance genes.

Cellular Sources of Axon Guidance Molecules

In the mammalian central nervous system, axon guidance cues are produced by a variety of neural and nonneural cell types. Midline glia cells localized at the floor plate in the midbrain, hindbrain, and spinal cord (Tessier-Lavigne and Goodman 1996; Bashaw et al. 2000; Chédotal 2011; Neuhaus-Follini and Bashaw 2015); the indusium griseum and glial wedge in the forebrain (Suárez et al. 2014); or the optic chiasm in the diencephalon (Kuwajima et al. 2012) are all major sources of signals that may attract precrossing commissural axons and repel ipsilateral and postcrossing axons. Radial glial cells, such as in the optic tectum (Drescher et al. 1995; Monnier et al. 2002), play a role in axon guidance.

More recently it has been found that transient corridors for growing axons are established at specific locations, such as the basal forebrain and corpus callosum, by migrating neurons, which express specific guidance cues for thalamocortical and callosal axons, respectively (López-Bendito et al. 2006; Niquille et al. 2009; Bielle et al. 2011a). Axon–axon interactions also play an important role to promote the fasciculation of follower axons and pioneer ones, as well as to interconnect neurons coming from distinct locations. One of the most classic examples is the so-called "handshake" between corticothalamic and thalamocortical axons (Molnár et al. 1998; Mandai et al. 2009; Deck et al. 2013). Notably, axons also express cues that guide migrating neurons. This happens, for instance, in the case of (a) olfactory and vomeronasal axons, which are followed by neurons secreting gonadotropin-releasing hormone (Messina et al. 2011; Casoni et al. 2016; Cariboni et al. 2012), and (b) some spinal cord ventral interneurons, which are guided by commissural axons (Laumonnerie et al. 2015).

Other types of cells also influence axon guidance. Meningeal cells produce chemokines such as SDF1/CXCL12 which influence the growth and migration of some hindbrain cortical neurons (Zhu et al. 2002, 2009; Borrell and Marín 2006). Netrin-1 and endothelins are produced by the vasculature and guide sympathetic axons innervating vessels in the periphery (Makita et al. 2008; Brunet et al. 2014), and this might also be the case in the CNS where vascular endothelial growth factor was already shown to pattern commissural projections (Erskine et al. 2011; Ruiz de Almodovar et al. 2011). Finally, microglia which invade the CNS at early embryonic ages (E9.5 in mice) appear to accumulate first at specific choice points for some axonal tracts (Squarzoni et al. 2015). Dopaminergic and callosal axons as well as cortical interneurons are misrouted following microglia depletion (Pont-Lezica et al. 2014; Squarzoni et al. 2014).

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Altogether these results suggest that intrinsic and extrinsic factors perturbing the development of cells expressing axon guidance cues could indirectly alter the development of neuronal connectivity.

Axon Guidance, an Intrauterine Process

In mammals, most neuronal networks are built during embryonic development. In the mouse CNS, the first axons are born at embryonic day 8 (E8) (Mastick and Easter 1996) around Carnegie stages 11–12 (CS11–CS12). This is equivalent to 23–30 postconception days (E23–E30) in humans (Rhines and Windle 1941; Humphrey 1944; O'Rahilly and Müller 1987). These pioneer neurons appear in the hindbrain and diencephalon following a developmental sequence that is largely conserved in all vertebrates.

In the human neocortex, cells expressing neuronal markers, called predecessor neurons (Bystron et al. 2006), were described as early as E33, before the initiation of cortical neurogenesis and are therefore suspected to originate from outside the cortical anlage. Interestingly, a recent study shows that in the postnatal mouse, meningeal-derived cells could generate cortical neurons (Bifari et al. 2017). The first postmitotic pyramidal neurons reach the cortical plate around E50, and extrinsic axons, including thalamocortical axons, enter the intermediate zone around the cortical plate (Larroche 1981; Bystron et al. 2006, 2008). The corpus callosum, the largest commissural tract in the CNS, is detectable as of gestation week 11 (GW11) and its size increases until after birth (Rakic and Yakovlev 1968). The corticospinal tracts (CST), the longest axonal tracts in the CNS, reach the spinal cord at CS23 (E56–E60) and their decussation is completed at GW15 (Eyre 2000, 2003; ten Donkelaar et al. 2004). They reach the lumbosacral region at the caudal end of the spinal cord by GW29 and contact motor neurons by GW37. Therefore, in humans, axonal development almost exclusively occurs during intrauterine life, with the noticeable exception of cerebellar granule cell interneurons, two-thirds of which are produced postnatally (Kiessling et al. 2014). This is not the case in rodents. In rats, for example, CSTs just reach the spinal cord at birth and their caudal growth proceeds at least until postnatal day 16 (P16) (ten Donkelaar et al. 2004).

Importantly, in vertebrates, including humans, the size of the CNS continues to expand well after axons have contacted their targets. It is estimated that the weight of the brain increases 40-fold between the end of the embryonic period and birth (O'Rahilly and Müller 2008). This "noncanonical" axonal growth, also known as stretch growth (Weiss 1941), involves mechanical forces (Franze 2013). Experimentally, axons can be forced to elongate at a speed of 400 μm/hr for at least two weeks (Pfister 2004; Heidemann and Bray 2015). Interestingly, in the fish lateral line, some sensory axons are towed by their target cells as they migrate (Gilmour et al. 2004). Mounting evidence suggests that mechanical forces and tension also influence axonal growth and guidance

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before axons contact their targets (Athamneh and Suter 2015; Polackwich et al. 2015). In the developing *Xenopus* retinotectal pathway, growing ganglion cell axons appear to respond, via piezo1 ion channels, to mechanical signals and probe the stiffness of the surrounding tissue (Koser et al. 2016). However, the molecular mechanisms that control mechanical axon growth and guidance and their possible contribution to neurological diseases are largely unknown (Budday et al. 2014). These observations raise an important question: How can axonogenesis and axonal tract development in human embryos/fetuses be technically studied *in utero*?

How Can We Study Axon Guidance in Humans?

Although a multitude of genetic and imaging methods can be used to study axon guidance in animal models, specific technical and ethical issues make this extremely difficult in human embryos and fetuses. Most studies are based on postmortem brains and incomplete analysis of a limited number of samples and tissue sections, in which axons are labeled with silver staining or immunostaining using only a few axonal markers, such as GAP43.

Moreover, most neuropsychiatric diseases are only diagnosed well after birth, and it is therefore difficult to link them to anomalies of axon guidance. This demonstrates the need for novel or improved imaging methods, in particular noninvasive ones, to visualize and follow the intrauterine development of neuronal connectivity in humans.

Important progress has been made in the noninvasive medical imaging of embryos and fetuses *in utero* during pregnancy to detect congenital anomalies and malformations. This now includes three- and four-dimensional obstetrical ultrasonography, which can generate holographic images of the embryo (Kurjak et al. 2005; Pooh et al. 2011; Baken et al. 2015) but mostly provides information about surface features and cavities. Likewise, 3D power Doppler ultrasound was used to visualize the embryo vasculature (Weisstanner et al. 2015). *In utero* magnetic resonance imaging (MRI) also provides a good appreciation of the development of the CNS (Weisstanner et al. 2015) in the fetus, and diffusion tensor imaging (DTI) tractography is now used as a prenatal diagnostic of callosal dysgenesis as early as GW20 (Jakab et al. 2015).

Validation of these *in utero* 3D data is challenging and problematic, as it currently relies on postmortem evaluation of histological sections.

A variety of tissue clearing techniques, such as Clarity and 3DISCO, have been developed over the past few years, and using them in combination with whole-mount immunostaining and light sheet fluorescence microscopy allows high-resolution three-dimensional images of adult mouse brains and embryos to be generated. This method, now adapted to human embryos and fetuses (Belle et al. 2017), should help us obtain a better understanding of the time course and characteristics of axon development before term in normal and

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pathological cases. It will also be useful in interpreting and validating the *in utero* images obtained using noninvasive methods.

Current Evidence Supporting the Developmental Origin of Some Neurological Disorders: Intrauterine Axon Guidance and Neuronal Migration Defects in Patients

The developmental origin of various monogenic diseases, with dominant or recessive inheritance, has been demonstrated (Blockus and Chédotal 2015; van Battum et al. 2015). This is the case for congenital cranial dysgeneses (Assaf 2011; Nugent et al. 2012), which are primarily due to a lack or mistargeting of oculomotor nerves and cause strabismus and other eye movement disorders. In albino patients, binocular vision is altered due to a significant reduction of the size of the ipsilateral contingent or retinal ganglion cell axons (Guillery and Kaas 1973; Neveu and Jeffery 2007). Likewise, abnormal corticospinal tract and corpus callosum decussation have been described in patients suffering from congenital mirror movements (Izzi and Charron 2011). *NTN1*, *DCC*, and *RAD51* (involved in DNA repair) are the three known causal genes (Srour et al. 2010; Depienne et al. 2011, 2012; Meneret et al. 2015). Patients suffering from the horizontal gaze palsy with progressive scoliosis syndrome (HGPPS) display a severe loss of commissural connections, including the CST and lateral lemniscus (Jen et al. 2004; Chédotal 2014; Zelina et al. 2014). All HGPPS patients carry autosomal recessive mutations in the *ROBO3* gene which in mammals encodes a transmembrane receptor involved in commissural axon attraction (Marillat et al. 2004; Sabatier et al. 2004; Zelina et al. 2014). Interestingly, Robo3 knockout mice completely lack commissures in the midbrain, hindbrain, and spinal cord, but axons that fail to cross the midline still connect to their proper target, albeit on the wrong side of the brain (Renier et al. 2010; Badura et al. 2013). Other diseases that have a clear axon guidance basis are corpus callosum dysgenesis/agenesis (Paul et al. 2007; Edwards et al. 2014; Suárez et al. 2014).

How then can we demonstrate that abnormal intrauterine neuronal guidance is involved in the etiology of polygenic and complex diseases, such as autism spectrum disorders (ASD), schizophrenia, bipolar disorders, and other psychiatric diseases, which are often linked to multiple genetic risk variants? Some genetic studies have identified mutations or single nucleotide polymorphisms (SNPs) in genes encoding axon guidance molecules (either ligand or receptors), suggesting that abnormal brain wiring might contribute to those diseases. For example, genome-wide association studies have shown that rare mutations in *PLXNA2* (a gene on chromosome 1q32 which encodes a semaphorin receptor) could contribute to schizophrenia in some individuals, although this is still under debate (Mah et al. 2006; Fujii et al. 2007; Allen et al. 2008; Ripke et al. 2013). A few studies show a possible involvement of *ROBO3* and *ROBO4*

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(Anitha et al. 2008; Suda et al. 2011) and *SEMA5D* in ASD (Melin et al. 2006; Weiss et al. 2009) and *ROBO1* in dyslexia (Hannula-Jouppi et al. 2005; Lamminmaki et al. 2012).

Interestingly, the *DCC* gene was also associated with schizophrenia and adolescence-related psychiatric diseases and suicidal behavior (Grant et al. 2012; Manitt et al. 2013). Finally, polymorphism and the identification of certain SNPs in axon guidance genes (e.g., *DCC*, *EphB1*, *SEMA5A*, *SLIT3*) might even predispose to Parkinson disease (Lesnick et al. 2007; Lin et al. 2009).

Although these data suggest the existence of a complex and precise genetic program for building neuronal networks, there is also evidence for axon guidance errors (Hutson and Chien 2002; Poulain and Chien 2013), stochastic events, and activity-dependent regulation of axonal development (Mire et al. 2012; Hassan and Hiesinger 2015). Thus the following questions should be addressed:

- How plastic is the system?
- Given evidence of extreme abnormalities in developing systems (e.g., Muckli et al. 2009; Hoffmann et al. 2012; Warner et al. 2015), how does the system accommodate intrauterine axon guidance errors or brain malformations?
- What role does timing play in the ability to reorganize?
- Are some circuits more plastic than others?
- How much interindividual variability exists in axonal connectivity?

Using iPSCs and Organoids to Study Axon Guidance

It will not be easy to obtain direct *in vivo* evidence linking axon guidance and neuronal migration defect and neurological disorders, because most of these developmental processes occur *in utero* and are currently unable to be assessed directly in humans using existing noninvasive imaging techniques. Moreover, neurological and psychiatric disorders are diagnosed postnatally, often years after developmental errors have occurred. News tools that would allow the recapitulation of normal and pathological brain development *in vitro* could provide important insights (Suzuki and Vanderhaeghen 2015; Quadrato et al. 2016).

In less than ten years, two major technical advances have completely revolutionized our ability to study the etiology of complex neurological diseases: somatic cell reprogramming and CRISPR/Cas9-mediate genome editing (Jinek et al. 2012; Cong et al. 2013; Doudna and Charpentier 2014; Hsu et al. 2014; Shi et al. 2017). Human-induced pluripotent stem cells (hiPSCs) have already been derived from normal individuals and patients suffering from various neurological and neuropsychiatric diseases, and a collection of differentiation protocols allow many different types or neuronal and glial cells to be produced (Yoon et al. 2014). Using CRISPR/Cas9, mutations of candidate genes can

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be introduced in control cells to test their pathogenicity and in patient cells to correct risk alleles.

The ability of hiPSCs-derived neurons to migrate and extend axons on various substrates can be easily studied and compared (Brennand et al. 2011) in classic 2D cultures, but this will not tell us much about the ability of those axons to find their targets in a complex cellular environment, like the embryonic brain. Importantly, each differentiation protocol produces, most often, a limited number of neuronal types, and the usual target cells are likely to be absent from the cultures.

Recently, organoid models have emerged that show the expansion, differentiation, and self-organization of hiPSC-derived cells. Such approaches can generate eye cups containing a pigmented epithelium and a simple retina with multiple neuronal types (Eiraku et al. 2011; Reichman et al. 2014), cerebellar (Muguruma et al. 2015), hippocampal (Sakaguchi et al. 2015), and forebrain organoids (Paşca et al. 2011). Although more complex and self-patterned cerebral 3D organoids have been produced (Li et al. 2017), the reconstitution of long-range projections circuits (e.g., CSTs, thalamocortical or nigrostriatal pathways) in hiPSC-derived miniature brains still appears beyond our reach (not even considering behaviors).

Grafting iPSC-derived neurons or organoids into the brain of animal models appears to be an interesting option, as shown for the dopaminergic system (Hargus et al. 2010; Korecka et al. 2016). Unless this is possible *in utero*, the grafted cells will develop in an environment quite different from their normal one. This disparity, in turn, could influence cellular growth potential and the ability to reach their target cell and integrate in a circuit, although there is evidence that some of the cues are still present. Despite these limitations, some recent results using embryonic derived stem cells (Michelsen et al. 2015) support the potential of this strategy for understanding the role of axon guidance disorders in the etiology of neuropsychiatric diseases.

Disruptors of Axon Guidance during Intrauterine Life

What is the evidence for disruption of axon guidance, and what factors might be involved? As discussed above, in humans most of the axon guidance process occurs *in utero* during the first semester of gestation. However, some deleterious agents (viruses or bacteria) and molecules (e.g., alcohol) that are able to pass through the placental barrier (Syme et al. 2004) can perturb the development of axonal connectivity.

Psychoactive drugs, such cannabinoids, are another candidate disruptor: they can regulate serotonin transporter (SERT) activity in the placenta, thereby influencing the clearance of serotonin (see below). Also, by acting on cannabinoid receptors, they can change Slit/Robo signaling (Alpár et al. 2014). A recent study showed that using SERT inhibitors for treating depression during

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pregnancy might also perturb the development of the enteric nervous system and contribute to gastrointestinal disturbances that accompany ASD (Margolis et al. 2016). Likewise, valproic acid, which is sometimes used in the treatment of epilepsy, influences axon outgrowth (Tashiro et al. 2011; Lv et al. 2012; Yang et al. 2012).

Conclusion

Our understanding of the etiology of axon guidance disorders is far from complete, and attaining this will not be easy. Currently, our ability to correct axon guidance defects or treat neuronal network dysfunction is severely lacking. Surgical methods being used to improve some forms of strabismus cannot be applied to more complex disorders. Thus we need to consider whether aberrant projections should be silenced or the growth of new connections promoted.

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