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Review

Genetics and mechanisms leading to human cortical malformations

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ABSTRACT

Cerebral cortical development involves a complex series of highly regulated steps to generate the laminated structure of the adult neocortex. Neuronal migration is a key part of this process. We provide here a detailed review of cortical malformations thought to be linked to abnormal neuronal migration. We have focused on providing updated views related to perturbed mechanisms based on the wealth of genetic information currently available, as well as the study of mutant genes in animal models. We discuss mainly type 1 lissencephaly, periventricular heterotopia, type II lissencephaly and polymicrogyria. We also discuss functional classifications such as the tubulinopathies, and emphasize how modern genetics is revealing genes mutated in atypical cases, as well as unexpected genes for classical cases. A role in neuronal migration is revealed for many mutant genes, although progenitor abnormalities also predominate, depending on the disorder. We finish by describing the advantages of human *in vitro* cell culture models, to examine human-specific cells and transcripts, and further mention non-genetic mechanisms leading to cortical malformations.

Contents

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1. Cortical development in mammals – a short overview, rodent versus human

1.1. Principal cell neurogenesis

A correctly functioning central nervous system (CNS) relies on the formation of neural circuits to control activity. For this, newborn neurons migrate, differentiate, form their dendrites and axons, and establish neuronal connections at the correct time and place in the CNS during embryogenesis [1,2].

In vertebrates, earliest stages of brain development involve segmentation of the neural tube into lineage-restricted compartments where a highly elaborated genetic program maintains the head-to-tail (anteroposterior; AP) and back-to-front (dorsoventral; DV) axes of the CNS [3]. After neural tube closure at around embryonic day (E) 30 or gestational week (GW4), neuroepithelial cells (NECs) convert into fate-restricted differentiated radial glial cells (RGCs), a process that in the mouse occurs at E9-10, and in human embryonic telencephalon at GW5-6. At these stages the ventricular zone (VZ) is the only proliferative region [4]. RGCs are polarized with an apical-basal orientation and show hallmarks of both astrocytes and NECs. RGC basal processes constitute the scaffold for migration of newly born neurons through the intermediate zone (IZ) to the cortical plate (CP). The RGC apical process allows attachment to the ventricular lining (VL) and also contains key elements of signaling pathways, such as the primary cilium and the centrosomes. Most neurons of the brain are derived, either directly or indirectly from RGCs [5]. These cells, expressing the marker Pax6, are either able to self-renew, generating two RGCs (symmetric cell division), or give rise by asymmetric cell divisions to basal or intermediate progenitors (BPs or IPs) which move basally to form the subventricular zone (SVZ). These cells are Tbr2-positive and in rodent give rise to post-mitotic neurons, thus indirectly from RGCs [6]. A more recently identified Pax6-positive VZ cell is the short neural precursor (SNP), which is similar to an RGC but has only a short basal process, and these cells generate post-mitotic neurons directly [7]. SVZ onset occurs at E12 in the mouse and at GW7-8 in humans [4], and neurogenesis in the SVZ contributes to the generation of upper-layer neurons [8], as well as other neurons in the deeper cortical layers [9].

In gyrencephalic species, apical RGCs divide asymmetrically to generate a more fate-restricted type of RG progenitor. Thus, the SVZ is composed of several types of BP: basal or outer radial glial (bRG) cells, as well as intermediate progenitors (also called bIPs) [10]. This thickened SVZ and particularly its division into an expanded outer SVZ (OSVZ), is predominantly linked to neocortex evolution and expansion, as well as formation of folds and fissures [11]. OSVZ progenitors undergo expansive proliferative divisions which contrasts the rodent SVZ, where IP cells usually divide only once. These cellular mechanisms are hence associated with the evolutionary expansion of human neocortex [12].

At GW5 in human there is already evidence of the primordial plexiform layer (PPL) or preplate (PP), visible also by approximately E11 in the mouse. The earliest born neurons form this layer which is later divided (around GW7-8, and accomplished by approximately E13 in the mouse) into the more superficial marginal zone (MZ) and the deeper subplate (SP) by the emerging CP [13,14]. Later-born neurons arriving in the CP migrate past earlier born neurons, to generate a multilayered neocortex [8]. Post-mitotic cortical neurons migrate radially along RGC processes toward the pial surface, giving rise to pyramidal neurons [15–17]. After PP splitting, the subsequent waves of migrating neurons successfully form in an inverse manner layers II–VI in the mouse, with layer-specific connectivity, morphological and physiological characteristics. Different classes of projection neuron are thus born in overlapping temporal waves [8,17].

In humans, the OSVZ forms at GW11, while the neuronal migration peak that in the mouse cortex takes place from E13-16, occurs from GW12-20 [12,16]. The IZ, located above the SVZ (see Fig. 1), contains radially migrating neurons and tangentially migrating interneurons (IN), the latter derived from the ganglionic eminence (GE). Before beginning radial migration into the CP, principal cells adopt first a multipolar morphology, basal to the VZ [18]. Then cells become bipolar, facilitated by different kinds of molecules that allow differentiation and locomotion along the basal process of RGCs towards the CP [8,16,19]. Extracellular guidance cues also promote the correct positioning of new-born neurons. The most well-known is the Reelin signaling pathway (see below). Reelin is secreted from Cajal-Retzius neurons to activate downstream factors within migrating neurons [16,20]. Cajal-Retzius cells are in place from very early corticogenesis [21].

1.2. Gliogenesis

Neurogenesis is generally followed by gliogenesis in the developing mammalian CNS, with the same progenitor domains switching the differentiation program to oligodendrocyte or astrocyte production [22]. Glia may constitute 50–90% of the cells in the human brain, and glial numbers are thought to be essential for achieving increased brain complexity. This involves the expansion of glial pool size and increased long range conduction across white matter tracts [22]. RGCs in the developing mouse and human cortex hence give rise to two main types of glia, astrocytes and oligodendrocytes, which are produced both pre- and postnatally. The third major type of glia of different origin is the microglia population which constitute the macrophages of the CNS, mediators of neuroinflammation which can induce or modulate a broad spectrum of cellular responses.

Astrocyte dysfunction can lead to developmental and/or psychiatric disorders [23,24]. Mutation of the α-2-delta subunit of the voltage gated calcium channel CACNA2D2 which is highly expressed in astrocytes and in the neocortex, has been linked with epileptiform activity in the mouse brain [25]. Mutations in this gene are also associated with polymicrogyria (PMG), global cortical atrophy, corpus callosum dysgenesis, intellectual disability (ID) and epilepsy in three non-related patients [26].

Furthermore, the role of glia in epilepsy has recently been reviewed, especially in association with cortical malformations [27]. These authors emphasize that gliosis is a common factor observed in histological brain samples from such patients. Glial uncoupling as a consequence of loss of expression of certain molecules which are normally expressed in glia could contribute to seizures, and targeting glial cell function in the treatment of epilepsy could be a key mechanism. Finally, these authors pro-