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Review

Genetic animal models of malformations of cortical development and epilepsy

Michael Wong[a,*], Steven N. Roper[b]

[a] Department of Neurology and the Hope Center for Neurological Disorders, Washington University School of Medicine, St. Louis, MO 63110, USA
[b] Department of Neurosurgery, University of Florida, Gainesville, FL 32610, USA

HIGHLIGHTS

- Genetic animal models mimic the spectrum of human malformations of cortical development.
- Advanced genetic methods have engineered increasingly sophisticated animal models of cortical malformations.
- Distinct and overlapping mechanisms of epileptogenesis occur across different animal models of cortical malformations.
- Animal models have identified novel therapeutic targets for epilepsy, such as the mTOR pathway.

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ABSTRACT

Malformations of cortical development constitute a variety of pathological brain abnormalities that commonly cause severe, medically-refractory epilepsy, including focal lesions, such as focal cortical dysplasia, heterotopias, and tubers of tuberous sclerosis complex, and diffuse malformations, such as lissencephaly. Although some cortical malformations result from environmental insults during cortical development in utero, genetic factors are increasingly recognized as primary pathogenic factors across the entire spectrum of malformations. Genes implicated in causing different cortical malformations are involved in a variety of physiological functions, but many are focused on regulation of cell proliferation, differentiation, and neuronal migration. Advances in molecular genetic methods have allowed the engineering of increasingly sophisticated animal models of cortical malformations and associated epilepsy. These animal models have identified some common mechanistic themes shared by a number of different cortical malformations, but also revealed the diversity and complexity of cellular and molecular mechanisms that lead to the development of the pathological lesions and resulting epileptogenesis.

Contents

* Corresponding author at: Department of Neurology, Box 8111, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO 63110, USA. Tel.: +1 314 362 8713; fax: +1 314 362 9462.
E-mail address: wong_m@wustl.edu (M. Wong).

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1. Introduction

Malformations of cortical development represent a spectrum of pathological abnormalities of the brain, which are commonly associated with epilepsy (Aronica et al., 2012; Guerrini and Dobyns, 2014). Depending on the type of cortical malformation, epilepsy is typically severe, often with onset of seizures early in childhood or infancy. In addition, epilepsy associated with malformation of cortical development is frequently intractable or resistant to available anti-seizure medications. Patients with localized, isolated cortical malformations, such as focal cortical dysplasia, may be candidates for epilepsy surgery (Hauptman and Mathern, 2012). However, many malformations of cortical development, such as lissencephaly, have extensive, bilateral involvement of the cortex and generate generalized or multifocal seizures, making epilepsy surgery difficult or impossible. Furthermore, even in patients with localized malformations, the actual region of cortical disorganization may extend microscopically beyond the gross anatomical lesion apparent on imaging tests, often leading to failure of epilepsy surgery. Thus, understanding the pathogenesis of malformations of cortical development and the associated mechanisms of epileptogenesis is critical for developing more effective therapies for epilepsy related to these cortical malformations.

Although some malformations of cortical development are caused by environmental insults that occur during cortical development in utero, genetic factors also play a critical role in the pathogenesis of many cortical malformations (Guerrini and Dobyns, 2014). With the explosion in diagnostic technologies in genetics, specific genetic mutations are increasingly identified as causes of different malformations of cortical development. Recognized gene defects may disrupt a variety of different cellular and molecular processes during cortical development. However, many of these genes are involved in relatively selective functions, such as regulation of cell proliferation and survival, cell cycle, and neuronal migration.

The impact of a genetic mutation in causing a particular type of cortical malformation also depends on the stage of cortical development that is most directly affected. Cortical development is divided into at least three, overlapping stages: cellular proliferation and differentiation, neuronal migration, and postmigrational cortical organization. The standard classification scheme for cortical malformations is based on the stage at which cortical development is first disrupted (Barkovich et al., 2012, 2009). Although there are numerous types of malformations of cortical development, only a few categories are most commonly utilized in clinical practice. For example, most types of focal cortical dysplasia and dysplastic megalencephaly are typically considered defects in cellular proliferation and differentiation. The spectrum of lissencephalies and heterotopias likely results from disorders of neuronal migration. Polymicrogyria may primarily relate to abnormalities in postmigrational cortical organization. Despite this logical mechanistic-based classification scheme, it is increasingly recognized that these categorizations are overly simplified. There is considerable overlap between different types of malformations of cortical development, and some may result from defects in multiple stages of cortical development. To a large extent, advances in genetics, and the associated biological pathways involved, will help refine the classification system and provide insights into the true mechanistic relationships between different types of cortical malformations.

Animal models, particularly transgenic mice, represent powerful tools for investigating genetic mechanisms of cortical malformations and epilepsy. Many genetic mutations causing human cortical malformations and epilepsy have been engineered in mice and other model systems. Although there are significant limitations to the degree and fidelity to which animal models may mimic human pathology and physiology, animal models have begun to reveal important, translationally-relevant insights into the pathogenesis of cortical malformations and associated mechanisms of epileptogenesis. In this paper, we will review selected examples of animal models of malformations of cortical development and epilepsy, representing different types within the mechanistic classification scheme, and discuss general limitations and future directions for these models.

2. Animal models of different types of malformations of cortical development

2.1. Focal cortical dysplasia

Focal cortical dysplasia is a common cause of drug-resistant focal epilepsy and often identified in pathological specimens resected from patients receiving epilepsy surgery. Pathologically, focal cortical dysplasia is primarily characterized by discrete localized regions of disorganized cortical lamination and morphologically abnormal cells. A standardized classification system for focal cortical dysplasia has been proposed, including three main tiers (Blumcke et al., 2011; Marin-Valencia et al., 2014). Type I primarily involves localized areas of abnormal cortical layering. In addition to cortical dyslamination, Type II is characterized by dysmorphic neurons, with the subtype IIb also containing stereotypic, undifferentiated balloon cells. Finally, Type III is associated with other dual pathologies, such as hippocampal sclerosis, developmental tumors, and vascular malformations. Many cases of focal cortical dysplasia Type I and Type III may result from late postmigrational cortical defects or injuries. In contrast, focal cortical dysplasia Type II represents the prototypical malformation of cortical development presumed to result from primary defects in cell proliferation and differentiation and has been strongly linked to genetic mutations in pathways controlling these functions, such as the mammalian target of rapamycin (mTOR) pathway.

2.1.1. Irradiation model in rats

In utero irradiation of rats serves as a model of Type Ib human focal cortical dysplasia. Although it has been included in this review article for comparison, it is not a genetic model of epilepsy. It is an injury-based model. Exposing fetal rats in utero to about 200 cGy of external radiation on embryonic day 17 (E17) results in offspring with diffuse (not focal) cortical abnormalities that include microcephaly, thinning of the cortical mantle, loss of lamination of the neocortex, and spatial disorientation of the neurons within the neocortex (Cowan and Geller, 1960; Roper et al., 1995). In addition, the animals show nodular periventricular and subcortical heterotopia. They also show focal areas of ectopic neurons in the CA1 region of the hippocampus, something that is not commonly seen in human malformations of cortical development. The mechanism of creating the dysplasia involves the selective killing of a large number of cells in the fetal cerebral hemispheres followed by an attempt by the surviving cells to create the cortex in an altered environment.