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Early Rescue of Interneuron Disease Trajectory in Developmental Epilepsies

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Abstract

The discovery of over 150 monogenic epilepsies and advances in early genetic diagnoses have launched a search for molecular strategies and developmental timetables to reverse or even prevent the course of these debilitating brain disorders. Orthologous rodent models of key disease genes are providing important examples of the range of targets, and serve as valuable test systems for perinatal therapeutic approaches. While gene-specific analyses of single rare ‘orphan’ diseases are each narrow in scope, they illuminate downstream pathways converging onto interneurons, and treatments that strengthen inhibition during cortical maturation may provide broad protection against these seemingly disparate gene errors. Several genes, even those linked to malformations, show promise for postnatal correction before the onset of their clinical phenotype.

Introduction

Over 150 single gene errors lead to seizure phenotypes, and many of these are early in onset, with life-long comorbid neurological phenotypes that carry a vast health care burden, including cognitive impairment, autism, depression, and premature mortality. Genetic and neurobiological evidence points to critical impairment of synaptic inhibition, the key regulator of dynamic balance of cortical network activity, as a shared hallmark of these neuronal synchronization disorders. Genes for pediatric epilepsy identified so far include those encoding transcription factors, signaling molecules, membrane proteins, and secreted proteins, and define a rich spectrum of biological defects in key programs of brain development, ranging from neuronal proliferation and migration to survival, connectivity and excitability. While interneurons are not alone in defining inhibition within a network, they are the target of at least one third of these genes [1].

The ability to perform repairs on the many roads leading to developmental disinhibition is entering an era when neural circuits can be stably modified by drugs that remodel gene

expression, insertion of genes, and the transplantation of cells, all justifiable strategies when other effective therapies are not available. Early modification may provide the greatest opportunity to harness the developmental plasticity of neural circuits. The current challenge is to identify in each case the deleterious events and critical periods to intervene before irreversible network defects appear (Figure 1). Once these obstacles are surmounted, the era of clinical management of gene expression in these cortical excitability disorders will have arrived.

Here we review recent studies that attempt to identify critical periods in brain development and how targeting mutant interneurons may alter the trajectory of disease. Since there are nearly one hundred different types of interneurons with their own connectivity, firing properties, and maturational profiles [2,3], an optimistic view amidst the expanding biological complexity is that many will respond to common proliferative, motogenic, and synaptogenic signals, and that therapies appropriately timed to alter their circuit dynamics during this developmental window may be shared to some degree across genes and phenotypes.

Estradiol rescue of *Arx* mutations in catastrophic epilepsies

Mutations in *Aristaless-Related homeobox* (*ARX*) (OMIM 300382) provide a prototypical example of how primary intrinsic interneuron abnormalities lead to a complex developmental epilepsy, X-linked Infantile Spasms Syndrome (ISSX). Defects in this X-linked transcription factor cause a pleiotropic array of neurodevelopmental disorders including infantile spasms, epilepsy, intellectual disability, and autism spectrum disorder [4,5]. *Arx* encodes a multidomain transcription factor expressed solely in developing and mature interneurons. Individuals with *ARX* mutations and orthologous mouse models exhibit losses of cortical interneuron subtypes due to de-repression of *Arx*- dependent growth signals [6–8]. Several allelic mouse models have been developed and display neurological phenotypes such as epilepsy, cognitive and behavioral phenotypes [9,10].

$ARX^{(GCG)10+7}$ (c.333_334ins$(GCG)_7$), a trinucleotide repeat expansion mutation in the first poly-alanine tract domain of *ARX*, is a common cause of ISSX [11]. Two models of this expansion mutation have been developed, $Arx^{(GCG)7}$ [12] and $Arx^{(GCG)10+7}$ [13]. In both models, ARX expression is reduced with selective loss of GABAergic and cholinergic interneuron immunoreactivity in the neocortex and striatum [12–14]. These expansion mutations result in loss of ARX binding to the transcriptional co-repressor, Groucho/transducin-like enhancer of Split (Tle1) [15], and lower transcription of the lysine-specific demethylase 5C (KDM5C), a histone demethylase [16]. This suggests that ARX poly-alanine expansion mutations disrupt the transcriptional regulation capacity of ARX and perturb histone methylation patterns in cortical interneurons, contributing to aberrant interneuronal phenotypes seen in patients [17].

ISSX has been a challenging disorder to treat as patients, like those with idiopathic infantile spasms, are poorly responsive to adrenocorticotropic hormone (ACTH) and antiepileptic drugs [18]. In search of alternative therapy, the effects of estrogen, a neuroprotective hormone, were explored. Daily postnatal treatment of $Arx^{(GCG)10+7}$ mutant mice for one

week with the neurosteroid 17β-estradiol (E2), restored the decreased forebrain interneuron numbers, reduced neonatal spasms, and prevented seizures in adults [19]. E2 treatment was ineffective when administered to adults, indicating a critical, neonatal window in which E2 corrects pathological processes and modifies disease (Figure 2) [19]. E2 acts on ERα and ERβ receptors located on the plasma membrane or in the cytoplasm, which then activate downstream pathways via transcriptional regulation or non-genomic mediated signaling [20]. ERs are expressed in developing interneurons, and stimulation of these complex pathways may increase migration and survival of these cells [21,22]. It is unclear what factors govern the critical neonatal treatment window, but this may be determined by cell-autonomous events of interneurons and mediated by ERs which display a developmentally-regulated expression pattern in the neonatal rodent cortex [23,24]. E2 and related estrogens show neural and glial protective effects in early CNS injury models [20], and activation of ERs may stimulate transcriptional rescue of *Arx* mutant interneurons either through recovery of *Arx*- deficient gene expression or other pathways. While E2 has not yet been used clinically in the treatment of ISSX, a clinical trial can be planned once safety concerns have been fully addressed. Future work is needed to understand the mechanism of E2 in the $Arx^{(GCG)10+7}$ model and its benefits in other genetic models of epilepsy with similar phenotypes.

Calpain inhibitor rescue of *Lis1* neuronal migration disorders

Abnormalities in neuronal migration perturb cortical layering patterns, disrupt the neural networks that rely on this cytoarchitecture, and may be tractable to reversal strategies [25]. Gene-linked migration disorders include lissencephaly, subcortical band heterotopia/double cortex syndrome, and focal cortical dysplasias [25,26]. Deletions in the *LIS1* gene (OMIM 607432) and a microdeletion that encompasses *LIS1* (Miller-Dieker Syndrome) are causes of lissencephaly and often have severe, intractable epilepsy appearing early in life [27]. Lis1 is essential for regulation and localization of cytoplasmic dynein [28], and knockout mouse models have revealed that cortical interneurons deficient in *Lis1* exhibit defective migration due to unstable leading neuritic branch processes [29–31]. *Lis1* +/− knockout mice display spontaneous seizures [32], cognitive deficits [33], and motor deficits [34]. Based on the finding that Lis1 protein is degraded by calpain proteases, Yamada and colleagues tested the effects of calpain protease inhibitors in normalizing Lis1 expression and rescuing aberrant phenotypes in *Lis1* heterozygous knockout mice [34]. Injection of calpain protease inhibitors and shRNA knockdown of calpain normalized Lis1 protein expression in $Lis1^{+/-}$ brains, rescued migration of cultured $Lis1^{+/-}$ cerebellar granule neurons, and partially rescued cortical lamination defects in the $Lis1^{+/-}$ neocortex [34]. *In utero* treatment with calpain inhibitors also rescued motor deficits in $Lis1^{+/-}$ mice, however, it has not yet been determined if calpain inhibitors have any effect on cortical interneuron migration, seizures or cognitive phenotypes in the $Lis1^{+/-}$ mice. Since calpain inhibitors were administered *in utero*, it is also unknown whether postnatal administration of calpain inhibitors in *Lis1* knockout mice can still increase *Lis1* expression, stimulate migration, and improve the neurological deficits. Even once the wave of normal interneuron migration is largely complete, data from transplanted newborn wild type interneurons show they can migrate short distances in a mature neocortex [35], and it is possible that calpain inhibitors may

improve migration and synaptic integration of *Lis1* mutant interneurons in cortical circuits regardless of anomalous laminar patterns.

Transgenic rescue of *Doublecortin* mutations

Doublecortin (*DCX*) (OMIM 300121) is located on the X-chromosome and *DCX* missense mutations are a common cause of X-linked lissencephaly and subcortical band heterotopia, with a high incidence of epilepsy [26,36]. *DCX* encodes a microtubule-associated protein expressed in migrating neurons and involved in microtubule stabilization [37]. Neuropathological case studies reveal that human *DCX* mutations result in loss of cortical GABAergic interneurons [17]. Studies in mouse and rat models have shown that *Dcx* is important for cortical interneuron migration and reduction of *Dcx* expression results in loss of interneuron subtypes in the neocortex and hippocampus [38,39]. Interestingly, while genetic deletion of *Dcx* in mouse fails to produce the same pattern of neocortical heterotopia, the hippocampal cortex is dyslaminated, and *Dcx* knockout mice still exhibit a seizure phenotype [39]. In rat however, knockdown of *Dcx* in the embryonic brain by shRNA led to aberrant lamination and morphology of cortical neurons [40]. Manent and colleagues demonstrated that postnatal re-expression of *Dcx* following embryonic *Dcx* knockdown rescued cortical lamination defects and the efficiency of rescue was developmentally dependent, since early rescue of *Dcx* expression was more effective in restoring cortical lamination than late postnatal rescue [41]. Knockdown of *Dcx* in the rat model has not been shown to cause spontaneous seizures, however postnatal re-expression of *Dcx* rescued the lowered pentylenetetrazol seizure threshold in *Dcx* knockdown rats [41]. This suggests that aberrant excitability phenotypes due to hypomorphic *DCX* mutations may be improved by increasing postnatal *DCX* expression despite the early migration defect during embryonic development.

mTOR inhibition in the “mTORopathies”

Hyperactivation of the mechanistic target of rapamycin (mTOR) signaling complex has been observed in several monogenic developmental epilepsies, and may represent a hub for early rescue. mTOR complexes control multiple cellular processes including autophagy, protein synthesis, actin dynamics, and mitochondrial function [42]. Somatic or inherited mutations in *TSC1* (OMIM 605284), *TSC2* (OMIM 613254), *PTEN* (OMIM 601728), *STRADα*(OMIM 608626), and *MTOR* (OMIM 601231) cause developmental epilepsies, brain malformation syndromes, and affect cellular development of glia and excitatory and inhibitory neurons in the developing brain [42–44]. *TSC1* and *TSC2* are potent negative regulators of mTOR, and mutations in these genes result in focal epilepsy and infantile spasms in up to 75 percent of cases [45,46]. Mouse models have defined several disinhibitory mechanisms by which dysfunction of *Tsc1* and augmented mTOR signaling generate seizures [42,44]. In particular, conditional deletion of *Tsc1* in interneuron progenitors increased mTOR signaling in GABAergic interneurons, leading to loss of interneuron subtypes, lower convulsant-induced seizure threshold, and early mortality [47].

Phosphatase and tensin homolog (*PTEN*), a tumor suppressor gene, encodes another upstream negative regulator of mTOR. Loss of function mutations in *PTEN* are associated

with brain malformation disorders and lead to a number of morphologic and functional abnormalities in the brain including dysmorphic neurons, macrocephaly, and seizures [42]. GABAergic interneuron subtypes are also affected by *Pten* knockout. Conditional deletion of *Pten* from GABAergic interneuron progenitors disrupted the ratios of two cortical interneuron subtypes, parvalbumin+ and somatostatin+ interneurons, and *Pten* expression was also crucial for cortical interneuron morphology [48]. Transplant of *Pten*-deficient cortical interneuron progenitors into fetal WT brain did not rescue their mutant cellular phenotypes, suggesting that *Pten* function during interneuron development is cell-autonomous [48].

Since pathophysiological mTOR upregulation is common amongst these monogenic disorders, it defines a broader therapeutic target, and recent data indicate that inhibitors of mTOR modify the course of disease in both animal models and in human clinical studies. Rapamycin and clinical analogs reduce seizures and improve other associated phenotypes in models of *Tsc1*, *Tsc2*, and *Pten* [42,44]. Rapamycin has been shown to not only reduce seizures once they have become manifest, but also to prevent epileptogenesis in these models [49–51]. Human studies with rapamycin analogs found these mTOR inhibitors reduced seizures and other clinical manifestations of tuberous sclerosis complex due to *TSC1/TSC2* mutations [45,52,53], and polyhydramnios, megalencephaly, and symptomatic epilepsy (PMSE) caused by STRADα mutations[54]. Despite their efficacy in seizure reduction, few studies have examined the effects of these inhibitors in *Pten* or *TSC1*/*TSC2*-associated infantile spasms. Vigabatrin, a GABA transaminase inhibitor that elevates GABA levels, has been shown to be effective for infantile epilepsies and has become a first-choice drug for treatment of *TSC1*/*TSC2*-associated infantile spasms [45,46]. The opportunity to diagnose these mutations prenatally in humans augurs a clinical trial of early pre-seizure intervention in this disorder.

Tau ablation rescue of ion channelopathy

Mutation of ion channel subunit genes comprises the largest fraction of known epilepsy mutations, and human and experimental evidence indicates that their phenotype is particularly susceptible to epistatic masking, even by subunits among the 400 member voltage-gated channel gene family [55,56]. Recent studies have defined MAPT (Tau), a microtubule stabilizing protein highly expressed in axons, as a particularly strong gene modifier of epilepsy arising from potassium (*Kcna1/Kv1.1*) [57] and sodium (*Scn1a/NaV1.1*) [58] channel mutants. Deletion of *Tau* rescued neural hyperexcitability, megencephaly, and early lethality in *Kcna1* knockout mice [57]. Recent work has also shown that loss of Tau in *Kcna1* knockout mice corrected the lower threshold for spreading depolarization in the brainstem, a mechanism thought to contribute to sudden, unexpected death in epilepsy (SUDEP) [59]. Despite being a potent phenotypic modifier, little is known about the mechanism of *Tau* loss in reducing hyperexcitability in models of ion channelopathy, and whether there is a critical developmental window for its therapeutic action.

Conclusion

New monogenic causes of epilepsy found in the clinical exome continue to emerge, and we are only at the beginning of exploring early reversibility in these gene disorders. Interneurons are an important common starting point, but certainly not the sole target to prevent the development of epilepsy. What is critical to realize is that even when gene defects are cell-type specific, both selective and non-selective treatment strategies can be developed, taking advantage of plasticity at this early stage by altering the cellular milieu. A second important take home message is that seizures may be separable from structural circuit abnormalities. For example, some genes produce striking brain malformations such as cortical dyslamination in the double cortex syndrome (*DCX*), or prominent balloon cells and tubers of tuberous sclerosis (*TSC1*), however, mouse models show that these structural defects are not essential for epilepsy to occur [26,42]. Thus partial phenotypic rescue, that is preventing seizures, may be possible even in the face of major brain malformations. These studies serve as optimistic reminders that just as many genes lead to epilepsy, there may be multiple ways of therapeutically masking the most deleterious effects and improving the outcomes of patients with developmental epilepsies.

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References

Papers of particular interest, published within the period of review, have been highlighted as:

• of special interest

•• of outstanding interest

1•. Noebels J. Pathway-driven discovery of epilepsy genes. Nat Neurosci. 2015; 18:344–350. This review surveys the genetic and neurogenetic pathways causing epilepsy. [PubMed: 25710836]

2. Rudy B, Fishell G, Lee S, Hjerling-Leffler J. Three groups of interneurons account for nearly 100% of neocortical GABAergic neurons. Dev Neurobiol. 2011; 71:45–61. [PubMed: 21154909]

3••. Kepecs A, Fishell G. Interneuron cell types are fit to function. Nature. 2014; 505:318–326. An excellent review of the development, functional properties, and classification of GABAergic interneurons. [PubMed: 24429630]

4. Stromme P, Mangelsdorf ME, Shaw MA, Lower KM, Lewis SM, Bruyere H, Lutcherath V, Gedeon AK, Wallace RH, Scheffer IE, et al. Mutations in the human ortholog of Aristaless cause X-linked mental retardation and epilepsy. Nat Genet. 2002; 30:441–445. [PubMed: 11889467]

5. Turner G, Partington M, Kerr B, Mangelsdorf M, Gecz J. Variable expression of mental retardation, autism, seizures, and dystonic hand movements in two families with an identical ARX gene mutation. Am J Med Genet. 2002; 112:405–411. [PubMed: 12376946]

6. Colasante G, Sessa A, Crispi S, Calogero R, Mansouri A, Collombat P, Broccoli V. Arx acts as a regional key selector gene in the ventral telencephalon mainly through its transcriptional repression activity. Dev Biol. 2009; 334:59–71. [PubMed: 19627984]

7. Poirier K, Van Esch H, Friocourt G, Saillour Y, Bahi N, Backer S, Souil E, Castelnau-Ptakhine L, Beldjord C, Francis F, et al. Neuroanatomical distribution of ARX in brain and its localisation in GABAergic neurons. Brain Res Mol Brain Res. 2004; 122:35–46. [PubMed: 14992814]

8. Colombo E, Galli R, Cossu G, Gecz J, Broccoli V. Mouse orthologue of ARX, a gene mutated in several X-linked forms of mental retardation and epilepsy, is a marker of adult neural stem cells and forebrain GABAergic neurons. Dev Dyn. 2004; 231:631–639. [PubMed: 15376319]

9. Marsh, ED.; Golden, JA. Developing Models of Aristaless-related homeobox mutations. In: Noebels, JL.; Avoli, M.; Rogawski, MA.; Olsen, RW.; Delgado-Escueta, AV., editors. Jasper's Basic Mechanisms of the Epilepsies. 4. 2012.

10•. Olivetti PR, Noebels JL. Interneuron, interrupted: molecular pathogenesis of ARX mutations and X-linked infantile spasms. Curr Opin Neurobiol. 2012; 22:859–865. This review summarizes murine *Arx* models and known mechanisms that contribute to *Arx* interneuronopathies. [PubMed: 22565167]

11. Poirier K, Eisermann M, Caubel I, Kaminska A, Peudonnier S, Boddaert N, Saillour Y, Dulac O, Souville I, Beldjord C, et al. Combination of infantile spasms, non-epileptic seizures and complex movement disorder: a new case of ARX-related epilepsy. Epilepsy Res. 2008; 80:224–228. [PubMed: 18468866]

12. Kitamura K, Itou Y, Yanazawa M, Ohsawa M, Suzuki-Migishima R, Umeki Y, Hohjoh H, Yanagawa Y, Shinba T, Itoh M, et al. Three human ARX mutations cause the lissencephaly-like and mental retardation with epilepsy-like pleiotropic phenotypes in mice. Hum Mol Genet. 2009; 18:3708–3724. [PubMed: 19605412]

13. Price MG, Yoo JW, Burgess DL, Deng F, Hrachovy RA, Frost JD Jr, Noebels JL. A triplet repeat expansion genetic mouse model of infantile spasms syndrome, Arx(GCG)10+7, with interneuronopathy, spasms in infancy, persistent seizures, and adult cognitive and behavioral impairment. J Neurosci. 2009; 29:8752–8763. [PubMed: 19587282]

14. Lee K, Mattiske T, Kitamura K, Gecz J, Shoubridge C. Reduced polyalanine-expanded Arx mutant protein in developing mouse subpallium alters Lmo1 transcriptional regulation. Hum Mol Genet. 2014; 23:1084–1094. [PubMed: 24122442]

15. Nasrallah MP, Cho G, Simonet JC, Putt ME, Kitamura K, Golden JA. Differential effects of a polyalanine tract expansion in Arx on neural development and gene expression. Hum Mol Genet. 2012; 21:1090–1098. [PubMed: 22108177]

16. Poeta L, Fusco F, Drongitis D, Shoubridge C, Manganelli G, Filosa S, Paciolla M, Courtney M, Collombat P, Lioi MB, et al. A regulatory path associated with X-linked intellectual disability and epilepsy links KDM5C to the polyalanine expansions in ARX. Am J Hum Genet. 2013; 92:114–125. [PubMed: 23246292]

17. Marcorelles P, Laquerriere A, Adde-Michel C, Marret S, Saugier-Veber P, Beldjord C, Friocourt G. Evidence for tangential migration disturbances in human lissencephaly resulting from a defect in LIS1, DCX and ARX genes. Acta Neuropathol. 2010; 120:503–515. [PubMed: 20461390]

18. Swann, JW.; Moshe, SL. On the Basic Mechanisms of Infantile Spasms. In: Noebels, JL.; Avoli, M.; Rogawski, MA.; Olsen, RW.; Delgado-Escueta, AV., editors. Jasper's Basic Mechanisms of the Epilepsies. 4. 2012.

19••. Olivetti PR, Maheshwari A, Noebels JL. Neonatal estradiol stimulation prevents epilepsy in Arx model of X-linked infantile spasms syndrome. Sci Transl Med. 2014; 6:220ra212. This study is the first to describe an early therapeutic intervention that prevents epilepsy and rescues interneuron subtypes in an *Arx* model of catastrophic epilepsy.

20. Arevalo MA, Azcoitia I, Garcia-Segura LM. The neuroprotective actions of oestradiol and oestrogen receptors. Nat Rev Neurosci. 2015; 16:17–29. [PubMed: 25423896]

21. Blurton-Jones M, Tuszynski MH. Estrogen receptor-beta colocalizes extensively with parvalbumin-labeled inhibitory neurons in the cortex, amygdala, basal forebrain, and hippocampal formation of intact and ovariectomized adult rats. J Comp Neurol. 2002; 452:276–287. [PubMed: 12353223]

22. Fan X, Warner M, Gustafsson JA. Estrogen receptor beta expression in the embryonic brain regulates development of calretinin-immunoreactive GABAergic interneurons. Proc Natl Acad Sci U S A. 2006; 103:19338–19343. [PubMed: 17159139]

23. Kritzer MF. Regional, laminar and cellular distribution of immunoreactivity for ERbeta in the cerebral cortex of hormonally intact, postnatally developing male and female rats. Cereb Cortex. 2006; 16:1181–1192. [PubMed: 16221921]

24. Sugiyama N, Andersson S, Lathe R, Fan X, Alonso-Magdalena P, Schwend T, Nalvarte I, Warner M, Gustafsson JA. Spatiotemporal dynamics of the expression of estrogen receptors in the postnatal mouse brain. Mol Psychiatry. 2009; 14:223–232. 117. [PubMed: 18982005]

25•. Manent, JB.; LoTurco, J. Reversing Disorders of Neuronal Migration and Differentiation in Animal Models. In: Noebels, JL.; Avoli, M.; Rogawski, MA.; Olsen, RW.; Delgado-Escueta, AV., editors. Jasper's Basic Mechanisms of the Epilepsies. 4. 2012. This review provides an overview of models of neuronal migration and therapies used to rescue these developmental defects

26. Wong M, Roper SN. Genetic animal models of malformations of cortical development and epilepsy. J Neurosci Methods. 2015

27. Kato M. Genotype-phenotype correlation in neuronal migration disorders and cortical dysplasias. Front Neurosci. 2015; 9:181. [PubMed: 26052266]

28. Yamada M, Toba S, Yoshida Y, Haratani K, Mori D, Yano Y, Mimori-Kiyosue Y, Nakamura T, Itoh K, Fushiki S, et al. LIS1 and NDEL1 coordinate the plus-end-directed transport of cytoplasmic dynein. EMBO J. 2008; 27:2471–2483. [PubMed: 18784752]

29. McManus MF, Nasrallah IM, Pancoast MM, Wynshaw-Boris A, Golden JA. Lis1 is necessary for normal non-radial migration of inhibitory interneurons. Am J Pathol. 2004; 165:775–784. [PubMed: 15331402]

30. Nasrallah IM, McManus MF, Pancoast MM, Wynshaw-Boris A, Golden JA. Analysis of non-radial interneuron migration dynamics and its disruption in Lis1+/− mice. J Comp Neurol. 2006; 496:847–858. [PubMed: 16628622]

31. Gopal PP, Simonet JC, Shapiro W, Golden JA. Leading process branch instability in Lis1+/− nonradially migrating interneurons. Cereb Cortex. 2010; 20:1497–1505. [PubMed: 19861636]

32. Greenwood JS, Wang Y, Estrada RC, Ackerman L, Ohara PT, Baraban SC. Seizures, enhanced excitation, and increased vesicle number in Lis1 mutant mice. Ann Neurol. 2009; 66:644–653. [PubMed: 19938147]

33. Paylor R, Hirotsune S, Gambello MJ, Yuva-Paylor L, Crawley JN, Wynshaw-Boris A. Impaired learning and motor behavior in heterozygous Pafah1b1 (Lis1) mutant mice. Learn Mem. 1999; 6:521–537. [PubMed: 10541472]

34••. Yamada M, Yoshida Y, Mori D, Takitoh T, Kengaku M, Umeshima H, Takao K, Miyakawa T, Sato M, Sorimachi H, et al. Inhibition of calpain increases LIS1 expression and partially rescues in vivo phenotypes in a mouse model of lissencephaly. Nat Med. 2009; 15:1202–1207. This study describes rescue of *Lis1* expression by treatment with a protease inhibitor, rescue of motor phenotypes and partial reversal of cortical lamination defects in *Lis1*$^{+/-}$ mice. [PubMed: 19734909]

35•. Southwell DG, Nicholas CR, Basbaum AI, Stryker MP, Kriegstein AR, Rubenstein JL, Alvarez-Buylla A. Interneurons from embryonic development to cell-based therapy. Science. 2014; 344:1240622. An excellent review on the state of interneuron transplantation research. [PubMed: 24723614]

36. Gleeson JG, Allen KM, Fox JW, Lamperti ED, Berkovic S, Scheffer I, Cooper EC, Dobyns WB, Minnerath SR, Ross ME, et al. Doublecortin, a brain-specific gene mutated in human X-linked lissencephaly and double cortex syndrome, encodes a putative signaling protein. Cell. 1998; 92:63–72. [PubMed: 9489700]

37. Gleeson JG, Lin PT, Flanagan LA, Walsh CA. Doublecortin is a microtubule-associated protein and is expressed widely by migrating neurons. Neuron. 1999; 23:257–271. [PubMed: 10399933]

38. Friocourt G, Liu JS, Antypa M, Rakic S, Walsh CA, Parnavelas JG. Both doublecortin and doublecortin-like kinase play a role in cortical interneuron migration. J Neurosci. 2007; 27:3875–3883. [PubMed: 17409252]

39. Nosten-Bertrand M, Kappeler C, Dinocourt C, Denis C, Germain J, Phan Dinh Tuy F, Verstraeten S, Alvarez C, Metin C, Chelly J, et al. Epilepsy in Dcx knockout mice associated with discrete lamination defects and enhanced excitability in the hippocampus. PLoS One. 2008; 3:e2473. [PubMed: 18575605]

40. Bai J, Ramos RL, Ackman JB, Thomas AM, Lee RV, LoTurco JJ. RNAi reveals doublecortin is required for radial migration in rat neocortex. Nat Neurosci. 2003; 6:1277–1283. [PubMed: 14625554]

41••. Manent JB, Wang Y, Chang Y, Paramasivam M, LoTurco JJ. Dcx reexpression reduces subcortical band heterotopia and seizure threshold in an animal model of neuronal migration disorder. Nat Med. 2009; 15:84–90. This study showed that postnatal reexpression of *Dcx* in a *Dcx* RNAi rat model, rescued neuronal migration defects, the first demonstration that neuronal migration can be rescued postnatally despite embryonic defects. [PubMed: 19098909]

42•. Lipton JO, Sahin M. The neurology of mTOR. Neuron. 2014; 84:275–291. A thorough review of the functions and molecular pathways of *mTOR*, *TSC1*, *TSC2*, and *PTEN* and accompanying mouse models. [PubMed: 25374355]

43. Nakashima M, Saitsu H, Takei N, Tohyama J, Kato M, Kitaura H, Shiina M, Shirozu H, Masuda H, Watanabe K, et al. Somatic Mutations in the MTOR gene cause focal cortical dysplasia type IIb. Ann Neurol. 2015; 78:375–386. [PubMed: 26018084]

44••. Crino PB. mTOR signaling in epilepsy: insights from malformations of cortical development. Cold Spring Harb Perspect Med. 2015; 5 An insightful review of the neurological conditions caused by various mutations that upregulate mTOR signaling. Also provides a review of somatic mutations in mTORopathies.

45. Curatolo P. Mechanistic target of rapamycin (mTOR) in tuberous sclerosis complex-associated epilepsy. Pediatr Neurol. 2015; 52:281–289. [PubMed: 25591831]

46. Overwater IE, Bindels-de Heus K, Rietman AB, Ten Hoopen LW, Vergouwe Y, Moll HA, de Wit MC. Epilepsy in children with tuberous sclerosis complex: Chance of remission and response to antiepileptic drugs. Epilepsia. 2015; 56:1239–1245. [PubMed: 26046563]

47. Fu C, Cawthon B, Clinkscales W, Bruce A, Winzenburger P, Ess KC. GABAergic interneuron development and function is modulated by the Tsc1 gene. Cereb Cortex. 2012; 22:2111–2119. [PubMed: 22021912]

48. Vogt D, Cho KK, Lee AT, Sohal VS, Rubenstein JL. The parvalbumin/somatostatin ratio is increased in Pten mutant mice and by human PTEN ASD alleles. Cell Rep. 2015; 11:944–956. [PubMed: 25937288]

49. Meikle L, Pollizzi K, Egnor A, Kramvis I, Lane H, Sahin M, Kwiatkowski DJ. Response of a neuronal model of tuberous sclerosis to mammalian target of rapamycin (mTOR) inhibitors: effects on mTORC1 and Akt signaling lead to improved survival and function. J Neurosci. 2008; 28:5422–5432. [PubMed: 18495876]

50••. Zeng LH, Xu L, Gutmann DH, Wong M. Rapamycin prevents epilepsy in a mouse model of tuberous sclerosis complex. Ann Neurol. 2008; 63:444–453. This study demonstrated that in a *TSC1* model of tuberous sclerosis and epilepsy, rapamycin treatment prior to the onset of neurological phenotypes prevents development of epilepsy. [PubMed: 18389497]

51. Rensing N, Han L, Wong M. Intermittent dosing of rapamycin maintains antiepileptogenic effects in a mouse model of tuberous sclerosis complex. Epilepsia. 2015; 56:1088–1097. [PubMed: 26122303]

52. Franz DN, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, Witt O, Kohrman MH, Flamini JR, Wu JY, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2013; 381:125–132. [PubMed: 23158522]

53. Krueger DA, Wilfong AA, Holland-Bouley K, Anderson AE, Agricola K, Tudor C, Mays M, Lopez CM, Kim MO, Franz DN. Everolimus treatment of refractory epilepsy in tuberous sclerosis complex. Ann Neurol. 2013; 74:679–687. [PubMed: 23798472]

54. Parker WE, Orlova KA, Parker WH, Birnbaum JF, Krymskaya VP, Goncharov DA, Baybis M, Helfferich J, Okochi K, Strauss KA, et al. Rapamycin prevents seizures after depletion of STRADA in a rare neurodevelopmental disorder. Sci Transl Med. 2013; 5:182ra153.

55. Glasscock E, Qian J, Yoo JW, Noebels JL. Masking epilepsy by combining two epilepsy genes. Nat Neurosci. 2007; 10:1554–1558. [PubMed: 17982453]

56. Klassen T, Davis C, Goldman A, Burgess D, Chen T, Wheeler D, McPherson J, Bourquin T, Lewis L, Villasana D, et al. Exome sequencing of ion channel genes reveals complex profiles

confounding personal risk assessment in epilepsy. Cell. 2011; 145:1036–1048. [PubMed: 21703448]

57•. Holth JK, Bomben VC, Reed JG, Inoue T, Younkin L, Younkin SG, Pautler RG, Botas J, Noebels JL. Tau loss attenuates neuronal network hyperexcitability in mouse and Drosophila genetic models of epilepsy. J Neurosci. 2013; 33:1651–1659. This study showed that genetic deletion of *Tau* prevents megencephaly, epilepsy, and extends lifespan of the *Kcna1* mouse model of ion channelopathy. [PubMed: 23345237]

58•. Gheyara AL, Ponnusamy R, Djukic B, Craft RJ, Ho K, Guo W, Finucane MM, Sanchez PE, Mucke L. Tau reduction prevents disease in a mouse model of Dravet syndrome. Ann Neurol. 2014; 76:443–456. This study also showed that genetic *Tau* deletion is a phenotypic modifier of epilepsy in *Scn1a* model of Dravet Syndrome. [PubMed: 25042160]

59••. Aiba I, Noebels JL. Spreading depolarization in the brainstem mediates sudden cardiorespiratory arrest in mouse SUDEP models. Sci Transl Med. 2015; 7:282ra246. This study showed that genetic *Tau* deletion prolonged survival in *Kcna1* and *Scna1* mutant mice by preventing cardiorespiratory collapse due to spreading depolarization in brainstem nuclei.

Highlights

- Interneuron defects are a common feature of monogenic epilepsies.
- Major modifiable targets include migration, differentiation, and excitability.
- Early intervention gene models include *Arx*, *Dcx*, *Lis1*, *Tsc1*, *Pten*, *Kcna1*, *Scn1a*.
- Brain developmental programs offer effective therapeutic targets for disease modification.

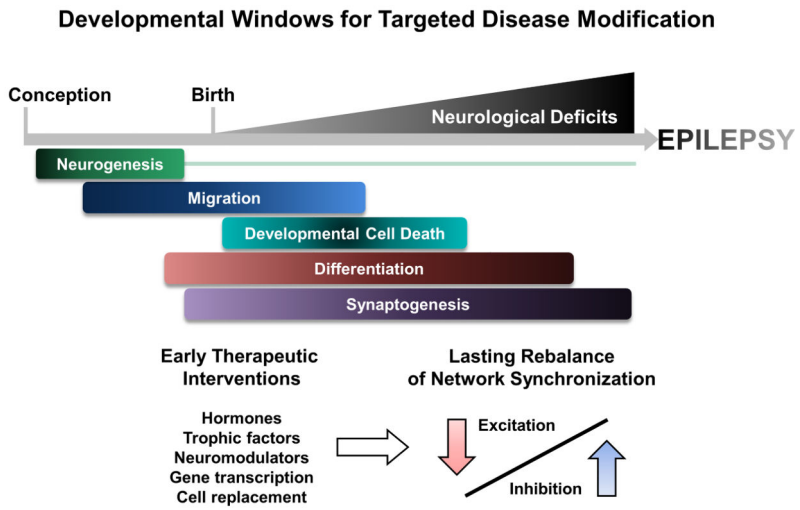

Figure 1.

Summary of developmental pathways for early interventions in the developmental epilepsies. Targeted therapies (e.g. hormones, trophic factors, neuromodulatory drugs, genetic therapy, or cell replacement) can modify the trajectory of disease and prevent epileptogenesis by permanently balancing excitatory and inhibitory network signaling. Cellular processes can be therapeutically targeted in developmental epilepsies. These processes include, but are not limited to, neuronal migration, developmental cell death, neuronal differentiation, and synaptogenesis. Modulating these events during a therapeutic window to rescue or repair damaged cellular processes, particularly interneuron defects, can modify the disease trajectory of developmental epilepsies.

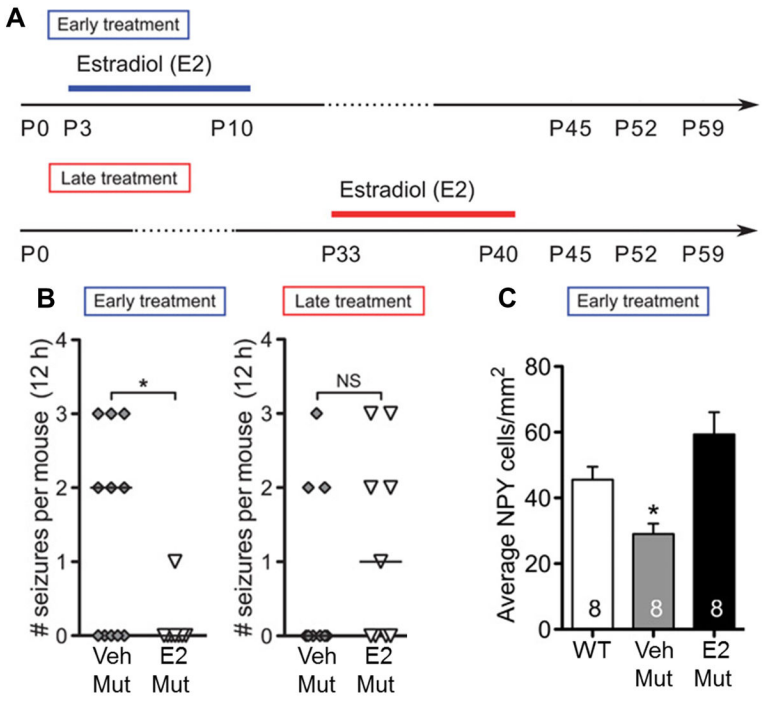

Figure 2.

Neonatal 17β-Estradiol (E2) prevents epilepsy and restores GABAergic interneurons in the *Arx*$^{(GCG)10+7}$ model of X-linked Infantile Spasms. **(A)** Estradiol treatment paradigms used in [19]. Neonatal *Arx*$^{(GCG)10+7}$ mice were treated with E2 from postnatal day (P)3 to 10 (Early treatment) and adult mice were treated from P33 to P40 (Late treatment). **(B)** Only early E2 treatment effectively prevented seizures in a majority (9 out of 10) of *Arx*$^{(GCG)10+7}$ mutant (Mut) mice as compared to vehicle (Veh) treated controls. Late treatment had no effect on seizure outcome. **(C)** Early treatment also rescued numbers of cortical GABAergic interneuron subtypes. For example, numbers of Neuropeptide Y (NPY)+ interneurons were rescued in *Arx*$^{(GCG)10+7}$ mutants with E2 treatment (E2 Mut) as compared to controls (Veh Mut).