Focal Cortical Dysplasia

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Abstract

Focal cortical dysplasias are common malformations of cerebral cortical development and are highly associated with medically intractable epilepsy. They have been classified into neuropathological subtypes (type Ia, Ib, IIa, IIb, and III) based on the severity of cytoarchitectural disruption—tangential or radial dispersion, or loss of laminar structure—and the presence of unique cells types such as cytomegalic neurons or balloon cells. Most focal cortical dysplasias can be identified on neuroimaging and many require resective epilepsy surgery to cure refractory seizures. The pathogenesis of focal cortical dysplasias remains to be defined, although there is recent evidence to suggest that focal cortical dysplasias arise from de novo somatic mutations occurring during brain development. Some focal cortical dysplasia subtypes show a link to the mammalian target of rapamycin signaling cascade; this has now extended to other cortical malformations, including hemimegalencephaly.

Keywords

- cortical dysplasia
- mTOR
- tuberous sclerosis

Focal cortical dysplasias (FCDs) comprise a spectrum of focal developmental malformations characterized by disruption of the normal cytoarchitecture of the cerebral cortex. They are highly associated with medically intractable epilepsy.[1–3] Focal cortical dysplasia and epilepsy were first associated in a report by Taylor[4] (although previously alluded to by Crome[5]), who reported 10 patients (adults and children) with refractory epilepsy undergoing surgical resection, who showed focal abnormalities of cortical cytoarchitecture that matched the proposed anatomical focus associated with their seizure semiology. They hypothesized that the focal pathological changes were probably developmental and that they accounted for their seizures. The description of other focal malformations of cortical development (MCD) subtypes sharing pathological changes with FCD—such as hemimegalencephaly[6] and tuberous sclerosis complex (TSC)[7]—dates back to the 1800s. There have also been recent descriptions of new FCD syndromes, including Pretzel syndrome, autosomal dominant temporal lobe epilepsy and cortical dysplasia, and familial focal epilepsy with variable foci (see below).

Classification and Neuropathology

Historically, several different FCD classification systems have been proposed,[8–10] trying to link the pathological findings with developmental mechanisms, although none has consistently linked the pathology to the clinical presentation or outcome. Distinct classification schemes have been proposed to define the relevant imaging and histological features of FCD.[8] The Palmini classification system[9] was restructured and further subdivided FCD into type IA, IB, IIA, and IIC. The International League Against Epilepsy (ILAE) task force of the Diagnostic Methods Commission generated a new consensus classification of distinct focal cortical dysplasia subtypes based on histopathological features[10] that yields consistent interobserver and intraobserver reliability. The ILAE classification scheme comprises a three-tiered system, including both isolated and associated FCD variants. A new and comprehensive classification scheme assumes that all MCD types result from distinct developmental and molecular genetic causes, and that these directly affect cortical development at distinct epochs and within distinct cell types.[11]

Focal cortical dysplasia type I is characterized by abnormal cortical layering with radial microcolumns, and is of three subtypes. Focal cortical dysplasia type Ia shows radial microcolumns resembling the microcolumnar organization pattern of the early stages of cortical development; FCD type Ib shows tangential layer alterations; FCD type Ic shows a combination of both. All the three variants can show heterotopic neurons in white matter and hypertrophic neurons (outside layer 5),

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as well as normal neurons with abnormal dendrites. Focal cortical dysplasia type I may affect one or multiple lobes, yet preoperative magnetic resonance imaging (MRI) may be normal. Focal cortical dysplasia type I may be subtle and challenging to detect on routine neuropathology, but should be specifically sought in cases with normal preoperative MRI scans.

Focal cortical dysplasia type II is common among epilepsy surgical series and is a major cause of antiepileptic drug-resistant epilepsy. It is more common in extratemporal areas, particularly in the frontal lobe, and is typically seen on preoperative MRI scans. Focal cortical dysplasia type IIa is characterized by dysmorphic and cytomegalic neurons, but lacking balloon cells; FCD Type IIb is characterized by dysmorphic/cytomegalic neurons *and* balloon cells. Balloon cells have an enlarged cell body and opalescent, glassy appearing, eosinophilic cytoplasm (►**Fig. 1**). Cortical tubers are a type of FCD found in TSC, though not included in the ILAE classification system, and occur as single or multiple lesions in more than 80% of patients with TSC. They are linked to both epilepsy and neurocognitive disabilities (for review, see[12]). Tubers are common in temporal and frontal regions and are characterized histopathologically by dyslamination, and heterogeneous cell types, such as dysmorphic neurons, reactive astrocytes, and so-called giant cells. Giant cells are histologically similar to the balloon cells found in FCD type IIb.

Both giant cells and balloon cells express proteins characteristic of neuroglial progenitor cells, such as SOX2, nestin, vimentin, and c-myc, suggesting a failure to differentiate before migration into the cortex.[13] The first study to examine lineage markers in FCD found that balloon cells and cytomegalic neurons expressed cell markers reflecting lineage derivation from the telencephalic ventricular zone, such as OTX-1 and MASH.[14] A subsequent study in FCD I[15] showed that FCD I specimens in younger patients characteristically have abnormal expression of Tbr1 and Otx1 in layer II, supporting their origins from radial glia; by contrast, FCDII showed distinct labeling of balloon cells (Pax6, ER81 and Otx1) and dysmorphic neurons (Tbr 1, N200, and Map1b), supporting their origins in intermediate progenitor cells. Tubers may be found as early as 20 weeks gestation,[16–18] indicating that tubers (and by extension, focal cortical dysplasias) form during embryonic brain development, probably between weeks 10 and 20 of human gestation.

A significant advantage of the ILAE classification was that pathological changes adjacent to or associated with substantive brain lesions (such as vascular malformations and tumors) could be defined as FCD type III. The four different subtypes of FCD type III include IIIa, associated with hippocampal sclerosis; IIIb, associated with tumors; IIIc, associated with vascular malformations; and IIId, associated with any other lesion acquired during early life. Histopathologically, FCD type III subtypes show type I abnormalities, including altered cortical lamination. However, finding an abnormal band of small and clustered "granular" neurons in the outer part of layer II can distinguish FCDI type I from subtypes IIIa–d.[19] Other types of focal MCD, such as TSC, hemimegalencephaly, and some of the newer focal cortical dysplasia syndromes have not yet been subsumed into the ILAE classification. However, cortical tubers are histologically similar to FCDIIb; hemimegalencephaly may occur both with and without balloon cells similar to FCDIIb; and familial focal epilepsy with variable features may show a "bottom-of-the-sulcus" dysplasia with a type IIa or IIb phenotype. An important corollary to these classifications is that FCDs are often heterogeneous lesions with local variations in regional cytoarchitectural abnormalities. For example, some resected lesions may contain both type I and type FCD pathologies. From a diagnostic perspective, while pathologists describe the histological variations, they tend to use the most severe FCD subtype for final diagnosis.

Clinical Presentation

Epilepsy, often intractable, remains the most common clinical presentation for all types of FCD as well as TSC and hemimegalencephaly.[1] Patients usually come to clinical attention with seizures in early childhood, although seizures may start at any age. In virtually all FCD subtypes, there is close concordance between the location of the seizure onset

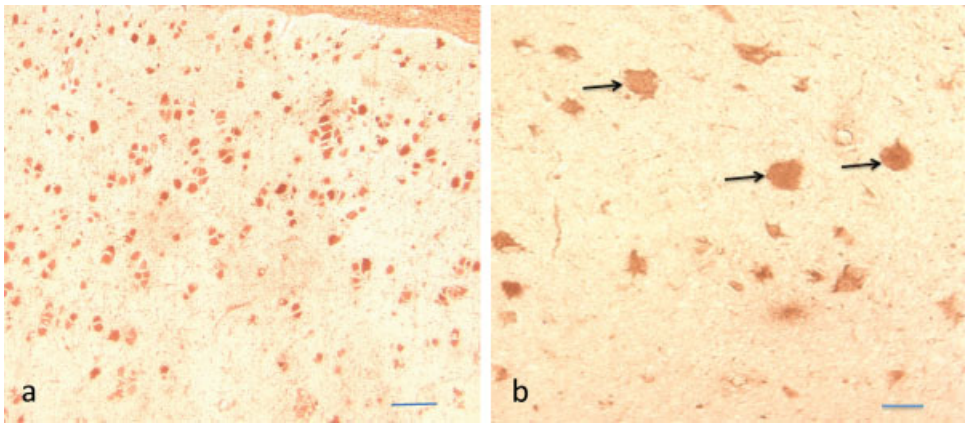

Fig. 1 (**A**) FCD type IIb (labeled with anti-nestin antibodies; modified from 14; scale bar = 400 microns). Note loss of cortical lamination and ovoid shape of balloon cells. (**B**) Balloon cells (*arrows*) in cortical tuber (modified from 31; scale bar = 100 microns).

defined by electroencephalography and the anatomic location of the FCD defined by MRI or intraoperative visualization. Furthermore, the anatomical location of FCD determines the seizure semiology. Frontal lobe epilepsy may manifest as sleep-related seizures characterized by stereotyped bilateral movements and vocalizations, sometimes with preserved consciousness. Patient with occipital lobe seizures may report visual symptoms, such as seeing dots or shapes in different colors. Regardless of semiology, recalcitrant and poorly controlled seizures contribute to cognitive impairment in children and adults. Other clinical presentations include developmental delay, behavioral issues, autism spectrum disorders, and sometimes focal neurologic deficits, depending on the size and location of the cortical lesion. The surgical outcome may vary with the pathological FCD subtype.[20]

Radiographic Findings

With greater availability of more advanced neuroimaging in the 1990s, specifically brain MRI, it became apparent that focal MCDs are more common in patients with intractable epilepsy than previously thought. Newer imaging shows MCD to be radiographically heterogeneous, with distinct signal characteristics, extent, and location. However, focal malformations of cortical development sometimes do not show on imaging, and can be found only on histopathological examination of resected tissue specimens.[21] Nevertheless, neuroimaging is central to identifying and diagnosing FCDs. Common findings on brain MRI include increased cortical thickness, subtle changes in the smoothness of gyri or sulci, and changes in subcortical white matter signal. Typically, FCDs do not enhance with gadolinium, although approximately 5% of tubers in TSC enhance very slightly. In terms of radiographic–pathologic correlation, FCD type I appears as mild hyperintensity of the white matter in T2/fluid-attenuated inversion-recovery (FLAIR) sequences with loss of gray/white matter differentiation. On the other hand, MRI findings in FCD type IIb (dysmorphic neurons with balloon cells) include thickening of the cortex with loss of gray/white matter differentiation as well as a "transmantle sign"–tapering of abnormal white matter signal from the FCD in the cortex to the ventricular surface. About 40% of patients with FCD type I and approximately 10% in type II have a normal brain MRI. Thus, a normal brain MRI in a patient with intractable epilepsy does not rule out FCD. Magnetic resonance imaging findings favoring FCD rather than a tumor include cortical gray matter thickening and a transmantle sign. Tubers are not static lesions and there may be dynamic changes over time including calcification and cystic degeneration. The evolution of cystic changes is associated with a *TSC2* gene mutation and with having more severe seizures.[22] More recently, three tuber types (A, B, C) have been distinguished from their MRI features.[23] However, there is as yet no histopathological classification scheme for tubers; this will represent an important advance in understanding of epileptogenesis in TSC patients. In addition to MRI, functional imaging such as fluorodeoxyglucose-positron emission tomography (FDG-PET) and single photon emission computed tomography (SPECT) can help, particularly in epilepsy localization before surgery. Focal cortical dysplasias typically show focal regional hypometabolism on FDG-PET imaging even in MRI-negative cases. Ictal SPECT detects enhanced cerebral blood flow during the seizures, confirmed with video-electroencephalogram (EEG) monitoring, and helps with localization in almost half of the patients with FCD. The sensitivity of FDG-PET scan in detecting FCD is 69 to 98%, and for ictal-SPECT it is 48 to 64%.

Focal Cortical Dysplasia: Pathogenesis and Molecular Genetics

Focal cortical dysplasia and cortical tubers are among the most common pathological substrates associated with medically intractable pediatric epilepsy.[1,24] Tuberous sclerosis complex is an autosomal dominant, multisystem disorder resulting from mutations in either *TSC1* or *TSC2*, and characterized by a spectrum of neurologic deficits including autism, intellectual disability, and intractable epilepsy.[12,25] Identification of the *TSC1* and *TSC2* genes and the links to mammalian target of rapamycin (mTOR) signaling (►**Fig. 2**) have provided critical insights into mechanisms of focal MCD, and in fact have provided the paradigm to study other focal MCD subtypes, such as FCDIIb. Tubers form during brain development as a consequence of loss of function mutations in either *TSC1* or *TSC2*, leading to constitutive mTOR activation and altered development of the cerebral cortex.[26] Numerous studies have shown phosphoactivation of mTORC1 substrates p70S6kinase, S6, and 4E-BP1 in resected and postmortem TSC tuber samples.[27–30] Two recent studies showed mTORC1 activation in fetal tubers,[17,18] suggesting very early activation of mTOR. Renal and pulmonary lesions in TSC follow a "two-hit" mutational model where a somatic inactivating mutation, including loss of heterozygosity or a point mutation in the unaffected allele, is superimposed on the existing germline mutation. Two recent reports suggest that tubers contain both germline and somatic mutations, implying a mechanism of bi-allelic gene inactivation.[31,32] Mouse models showing abnormal cortical structure have required full Tsc1 or *Tsc2* knockout[33]; heterozygous mice do not show significant neuropathological changes.

In contrast to TSC, in FCD, a sporadic disorder with few defined family pedigrees, the pathogenesis remains unknown, but there are some proposed potential pathogenic mechanisms, including somatic gene mutation, or a toxic insult to the developing brain.[34–36] The pathological similarities between FCDIIb and tubers suggested a mechanistic link between these lesions, and even that FCD represented a sporadic, somatic mosaic form of TSC. Studies have identified *TSC1* and *TSC2* gene sequence polymorphisms, but not somatic mutations, in FCDIIb.[37,38] Focal cortical dysplasia can be associated with *DEPDC5* mutations (see below), suggesting that syndromic forms of FCD may be identified in association with mutations in mTOR regulatory genes.[39] A recent study identified somatic trisomy of 1q21–1q44, a region that encompasses the *AKT3* gene, in FCD brain tissue but not in blood or saliva, suggesting a somatic mutational

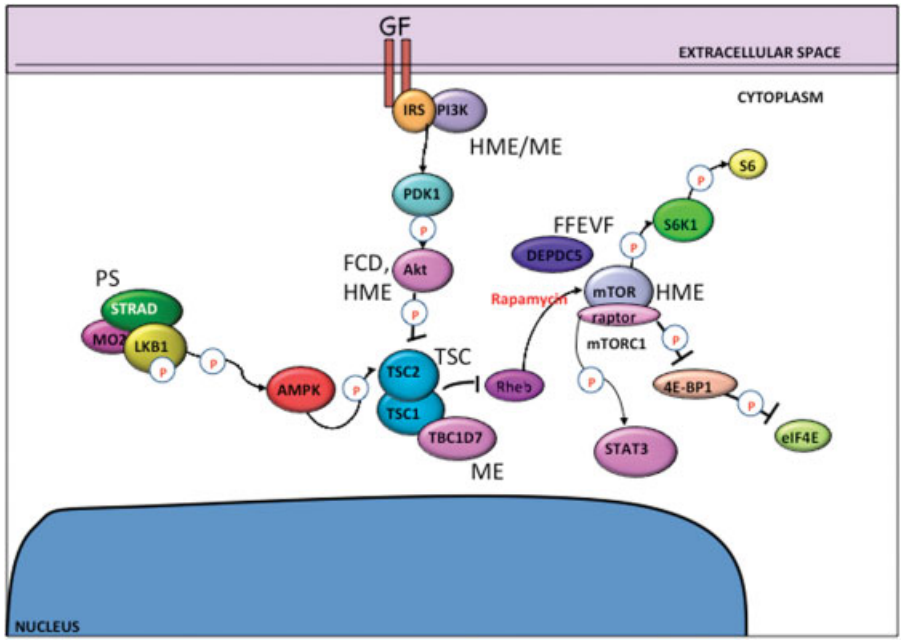

Fig. 2 Schematic depicting mTOR pathway components. Growth factor (GF) receptor-mediated signaling drives the mTOR pathway. Note the mTOR inhibitor rapamycin site of effect. At several key points, individual focal cortical dysplasia (FCD) subtypes are listed next to site of gene mutation in the pathway. For example, tuberous sclerosis complex (TSC) is associated with mutations in either *TSC1* or *TSC2*, FCD with *AKT* mutations, and FFEVF to *DEPDC5* mutations. Hemimegalencephaly has been linked to mutations in *PI3K, MTOR*. Megalencephaly (ME) has been associated with mutations in *PI3K*, *TBC1D7*, and *MTOR*. Pretzel syndrome (PS) is linked to *STRADA* mutations and is associated with ME and FCD. For other associations, see text.

mechanism.[40] Interestingly, another study found FCD type Ia and IIA in a small cohort of patients with mutations in the sodium channel *SCN1A*.[41] It is unclear at present how mutations within this channel, which is commonly associated with Dravet syndrome, can alter cortical development; clearly this warrants further investigation.

Enhanced mTOR signaling, evidenced by phospho-p70S6K and phospho-S6 isoforms first identified in FCDIIb,[27,28] set the stage for subsequent studies (see below), which showed mTOR activation in hemimegalencephaly[29,42] and ganglioglioma.[43] In contrast, there is no enhanced p70S6Kinase and S6 phosphorylation (e.g., mTOR activation) in FCD type Ia or Ib.[13] The central hypothesis of these studies was that molecular events causing abnormal brain development resulted in mTOR activation, evidenced by hyperphosphorylation of mTOR, p70S6K, and S6 proteins. As in tubers, p70S6K and S6 phospho-isoforms were identified in cells with enlarged somas—dysmorphic neurons and balloon cells in FCDIIb. For example, in tubers or FCDIIb, > 80% of morphologically defined balloon cells show phospho-S6 labeling.[13] Furthermore, within any one tuber or FCDIIb specimen, there can be tremendous variability in the number and the distribution of giant cells/balloon cells in the white matter and through the depth of the lesion. Recent studies suggest that a range of epilepsy-associated pathologies, including FCD type III and Rasmussen's encephalitis, may show enhanced mTOR signaling.[44]

Enhanced mTOR signaling is further supported by altered expression of up- and downstream components of the mTOR pathway in FCD. For example, activation of mTOR signals via HIF1α, initiates vascular endothelial growth factor expression in cortical tubers[45] and in FCDIIb.[46] Phosphoactivation of STAT3, a transcription factor regulated by mTOR, is identified in FCDIIb and tubers.[27] Interestingly, the profiles of phosphorylated proteins in tubers versus FCDIIb are not identical, suggesting potentially different roles for mTOR signaling in the formation of these lesions. For example, phosphoactivation of the upstream cascade proteins p-PDK1 (S241), p-Akt (S473), and p-tuberin (T1462) in FCDIIb is distinct from tubers.[47] Interestingly, recent studies have suggested possible autophagy induction in FCDIIb and TSC by showing autophagic vacuoles and p62 expression.[48] Recent observations suggest that the abnormal activation of mTOR may contribute to apoptosis signaling pathways and premature activation of neurodegeneration cascades in both FCD II and TSC.[49] For example, tau-immunoreactive neuropil fibrils occur in areas of FCD and hyperphosphorylated tau is detected in pS6 positive dysmorphic neurons.

Two recent studies suggest a viral association for FCD II,[50,51] which may link to mTOR activation as well as the extant evidence for both innate and adaptive immune responses observed in FCD type II. Human papilloma virus type 16 (HPV16) has been previously associated with dysplasia and cancer of the cervix. The HPV16 oncoprotein E6 is a potent activator of mTOR signaling and was found in FCDIIb specimens by two distinct investigations,[50,51] although a third investigation did not detect human papilloma virus DNA.[52] One of these studies also found cytomegalovirus and human herpes virus type 6.[51] Exogenous expression of E6 in fetal mouse brain causes disorganized cerebral cortical lamination.

In view of these findings, several future steps will be necessary. First, it must be shown that human papilloma virus can actually infect the brain, for example, neurons or astrocytes, in experimental model systems. Second, analysis of a larger number of cases will be necessary to demonstrate the distribution of FCD specimens with human papilloma virus or other viral species such as cytomegalovirus, which has been previously linked to some types of cortical malformation including pachygyria.[34] Third, we need to establish the pathogenicity, if any, of human papilloma virus in FCD. Although human papilloma virus is universally associated with cervical cancer, there are distinct subsets of head and neck cancer that either are or are not associated with this virus; thus, stratification of FCD cases may be necessary. Finally, future studies to define the mode of transmission, such as blood borne, must be established. Alternatively, human papilloma virus may have no pathogenic role in FCD.

Familial Focal Epilepsy with Variable Foci

Recently, mutations were identified in *DEPDC5,* a gene encoding a protein with tandem N-terminal DEP (disheveled, egl-10, pleckstrin) domains; this was in several Australian pedigrees with a clinical phenotype characterized by focal epilepsy arising from distinct lobar locations in different family members.[39,53] The syndrome, termed familial focal epilepsy with variable foci (FFEVF), is an autosomal dominant disorder associated with epilepsy of varying severity and variable intellectual and neuropsychiatric disorders, including anxiety, depression, and intellectual disability. Some affected patients had "bottom-of-the-sulcus" dysplasias on brain MRI although some patients had other MCD subtypes, such as band heterotopia.[54] Interestingly, in another report, *DEPDC5* mutations were associated with nonlesional focal epilepsies including benign epilepsy with centrotemporal spikes.[55] DEPDC5 is an important component of the GATOR-1 complex, a modulator of mTOR regulator in response to cellular amino acid levels.[56] DEPDC5 knockdown leads to enhanced mTORC1 signaling in vitro and thus, FCD in the setting of *DEPDC5* mutation has been postulated to be mediated through the mTOR pathway. Further studies will be needed to define the role of DEPDC5 in cortical lamination and epileptogenesis and whether mTOR inhibitors can alter seizure frequency in FFEVF.

CASPR2 and Focal Cortical Dysplasia

Contactin-associated protein-like 2 (CASPR2) is encoded by *CNTNAP2* and functions to cluster voltage-gated potassium channels, such as K(v)1.1, at the nodes of Ranvier. Homozygous mutations of *CNTNAP2* in Old-Order Amish children were linked to cortical dysplasia, focal epilepsy, and macrocephaly.[57] In these patients, intractable seizures started in early childhood, after which language regression, hyperactivity, impulsive and aggressive behavior, and intellectual disability appeared in all affected children. Interestingly in the original report, resective surgery did not cure the seizures. Neuropathological examination of resected temporal-lobe specimens showed focal cytoarchitectural abnormalities suggesting a type IIA FCD, as well as widespread astrogliosis and reduced expression of CASPR2. Further studies are clearly warranted to define this mutation outside of the Amish community as well as to define the role of CASPR2 in cortical development.

mTOR, FCD, and Epileptogenesis

The mechanisms of seizure onset and propagation across the FCD subtypes have not been fully defined.[58–60] Despite the known association between FCD and intractable seizures, there are many remaining challenges that will help us to understand epileptogenesis (►**Fig. 2**); these include distinguishing the differential contributions of altered brain structure; the effects of mutations on downstream gene and protein expression; and in the case of FCDIIb, the effects of mTOR hyperactivation on excitability. Although enhanced mTOR signaling is detected in *Tsc1*, *Tsc2*, and *Pten* knockout mouse models associated with spontaneous seizures, hyperactive mTOR signaling also occurs in kainic acid-induced seizures[61,62] or seizures resulting from electrical brain stimulation[63] without structural changes in the neocortex or genetic alterations causing increased mTOR activation. Enhanced mTOR activation has been linked to mouse models of infantile spasms[64] and seizures induced in a hypoxia model lead to increased expression of genes encoding mTOR pathway components.[65] PI3K- and Akt-dependent mTOR activation has been reported in a rat hippocampal organotypic culture model of posttraumatic epilepsy, and inhibition of PI3K, mTOR, or both (using a dual inhibitor) prevented ictal activity and cell death.[66] Enhanced mTOR activation is found in human temporal lobe epilepsy specimens.[67] Mutations in *MTOR* have been recently identified in epileptic encephalopathies without MCD,[68] suggesting that enhanced mTOR signaling in the absence of structural abnormalities may lead to epileptogenesis by a yet undefined mechanism. Thus, it appears that while mTOR activation caused by gene mutations in mTOR regulatory elements can induce epileptogenesis, the pathway may also serve as a biomarker for epileptogenic brain tissue.

Human electrophysiological studies have shown the intrinsic epileptogenicity of FCDs.[69–71] Patients with FCD and TSC have altered numbers and distribution of glutamate and GABA receptor subunits; also electrophysiological recording in surgical FCD specimens in vitro have identified neuronal cells—likely cytomegalic dysmorphic neurons—with hyperexcitable intrinsic membrane properties.[71–73] In contrast, balloon cells show neither hyperexcitability nor epileptogenicity. Hyperexcitability likely reflects developmental alterations of the balance between excitation and inhibition in the pathogenesis of epileptic focal discharges in FCD including changes in glutamate and GABA receptor expression.[74–77] Several other studies point to a deregulation of inhibitory synaptic transmission in FCD.[78,79] Focal cortical dysplasia specimens show downregulation of $GABA_AR$ subunits and reduced numbers of inhibitory (GABAergic) neurons, suggesting impaired GABAergic inhibition.[19,80–82] Electrophysiological studies performed in brain

slices from FCD tissue show immature GABA receptor-mediated responses; GABA receptor-mediated synchronization appears to be involved in the mechanism leading to in vitro ictal activity in FCD.[78,83]

Clinical Therapeutics

There have been no clinical trials of mTOR inhibitors such as rapamycin or everolimus for epilepsy associated with FCD. Everolimus reduces the size and volume subependymal giant astrocytomas (SEGA) in TSC.[84] In a cohort of 26 patients, 16 suffered from seizures, and everolimus treatment modestly improved seizure control in 9 patients. Everolimus also reduces seizure frequency in TSC patients.[85] Clearly, mTOR inhibition may provide a new target for patients with mTOR-associated refractory epilepsy. Polyhydramnios–megalencephaly–symptomatic epilepsy syndrome (Pretzel syndrome) is a neurodevelopmental disorder found in the Old-Order Mennonite community associated with severe epilepsy and caused by mutations in the mTOR regulatory gene *STRADA*.[86] A small trial in five children with Pretzel syndrome for between 8 months and 4 years showed that rapamycin (sirolimus in clinical parlance) prevented seizures.[87] This was the first study to show epilepsy prevention with an mTOR inhibitor and suggested that early treatment could dramatically alter clinical seizure onset. Clearly, we need further consideration of using mTOR inhibitors in other mTOR-associated FCD such as hemimegalencephaly or familial focal epilepsies that are linked to mTOR signaling genes, such as *DEPDC5*.

Future Considerations

mTOR hyperactivation during brain development appears to lead to abnormal cortical lamination, cell size, and cell lineage, culminating in intractable epilepsy associated with FCD and TSC, as well as hemimegalencephaly and several other new FCD syndromes. The logical next experimental steps will be to define how each genotype alters mTOR activation, and in turn disrupts cortical development, and to define other factors that contribute to the heterogeneous features of each focal MCD subtype. From a clinical perspective, the mTOR pathway provides new avenues for clinical investigation and for clinical therapeutic trials. In contrast, a uniform mechanism to account for type I FCDs that appear not to be associated with mTOR activation, remains to be identified. We have much work ahead to uncover pathogenic mechanisms for these FCD subtypes, including further investigation into environmental risk factors for FCD, such as viral infection and toxic exposure that may lead to somatic mutations.

Note

There has been a recent publication reporting somatic mutations in MTOR in FCDIIa and FCDIIb (Lim JS, Kim WI, Kang HC, et al. Brain somatic mutations in MTOR cause focal cortical dysplasia type II leading to intractable epilepsy. Nat Med 2015;21(4):395–400).

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