Epilepsy Related to Developmental Tumors and Malformations of Cortical Development

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Abstract Structural abnormalities of the brain are increasingly recognized in patients with neurodevelopmental delay and intractable focal epilepsies. The access to clinically well-characterized neurosurgical material has provided a unique opportunity to better define the neuropathological, neurochemical, and molecular features of epilepsy-associated focal developmental lesions. These studies help to further understand the epileptogenic mechanisms of these lesions. Neuropathological evaluation of surgical specimens from patients with epilepsy-associated developmental lesions reveals two major pathologies: focal cortical dysplasia and low-grade developmental tumors (glioneuronal tumors). In the last few years there have been major advances in the recognition of a wide spectrum of developmental lesions associated with an intractable epilepsy, including cortical tubers in patients with tuberous sclerosis complex and hemimegalencephaly. As an increasing number of entities are identified, the development of a unified and comprehensive classification represents a

great challenge and requires continuous updates. The present article reviews current knowledge of molecular pathogenesis and the pathophysiological mechanisms of epileptogenesis in this group of developmental disorders. Both emerging neuropathological and basic science evidence will be analyzed, highlighting the involvement of different, but often converging, pathogenetic and epileptogenic mechanisms, which may create the basis for new therapeutic strategies in these disorders.

Key Words Epilepsy · development · malformations · tumors · epileptogenesis

Introduction

Developmental brain lesions, in particular glioneuronal tumors (GNT) and malformations of cortical development (MCD) are among the most common causes of pharmacologically intractable epilepsy (for reviews see [1–5]).

Recent advances in neuroimaging and neurophysiology have allowed the recognition of more subtle epilepsy-associated focal cortical changes, improving our understanding of the complex functional relevance of these lesions for seizure development and other associated neurologic deficits, such as cognitive dysfunction. Thus, an increasing number of epilepsy patients are appropriate for surgical therapy, and neuropathologists are confronted with a larger availability of surgical specimens, playing a more active role in the interdisciplinary approach to the diagnosis of epilepsy-associated developmental focal lesions. This integrated approach is fostered by a strong interaction between the fields of neurogenetics and basic neuroscience, and requires the implementation of new molecular diagnostic techniques in human

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tissue. The increasing knowledge in genetics, imaging, and pathologic features of epileptogenic developmental lesions has provided the basis for proposing new classification systems [5, 6], which are used to evaluate clinical outcome and to guide more targeted studies for the identification of new antiepileptic drugs. Major advances in our understanding of the molecular pathogenesis and the pro-epileptogenic cellular mechanisms of a variety of focal developmental lesions have been made over the last decade, resulting in interesting scientific discoveries. In this article we will review the clinical and experimental observations concerning the molecular pathogenesis and the mechanisms of epileptogenesis in developmental GNT and MCD, highlighting potential emerging therapeutic strategies targeting epilepsy, as well as other associated neurologic deficits.

Developmental Brain Tumors: GNT

Clinical and Neuropathologic Features

In recent years, the concept of long-term epilepsy associated tumors (LEAT) has been introduced [4, 7]. LEAT are low grade, slowly growing, cortically-based tumors, often with a temporal lobe localization. They predominantly occur in young patients with long histories (often ≥ 2 years) of drug-resistant epilepsy. GNT, including gangliogliomas (GG) and dysembryoplastic neuroepithelial tumors (DNTs), represent the most common tumor within the spectrum of LEAT, often arising in younger age groups (for a review see [4]; Table 1). Seizures are most likely to be the first, and often the only, clinical manifestation, and are often represented by drug-resistant complex partial seizures. By definition, GNT exhibit both neuronal and glial differentiation [8].

GG (Fig. 1a–d) consist of a mixture of dysplastic neurons and glial tumor cells mainly represented by a large spectrum of astroglial cells, but cells resembling oligodendrocytes (clear cell morphology) can be detected. The neuronal component, which varies in amount, is represented by dysplastic neurons with abnormal shapes and sizes lacking uniform orientation,

and often having prominent Nissl substance, vesicular nuclei, and prominent nucleoli. Bi- or multinucleate neurons may also be detected. Additional histopathologic features commonly observed in GG include the presence of eosinophilic granular bodies, Rosenthal fibers, and calcifications. In addition, perivascular lymphocytic infiltration and activated microglial cells are commonly encountered. The large majority of GG correspond to World Health Organization (WHO) grade I. According to the WHO classification [8], GG with anaplastic glial features are considered WHO grade III. Early surgical resection of GG reduces long-term morbidity and mortality from seizures, making surgery the treatment of choice [9–11]. Gross total resection is recommended, even if significant reduction of symptoms, including freedom from seizures, can be often achieved with partial resection. However, resection of tumor alone (lesionectomy) has been associated with a less satisfactory outcome in temporo-mesial GG, supporting the epileptogenic contribution of the peritumoral zone, especially in temporal GG [11, 12]. In addition, association with cortical dysplasia has been reported to determine a less effective control of seizures after surgery [13].

DNT (Fig. 1e, f) are characterized by mixed neuroepithelial cell types, including oligodendrocyte-like cells and astrocytes [8]. They often display an intracortical, nodular growth pattern, and a specific feature of these tumors is the presence of the glioneuronal element, characterized by a typical cortical growth pattern of microcolumns of oligodendrocyte-like cells arranged along axons and vessels and separated by a myxoid matrix that contains floating neurones. Additional histopathological features, including calcifications and dysmyelination, or rarefaction of the peritumoral white matter, have been reported [14]. DNT are slowly growing WHO grade I tumors with a chance of malignant transformation of $<1\%$ [8]. Similarly to GG, early surgical gross total resection represents the treatment of choice [9, 15–18]. Whether the presence of associated cortical dysplasia may influence the seizure outcome is still unclear [19, 20].

Pathogenesis and Molecular Genetics

The molecular pathogenesis of GNT has only recently begun to be elucidated. Studies using array comparative genomic hybridization have identified several genomic aberrations in a cohort of 61 young adult patients with GG [21]. The most frequent aberration was represented by a gain of chromosome 7 (with additional gains of 5, 8, or 12). The authors localized the imbalances at the cellular level to a subpopulation of glial cells, and analysis of two primary GG and their anaplastic recurrences identified genetic aberrations commonly associated with malignant gliomas [21]. Recently, analysis of chromosomal copy number aberrations in a large cohort of 131 GNT patients also confirmed the occurrence of gains of chromosomes 5 and 7 in DNTs [22]. In addition, in 4 tumors (2

Table 1 Long-term epilepsy associated tumors subtypes [4, 8]

Glioneuronal tumors	Glial tumors
Common types:	Common types:
Ganglioglioma (WHO I)	Pilocytic astrocytoma (WHO I)
Dysembryoplastic neuroepithelial tumor (WHO I)	Pleomorphic xanthoastrocytoma (WHO II)
Less common subtypes:	Oligodendroglioma (WHO II)
Papillary glioneuronal tumor	Diffuse astrocytoma (WHO II)
Rosette-forming glioneuronal tumors	Less common subtypes:
Glioneuronal tumors with neuropil islands	Angiocentric glioma
	Isomorphic glioma

WHO=World Health Organization

Fig. 1 Histopathological features of glioneuronal tumors, focal cortical dysplasia (FCD), tuberous sclerosis complex (TSC), and hemimegalencephaly (HME). **(a–d)** Ganglioglioma (GG). **(a)** Hematoxylin/eosin (HE) staining of GG showing large dysplastic neurons (arrows and insert) and glial cells. **(b)** NeuN staining detects the neuronal component (nuclear staining) of GG. **(c)** Phosphorylated ribosomal S6 protein (pS6) expression in dysplastic neurons (arrows). **(d)** *BRAF* V600E immunostaining showing prominent expression in large dysplastic cells (arrows). **(e, f)** Dysembryoplastic neuroepithelial tumor (DNT). **(e)** HE staining of DNT showing a typical heterogeneous cellular composition, with floating neurons (arrow) surrounded by a prominent population of oligodendroglia-like cells. **(f)** NeuN staining detects the neuronal component of DNT. **(g–j)** FCD. **(g)**

FCD NeuN staining showing cortical dyslamination. **(h)** HE staining showing a dysmorphic neuron with enlarged nucleus and aggregates of Nissl substance (arrow) and a balloon cell (*). **(i)** Vimentin (Vim) staining of balloon cells. **(j)** pS6 expression in dysmorphic neurons (arrows) and a balloon cell (insert). **(k–n)** TSC, cortical tubers. **(k)** Luxol–Periodic acid–Schiff (PAS) staining showing a cortical tuber (arrow) with decreased density of myelinated fibers. **(l)** NeuN staining showing cortical dyslamination within the tuber. **(m, n)** pS6 expression in a giant cell (**m**; cortical tuber from adult TSC patient) and within a focal lesion in a fetus at 23 gestational weeks. **(o)** HME. NeuN staining showing cortical dyslamination within the enlarged hemisphere, inset shows pS6 expression in dysmorphic neurons. Scale bar: A, B, D–F, J, N=80 μ m; C, I, M=30 μ m; H=40 μ m; G, L, O=500 μ m; K=1.2 cm

DNTs, 1 GG WHO I, and 1 GG WHO III) somatic intra- and/or interchromosomal chromothripsis, a recently described massive genomic rearrangement acquired in a single catastrophic event [23], was detected in chromosomes 7 and 12 [22].

The histopathologic features of GNT with a differentiated glioneuronal phenotype, the expression of the precursor cell marker (CD34), and the coexistence with cortical dysplasia suggests a developmental pathogenesis for these lesions [1, 4, 24, 25]. The possible origin of GG from a precursor lesion is

also supported by the reported association with molecular alterations of signaling pathways, such as reelin and the mammalian target of rapamycin (mTOR), which play critical roles in cell size and growth control, cortical development, and neuronal migration [26–28]. In particular, the deregulation of the mTOR pathway reported in GNT [28, 29] may represent the link between these tumors and focal MCD, such as focal cortical dysplasia (FCD) and tubers in tuberous sclerosis complex (TSC), associated with epilepsy and neurobehavioral disabilities (for a review see [30]; Fig. 2). Enhanced mTOR signaling pathway activation has been detected in both GG and DNT (Fig. 1c) [28, 31]. These findings support the inclusion of GNT within the group of MCD (such as FCD and TSC), characterized by cortical dysgenesis with abnormal cell proliferation ([5]; Table 2). Mutational analysis of *TSC1* and *TSC2* failed to identify mutations in GGs [32], and only a somatic mutation in intron 32 of the *TSC2* gene was reported in one GG patient in glial cells, but not in dysplastic neurons [33].

Recent studies have reported a mutation of the *BRAF* oncogene [a member of the Raf (Rapidly Accelerated Fibrosarcoma) family of serine/threonine protein kinases involved in the Ras–RAF–MEK–ERK (extracellular signal regulated kinases)–MAP

(mitogen activated protein) kinase signaling pathway] in up to 50 % GG [34–37] (Fig. 1d), desmoplastic infantile GGs [38], and DNTs [31, 39]. The presence of the *BRAF* V600E mutation in DNTs strongly supports a relationship between DNTs and GGs, pointing to the pathogenic role of *BRAF* in different entities within the large spectrum of GNT, including other low-grade tumors arising in young age groups, such as pilocytic astrocytomas and pleomorphic xanthoastrocytoma [36, 40]. Interestingly, the *BRAF* V600E mutation has been shown to be associated with the expression of phosphorylated ribosomal S6 protein (pS6; marker of mTOR pathway activation) in GNT [31]. Accordingly, the *BRAF* V600E mutation has been linked to enhanced mTOR signaling via regulation of the protein kinase B (Akt) pathway [41]. In addition, other studies indicate that *BRAF* V600E mutant cells have a dysfunctional tumor suppressor liver kinase B1 (LKB1)–adenosine monophosphate-activated protein kinase–mTOR signaling [42, 43], and a positive association between the *BRAF* V600E mutation and mTOR pathway activation has been reported in *BRAF*-associated papillary thyroid carcinoma [44]. Thus, *BRAF*-induced phosphorylation of LKB1 may represent a possible additional mechanism contributing to mTOR activation in *BRAF* V600E-mutated GNTs, possibly

Fig. 2 Schematic of epileptogenic developmental brain lesions as mammalian target of rapamycin (mTOR)opathies. Overactivation of the mTOR signaling in glioneuronal tumors (GNT), focal cortical dysplasia (FCD) IIf, and hemimegalencephaly (HME), as well as tubers in tuberous sclerosis complex (TSC), suggests a pathogenic link between these malformations and reflects a spectrum of disorders of mTOR signaling (mTORopathies; see text). P=phosphorylation; IGF-1=insulin-like growth factor-1; PI3K=PI3kinase; PDK1=phosphoinositide-dependent kinase-1; LKB1=tumor suppressor liver kinase B1; AMPK=AMP-

activated protein kinase; HPV=human papilloma virus; S6K1=p70S6kinase; 4E-BP1=elongation binding protein 1; pS6=phosphorylated ribosomal S6 protein; Erk=extracellular signal regulated kinase; IRS=insulin receptor substrate; PTEN=Phosphatase and tensin homologue; Akt=protein kinase B; Rheb=ras homolog enriched in brain; mTORC=mammalian target of rapamycin complex; REDD1=regulated in DNA damage and development 1; DEPTOR=DEP domain containing MTOR-interacting protein

Table 2 Malformations of cortical development [5, 6]

Group I: malformations secondary to abnormal neuronal and glial proliferation or apoptosis	Group II: malformations due to abnormal neuronal migration	Group III: abnormal postmigrational development
Groups I.A: microcephaly	Group II.A: heterotopia	Group III.A: polymicrogyria and schizencephaly
Group I.B: megalencephalies	Group II.B: lissencephaly	Group III.B: cortical dysgenesis secondary to inborn errors of metabolism
Group I.C: cortical dysgenesis with abnormal cell proliferation without neoplasia	Group II.C: subcortical heterotopia and sublobar dysplasia	Group III.C: focal cortical dysplasias
<i>Hemimegalencephaly</i>	Group II.D: cobblestone malformations	<i>FCD Ia-c/FCD IIIa-d</i>
<i>FCD IIa/ FCDIb</i>		Group III.D: postmigrational microcephaly
<i>Tuberous sclerosis</i>		
Group I.D: cortical dysgenesis with abnormal cell proliferation with neoplasia		
<i>Dysembryoplastic neuroepithelial tumor Ganglioglioma</i>		

FCD=focal cortical dysplasia

through uncoupling of the LKB1–adenosine monophosphate-activated protein kinase–mTOR signaling. Interestingly, GGs have been reported in Peutz–Jeghers patients with a mutation of the *LKB1* gene [45, 46] and pLKB1 expression has been reported in GNT with the *BRAF* mutation [31]. These observations indicate that detection of *BRAF* V600E-mutated protein together with pS6 may be valuable in the diagnostic evaluation of GNT and may aid development of targeted treatment involving specific pathogenic pathways.

Epileptogenesis

Understanding the mechanisms that underlie epileptogenesis in GNT is essential to develop effective treatment in young patients in which pharmacologically intractable epilepsy (as discussed above) represents the initial, and often the only, clinical manifestation of the tumor and critically affects the patient's daily life.

Several hypotheses have been put forward during the last few decades to explain the epileptogenesis in patients with brain tumors. Both clinical and experimental studies suggest the involvement of multiple mechanisms, including both tumor-related factors (tumor size, tumor location) and peritumoral changes ([47–49]; Fig. 3).

Low-grade tumors that present with epilepsy are often large tumors, and the propensity to develop seizures is higher in temporal or frontal located low-grade tumors, such as GNT [47, 50]. The peculiar cellular composition and neurochemical profile of GNT, with the presence of a hyperexcitable neuronal component, may also be relevant for epileptogenesis (for reviews see [1] and [24]). Accordingly, intralesional recordings provide evidence of the high intrinsic epileptogenicity of GG [51] and DNT [52]. Moreover, a relatively high neuronal density within the tumor has been shown to be associated with highly epileptiform electrocorticographic discharge patterns in GNT,

supporting the concept of a neuronal tumor component functionally integrated into excitatory circuitries [53].

The presence of a hyperexcitable neuronal component is also supported by immunocytochemical studies showing high expression of specific glutamate receptors (GluR) subtypes, including both ionotropic (iGluR) and metabotropic glutamate receptors (mGluR) in the neuronal component of GNT [54–56]). In addition, analysis of the gene expression profile of GG highlights developmental alterations of the balance between excitation and inhibition, with a prominent expression of mGluR5 and downregulation of several gamma-aminobutyric acid (GABA)_A receptor (GABA_AR) subunits (including $\alpha 1$, $\alpha 5$, $\beta 1$, $\beta 3$, and δ), suggesting impairment of GABAergic inhibition [29, 57, 58]. A deregulation of the cation–chloride (NKCC1 and KCC2) cotransporters (CCTs), resembling the expression patterns observed in immature brain, has been reported in GGs [57, 59], and may also actively contribute to the epileptogenicity of this tumor type via modulation of GABA receptors [60].

GluR (iGluR and mGluR) in glial cells may also contribute to the epileptogenicity of glial tumors and GNT [55, 56, 61]. Several studies suggest a deregulation of glutamate uptake and release, with a consequent increase of the extracellular glutamate concentration [61, 62]. Accordingly, a decreased expression of glial glutamate transporters has been observed in both glial tumors and GNT [29, 63]. Moreover, activation of mGluR5, which is highly expressed in GNT, has been shown to downregulate the expression of glial glutamate transporters in vitro [64, 65]. Recent studies point to the critical role of the system X_c[−] (an Na⁺-independent cystine–glutamate transporter), which regulates glutamate production and release from glioma cells, influencing neuronal hyperexcitability and seizure development [61, 66, 67].

Altered expression of gap junction channels (connexins) resulting in a disturbed communication between glial cells

Fig. 3 Schematic depicting mechanisms contributing to epileptogenesis in developmental tumors (glioneuronal tumors) and malformations of cortical development. A better understanding of these mechanisms may create the basis to develop effective therapeutic strategies to control seizures. TLR2=Toll-like receptor 2; RAGE=receptor for advanced glycation end products; IL-1R1=interleukin 1 receptor; mTOR=

mammalian target of rapamycin; Glu=glutamate; Kir=inward-rectifying potassium channel; BBB=blood-brain barrier; iGluR=ionotropic glutamate receptor; mGluR=metabotropic glutamate receptor; CCT=cation-chloride (NKCC1 and KCC2) cotransporter; GABA_AR=gamma-aminobutyric acid A receptor

may also contribute, potentially, to seizure development in brain tumors, including GNT [68, 69]. Furthermore, the low expression of several potassium channel genes observed in GG suggests a disturbed ion homeostasis and transport that could represent an additional potential mechanism leading to increased excitability in GNT [57]. Interestingly, evaluation of the inward-rectifying potassium channel on astrocytes Kir4.1 in tumor specimens showed a significantly lower Kir4.1 expression in the specimens of patients with epilepsy compared to patients without epilepsy [70].

Over the last decade, an increasing number of observations support the role of inflammation in the pathophysiology of human epilepsy (for reviews see [71–74]; Fig. 3). Pro-inflammatory molecules have been shown in experimental models to decrease the seizure threshold [72–74] and may also contribute to the generation of seizures in brain tumors, particularly in GNT (for review, see [49] and [71]). They can increase neuronal excitability through different mechanisms, for example enhancing the extracellular glutamate concentrations, as well as modifying the function of both glutamate and GABA receptors (for reviews see [72–74]).

Interestingly, both gene expression and immunocytochemical studies provide evidence for a prominent activation of both the innate and adaptive immune system in GNT [57, 75, 76]. In particular, a prominent expression of components of the interleukin (IL)-1/Toll-like receptor (TLR) signaling and complement cascade has been observed in GNT [57, 77]. Recent findings indicate a prominent upregulation of major histocompatibility complex class I (MHC-I) in neuronal cells as part of the immune response occurring in different epileptogenic glioneuronal lesions characterized by mTOR pathway activation (GG, FCD, and TSC; [76]).

In GNT, particularly in GG, the prominent inflammatory changes are associated with evidence of alterations in blood-brain barrier (BBB) dysfunction, with albumin extravasation and uptake in tumor astrocytes [31, 76, 78], which could play an additional role in the tumor epileptogenicity [79]. Interestingly, in GGs, a positive correlation between pS6 expression and the presence of perivascular cuffs of lymphocytes, as well as with MHC-I and MHC-II expression and albumin extravasation/glia uptake within the tumor, has been detected [31]. These observations suggest a potential relationship between mTOR activation

and the immune response. Accordingly, mTOR has been shown to influence both the innate and adaptive immune response [80–82], and selectively regulate microglial activation in response to pro-inflammatory cytokines, influencing microglial viability [83]. The prominent upregulation of the mTOR pathway observed in GNT, particularly in GG, is especially interesting in view of the observations supporting the role of mTOR as a key regulator of cellular changes involved in epileptogenesis (for reviews see [84–87]). Recent observations suggest a prognostic value for *BRAF* V600E and pS6 (as marker of mTOR activation) as potential indicators of worse postoperative seizure outcome in GNT [31].

There have been several additional proposed mechanisms to account for enhanced excitability in GG. For example, hypoxia and acidosis, ionic changes, and deposition of hemosiderin in the peritumoral region have also been suggested as potential mechanisms affecting epileptogenesis in gliomas [47, 48, 69]. A complex alteration of the GABAergic system, also involving the perilesional epileptic cortex, has been reported in patients with GG [88, 89] and a recent study supports the key role of CCTs in tumor-related epilepsy [90]. Enzymatic changes may also occur in peritumoral tissue, impairing neurotransmitter synthesis and storage, and contributing to tumor-associated epilepsy [79]. Attention has been particularly focused on the changes in adenosine kinase (key metabolic enzyme for the regulation of extracellular adenosine levels) occurring in peritumoral tissue of glioma patients ([91]; for a review see [92]) Finally, association with cortical dysplasia (as discussed below; [6]) also has to be considered in the evaluation of the epileptogenicity of GG.

MCD

MCD include a large spectrum of developmental disorders and an increasing number of entities are continuously described, thus a proposal of a unified and comprehensive classification of MCD represents a great challenge and requires continuous updates. In 2005, Barkovich et al. [93] developed a classification of MCD based on the major stages of cortical development that are possibly affected. Recently, this classification system has been revised [5] on the basis of new developments in molecular biology, genetics, and imaging features of MCD and neuropathological classifications (Table 2).

FCD

Clinical and Neuropathologic Features

FCD are localized MCD, which are recognized causes of chronic medically intractable epilepsy in children and young adults [1, 2, 94]. Since the first description of the neuropathologic features of

FCD provided by Taylor et al. in 1971 [95], different FCD classification systems have been proposed [93, 94, 96–98]. A task force of the Diagnostic Methods Commission of the International League Against Epilepsy (ILAE) has recently generated a new consensus classification of distinct FCD subtypes based on histopathological features [6]. A recent evaluation of this classification system showed good inter- and intra-observer agreement [99], with considerable improvement compared with a previous study evaluating the 2004 Palmini FCD classification [100]. This 2011 ILAE classification consists of a three-tiered system, including both isolated and associated FCD variants [6].

FCD type I may affect one or multiple lobes, and is often observed in young patients with severe epilepsy and psychomotor retardation [6, 101–103]. FCD type I is characterized by abnormal cortical layering with radial microcolumns (FCD type Ia; resembling the microcolumnar organization pattern described during the early stages of cortical development [104]), tangential layer alterations (FCD type Ib), or by a combination of both (FCD type Ic). In all three variants heterotopic neurons in white matter and hypertrophic neurons (outside layer 5) can be encountered, as well as normal neurons with disoriented dendrites [6, 105].

FCD type II (Fig. 1g–j) is highly represented in epilepsy surgical series, being a major cause of drug-resistant epilepsy. The clinical presentation is variable and depends on age of onset of seizures and the location of the lesion. FCD type II is more frequently encountered in extratemporal areas, particularly in the frontal lobe (for reviews see [1, 2], and [94]). Histopathologically, FCD type II refers to an isolated malformation characterized by abnormal cortical layering and cytological abnormalities, and includes two subtypes: FCD type IIa (with dysmorphic neurons, but without balloon cells) and FCD type IIb (with dysmorphic neurons and balloon cells; [6]).

A major challenge in the ILAE classification was the reclassification of subtle pathological changes that are adjacent to or associated with other principal lesions, with the introduction of FCD type III [106]. FCD type III includes four different subtypes: 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 [6]. Histopathologically, FCD type III subtypes are often characterized by alterations in cortical dyslamination similar to those described in FCD type I. However, a distinct pattern can be identified in FCD type IIIa, consisting of an abnormal band of small and clustered “granular” neurons in the outer part of layer II [107–109]. Recent data indicate a reduction of myelinated axons in the white matter of FCD type II rather than dysmyelination as the primary pathologic process underlying the white matter abnormalities observed in this FCD type [110].

The ILAE classification represents the basis for clinical studies to better define specific clinical, electrophysiological,

and imaging features [111, 112], but may also guide prospective studies addressing the molecular pathogenesis and epileptogenicity of different FCD variants.

Pathogenesis and Molecular Genetics

The cellular and molecular mechanisms underlying FCD are still unclear, in particular our knowledge of the pathogenesis of FCD I is still rather limited, and animal models that precisely replicate the specific histopathological features of FCD variants are not yet available. However, new hypotheses are emerging on the molecular pathogenesis of FCD II (Fig. 2).

The histopathologic similarities between FCD IIb and TSC cortical lesion (cortical tubers), has led to several studies with the aim of finding a pathogenetic link between these two pathologies. TSC (see description below) is an autosomal dominant, multisystem disorder that results from mutations in the *TSC1* or *TSC2* genes, and is characterized by overactivation of the mTOR pathway [113, 114].

Several immunohistochemical studies provide evidence of enhanced mTOR signaling in FCD II with strong expression of the mTOR marker pS6 in dysmorphic neurons and in balloon cell ([115–117], reviewed in [30, 118]; Fig. 1j; Fig. 2). Although both FCD II and tubers are characterized by mTOR activation slight differences in the phosphorylation signaling steps have been reported [119]. In contrast, activation of the mTOR pathway has not been reported in FCD type I [117, 120, 121], supporting the notion that FCD I and FCD II represent two pathogenetically distinct entities.

The mechanisms underlying activation and upregulation of mTOR signaling in FCD II are still a matter of discussion. The secretion of growth factors, such as vascular endothelial growth factor (VEGF), in the microenvironment of these tumors has been also suggested to contribute to the activation of the mTOR pathway [122–124]. Whether seizure activity contributes to mTOR activation also has to be taken into consideration (for reviews see [84–86]). Mutational analysis of *TSC1* and *TSC2* demonstrated *TSC1* sequence alterations in FCD IIb [125]. In contrast in FCD Type IIa no allelic variants in exon 17 of *TSC1* were observed, but genomic polymorphisms were detected in intron 4 of *TSC2* [125]. The allelic variants in *TSC1* may affect the cellular localization of hamartin and its interaction with tuberlin [125, 126]. Interestingly, a recent study has suggested a novel viral etiology for FCD II [127, 128], which may explain the constitutive activation of mTOR [129], as well as the prominent activation of both innate and adaptive immunity [120] observed in FCD II. Human papilloma virus type 16 has been previously associated with dysplasia and cancer of the cervix. The human papilloma virus type 16 oncoprotein E6 is a potent activator of mTOR signaling and was detected in FCDIIb specimens [127]. Expression of E6 in fetal mouse brain causes disorganized cerebral cortical lamination. Future studies to define the

mode of transmission and potential pathogenic effects in the developing brain are necessary.

Recent observations suggest that abnormal activation of mTOR may contribute to apoptosis signaling pathways and premature activation of mechanisms of neurodegeneration in both FCD II and TSC [121]. Interestingly, tau-positive neuropil threads are observed in cortical regions with prominent immunoreactivity for pS6 and hyperphosphorylated tau is detected in pS6-positive dysmorphic neurons. Moreover, dysmorphic neurons and balloon/giant cells show nuclear and cytoplasmic accumulation of p62 [121], a stress-inducible intracellular protein, which is known to regulate different signal transduction pathways, and has been recently identified as a key target of autophagy (for reviews see [130, 131]. A recent study confirms the mTOR-dependent abnormalities in autophagy, indicating a defect in autophagy as a common feature of FCD II and TSC [132]. The mTOR signaling (overactivated in both TSC and FCD II) is, indeed, a major negative regulator of autophagy ([133]; for a review see [134]), and gene expression analysis of TSC cortical tubers revealed a deregulation of genes associated with ubiquitination [135].

Besides mTOR, other major pathways/proteins essential for normal cortical development (e.g., cyclin-dependent kinase 5 [136] and doublecortin-like [137]) have also shown to be deregulated in FCD II. Evaluation of doublecortin expression patterns in FCD I, compared with normal developing and mature cortex, indicates delayed or abnormal cortical maturation rather than ongoing cytogenesis [138]. Moreover, the application of different cortical layer markers in the evaluation of FCD I and FCD II [109, 139] demonstrates that FCD I cases in younger patients were characterized by abnormal expression in layer II for *Tbr1* and *Otx1*, whereas FCDII showed distinct labeling of balloon cells (*Pax6*, *ER81*, and *Otx1*) and dysmorphic neurones (*Tbr 1*, *N200*, and *Map1b*), supporting origins from radial glia (as previously shown [139]) and intermediate progenitor cells, respectively [109].

Epileptogenesis

The intrinsic and high epileptogenicity of FCD is clearly supported by different clinical and electrographic features [140–145]. Particular attention has been focused on the contribution of the population of dysplastic neurons to the epileptogenesis of FCD. Several studies using in vitro electrophysiological recording in FCD surgical specimens have provided support for the presence of neuronal cells, which are functionally integrated in the immature cortical network, with hyperexcitable intrinsic membrane properties (for reviews see [146–148]). Increasing evidence supports the role of developmental alterations of the balance between excitation and inhibition in the pathogenesis of epileptic focal discharges in FCD (Fig. 3). Attention has first been focused on the local pathways of excitatory amino acid synaptic transmission in the

dysplastic cortex. Among the iGluRs, the role of N-methyl-D-aspartate (NMDA) receptors (GluN) in cortical hyperexcitability has received considerable attention. Several studies have shown alteration in GluN subunit expression in human epileptic tissue with increased expression of the subunit NR2B [149–152]. Changes in the expression of components of the membrane-associated guanylate kinase (MAGUK) protein family, interacting with GluN, has been also reported [153, 154]. In particular, recent data showing upregulation of NMDA regulatory subunits and related MAGUK proteins in epileptogenic/dysplastic areas suggest that glutamate/NMDA/MAGUK dysregulation might also represent the intracellular trigger that modifies brain morphology and induces cell death [154]. Alteration in the expression of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor subtypes has been also reported ([150]; for reviews see [146] and [147]). In addition to the deregulation of iGluR, the cellular distribution of mGluR subtypes, with high expression of mGluR1 α and mGluR5 in dysmorphic neurons, suggests a possible contribution of group I mGluRs to the intrinsic and high epileptogenicity of dysplastic cortical regions [155].

Several other studies point to a deregulation of inhibitory synaptic transmission in FCD (for reviews see [146–148]). Downregulation of several GABA_AR subunits, as well as a reduction in the number of inhibitory cells, has been shown in FCD, supporting the impairment of GABAergic inhibition [107, 156–159]. In addition, electrophysiological studies performed in brain slices from FCD tissue show immature GABA receptor-mediated responses, and GABA receptor-mediated synchronization appears to be involved in the mechanism leading to in vitro ictal activity in FCD [147, 148, 160]. Interestingly (similarly to GNT), a deregulation of cation–chloride (NKCC1 and KCC2) CCT expression has been observed in FCD [161]. The CCT expression pattern supports the hypothesis that human dysplastic tissue may retain immature properties, displaying mechanisms of seizure generation similar to that observed during development in the immature brain. A recent study demonstrates the relative benzodiazepine insensitivity and more excitatory action of GABA in FCD IIb and TSC compared to FCD type IIa, suggesting the possible add-on trials of the NKCC1 inhibitor bumetanide for the treatment of epilepsy in TSC and FCD type IIb [162].

Additional observations also point to the role of voltage-gated potassium (Kv) channels, showing the occurrence of post-translational Kv4.2 channel modifications, which may potentially contribute to the hyperexcitability of MCD, including FCD [163].

Increasing evidence suggests that dysfunction of neuron–glia interactions and modification of the extracellular space, induced by astrogliosis or by modified extracellular matrix composition might be involved in the epileptogenic mechanisms of FCD (for reviews see [164–166]). Accordingly,

changes in the expression of gap junctions [167], glial glutamate transporters [168], water channels (aquaporin-4; [169]), and matrix metalloproteinases (MMP-9 [170]) have been reported in FCD. Recently, changes in extracellular matrix composition with associated altered extracellular space diffusion properties have been detected in both FCD I and II [171].

Finally, inflammatory changes may also play a role in the epileptogenicity of FCD, particularly in FCD II. As discussed above, the activation of inflammatory pathways and the consequent release of inflammatory molecules alter neural network excitability, inducing various mechanisms, with either a direct or indirect impact on neuronal functions (for reviews see [71–74]). Activation of cells of the microglia/macrophage lineage and astrocytes and concomitant induction of various inflammatory pathways have also been observed in FCD with activation of both innate and the adaptive immune response [77, 120, 172, 173]. In a cohort of FCD II patients, the density of activated microglial cells correlated significantly with the duration of epilepsy, as well as with the frequency of seizures prior to surgical resection [172]. However, the number of activated microglial cells, as well as the number of T lymphocytes (CD3/CD8-positive T-cells), was significantly higher in FCD type II than in specimens from patients with FCD type I (despite no significant differences in seizure frequency and duration [120]). Recent findings indicate a prominent upregulation of MHC-I in FCD II, but not in FCD I [76]. In FCD II there is evidence of activation of the plasminogen [174] and focal BBB disruption, with perivascular parenchymal leakage of serum albumin and uptake into astrocytes [76]. A growing body of evidence confirmed that BBB dysfunction is critically involved in the development of epilepsy (reviewed in [175]).

Prominent activation of complement, IL-1 β , as well as overexpression of high mobility group box 1 and its cognate receptors (TLR2, TLR4, and receptor for advanced glycation end products), are other features of FCD II [77, 120, 176]. These observations provide evidence of a chronic inflammatory state in FCD II supporting the role of high mobility group box 1–TLR/receptor for advanced glycation end products pathways in the mechanisms underlying the intrinsic high epileptogenicity of these developmental lesions. Accordingly, the activation of these pathways has been shown to play a pivotal role in seizure precipitation and recurrence using a post-translational mechanism independent of transcriptional activation nuclear factor kappa-B and involving the rapid activation of Src kinases and phosphorylation of the NMDA–NR2B receptors [177–179]. IL-1 β may also regulate the expression of inward-rectifying potassium channels on astrocytes (such as Kir4.1), influencing the potassium buffering, which could represent an additional mechanism contributing to neuronal hyperexcitability and seizure development [70].

TSC

Clinical and Neuropathologic Features

TSC is an autosomal dominant disorder that results from mutations in the *TSC1* or *TSC2* genes [113, 114]. Although TSC affects different organ systems, central nervous system involvement is common, resulting in developmental delay, neurobehavioral disability (such as autism), and often severe epilepsy [117, 180, 181]. Genotype–phenotype correlation studies suggest that patients with *TSC2* mutations may have a more severe neurologic phenotype [182–185].

Neuropathological examination of TSC brains specimens reveals 3 major lesion types: cortical tubers, subependymal nodules, and subependymal giant cell tumors [185–187] (Fig. 1k–n). Cortical tubers are focal developmental malformations of the cerebral cortex detected as single or multiple lesions in >80 % of patients with TSC, and linked to both epilepsy and neurocognitive disabilities (for reviews see [117] and [188]). Tubers are frequently encountered 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” [185, 186, 189, 190]. The giant cells in TSC are histologically similar to balloon cells detected in FCD type IIb in that they exhibit an enlarged cell body and opalescent, glassy-appearing, eosinophilic cytoplasm [6]. Both giant cells and balloon cells express cell proteins characteristic of neuroglial progenitor cells such as SOX2, nestin, vimentin, and c-myc, suggesting a failure to differentiate prior to migration into the cortex [137, 191–193]; for reviews see [117] and [185]). With the recent advances in both fetal ultrasonography and magnetic resonance imaging, tubers can be detected during the prenatal period in TSC patients [194–196]. Tubers have been detected as early as 20 weeks gestation [197, 198], indicating that tubers form during embryonic brain development, probably between week 10 and 20 of human gestation.

Tubers are not static lesions, and dynamic changes may occur over time, including calcification and cystic changes. The presence of inflammatory cells/molecules [198, 199] and astrogliosis [200, 201] may contribute to the changes in cell morphology in tubers. Interestingly, the development of cystic changes (end-stage of degenerative changes, affecting the white matter) has been shown to be associated with a *TSC2* gene mutation and with a more aggressive seizure phenotype [202, 203]. More recently, three different types of tubers (type A, B, C) have been described on the basis of the magnetic resonance imaging features [204]. However, a histopathological classification scheme for tubers has not yet been proposed and could represent an important advance in understanding of epileptogenesis in TSC patients.

Enhanced expression of several factors involved in the regulation of angiogenesis has been reported in cortical tubers [135]. In particular, epidermal growth factor, hepatocyte growth factor, and VEGF, which regulate angiogenesis and cell growth in the developing brain, have been recently shown to be upregulated in tubers, as well as in a mouse model of TSC, providing potential new targets for therapy development in TSC [205].

Besides the cortical tubers, subtle abnormalities have been also detected in both fetal and adult TSC brains, and may underlie the complex neurologic disabilities encountered in TSC patients [198, 206]. Moreover, similarly to FCD II, induction of apoptosis signaling pathways and premature activation of mechanisms of neurodegeneration, as well as a defect in autophagy [132], has also been observed in the tubers.

Pathogenesis and Molecular Genetics

The identification of the *TSC1* and *TSC2* genes has facilitated our knowledge of the mechanisms of brain lesion formation in TSC. Inactivating *TSC1* or *TSC2* mutations in neuroglial progenitor cells has been shown to result in constitutive activation of the TORC1 signaling cascade, which plays a critical role in the regulation of cell growth and proliferation (Fig. 2) [117, 118, 207, 208]. Cell-associated activation of the target-of-rapamycin complex 1 pathway has been detected in dysmorphic neurons and giant cells [115–117, 137, 193]. Detection of activated (phosphorylated) components of the mTOR pathway (such as pS6) now permits analysis of the cellular components of tubers not simply on the basis of their morphology, but on the basis of the specific pathogenetic defect underlying the development of these lesions (Fig. 1m, n). Interestingly, recent observations indicate that brain malformations in TSC are likely a consequence of increased mTOR activation during fetal brain development [198, 209].

Loss of heterozygosity at either the *TSC1* or *TSC2* locus has been shown in many TSC-associated tumors [207, 210, 211]. However, there is still debate about whether this “two-hit” hypothesis explains tuber formation [212]. By sequencing *TSC1* and *TSC2* in microdissected pS6-immunolabeled giant cells, a recent study demonstrated that somatic inactivating mutations may be detected in tubers, thus supporting a “two-hit” mechanism for tuber formation [213]. However, another study implementing deep sequencing technologies of genomic DNA extracted from whole tubers reported a somatic mutation in *TSC1* in only 1 out of 46 tuber samples [214]. The differences in results between these two studies may reflect differences in sequencing approaches, for example DNA extracted from single cells *versus* whole tubers.

Epileptogenesis

Epilepsy is reported in >80 % of patients diagnosed with TSC and significantly affects psychomotor development and quality of life, as failure to respond to anticonvulsant drug treatment is particularly common in TSC patients [180, 215]. Cortical tubers are considered to represent the neuropathologic substrate of epilepsy in TSC patients. Despite recent advances in imaging and electrophysiologic techniques, the functional role of tubers as the epileptogenic zone remains a matter of some debate [216–219]. Increasing evidence supports the importance of the perituberal cortex in TSC (for reviews see [165, 218] and [219]). Accordingly, although epilepsy surgery targeting tubers may result in seizure freedom, [216, 220] some patients continue to have seizures after tuber resection and, in fact, cases of TSC patients becoming seizure-free after resection of nontuberal cortex have been reported [221] (for a review see [165]).

The cellular mechanism(s) underlying the epileptogenicity of cortical tubers has(have) not yet been completely clarified. As discussed earlier for GNT and FCD, several observations also support the role of developmental alterations of the balance between excitation and inhibition in the epileptogenicity of cortical tubers (Fig. 3) (for reviews see [165, 185] and [222]). For example, large-scale gene expression studies indicate alterations in glutamatergic and GABAergic synaptic transmission in cortical tubers, involving reduced expression of the glial glutamate transporter (GLT-1 or EAAT2), reduced expression levels of GABA_A receptor subunits, and reduced expression of potassium channels [135]. Selective alterations of iGlu subunits, as well as of mGluR subtypes (with prominent group I mGluR expression, mGluR1, and mGluR5) have been reported in tubers [193, 223, 224]. In addition (as discussed above) an excitatory action of GABA has been reported in TSC [162]. Mouse models of TSC point to additional mechanisms that would support seizure generation, such as abnormal glutamate homeostasis, increased α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-receptor-mediated currents, impaired astrocytic gap junction coupling, and potassium buffering [221, 225, 226].

As discussed earlier, activation of inflammatory pathways may also contribute to neuronal hyperexcitability and seizure development. Accordingly, tubers are characterized by a complex activation of pro-inflammatory signaling pathways, including chemokines, complement, and IL-1 β and TLR-mediated pathways [135, 176, 199]. Activation of the plasminogen system [174] and focal BBB disruption [199] have been also described in tubers. Moreover, a recent study provides evidence for prenatal activation of key inflammatory pathways in developing TSC brain lesions [198], supporting the role of immune-inflammatory responses in the dynamic changes, which, over time, may contribute to the pathogenesis of seizures and cognitive impairment in TSC patients.

Hemimegalencephaly

Clinical and Neuropathological Features

Hemimegalencephaly (HME) is a malformation of cortical development characterized by unilateral enlargement of the cerebral hemisphere and severe architectural and cellular abnormalities. Clinically, HME is associated with developmental delay and severe epilepsy with onset typically within the first few months of life [227–231]. Epilepsy is often resistant to pharmacological treatment, requiring surgical intervention to remove or functionally disconnect the epileptogenic area within the affected hemisphere [232].

HME can occur as an isolated malformation or associated with several syndromes [230, 231, 233, 234]. A large spectrum of central nervous system structural abnormalities have been reported, including cases variously defined as “hemimegalencephaly”, “focal megalencephaly” “lobar dysplasia”, or “localized megalencephaly”, in which the abnormalities are detected only over a partial area of one hemisphere [235–237]. In these cases, the detection of associated extracerebral abnormalities (e.g., ipsilateral olfactory nerve enlargement, cerebral vascular dilations, cerebellar enlargement with abnormal architecture of the cerebellar folia) has been suggested to provide help in differentiating localized megalencephaly from multilobar cortical dysplasia [237]. Histopathologically, a large spectrum of morphologic alterations with a combination of different features of MCD (i.e., pachygyria, polygyria, polymicrogyria) can be observed in both isolated and syndromic forms (for reviews see [233, 238] and [239]). Microscopically, the cortex displays alterations in cortical dyslamination with the presence of hypertrophic and dysmorphic neurons, as well as heterotopic neurons in the white matter and leptomeningeal glioneuronal heterotopia (Fig. 1o) [238, 240–245] (for reviews see [233, 238] and [239]). The presence of balloon cells has been also reported in HME [244, 246]. Moreover, a recent report shows enhanced levels of phosphorylated tau protein and evidence of neuronal lipidosis in 3 male infants with HME [246].

Pathogenesis and Molecular Genetics

With the recent advances in fetal imaging HME can be detected prenatally [246], even at a fetal age of 22 weeks [239], supporting the hypothesis of an underlying primary genetic defect that affects the early stages of cortical development (probably between weeks 10 and 20 of human gestation). On the basis of the histopathologic features, it has been suggested as a primary deregulation of proliferation [247], or a disturbance of cellular growth and cellular lineage [233, 234]. Salamon et al. [244] indicate an increased proliferation of the progenitor cells together with partial failure of postneurogenesis apoptosis in the molecular layer and

subplate as possible mechanisms underlying the pathogenesis of HEM. The possibility of an accelerated neuronal differentiation has also been suggested, emphasizing the importance of migration abnormalities [239]. Attention has been also focused on the excessive production and/or function of neuronal growth factors (e.g. epidermal growth factor, nerve growth factor and VEGF) which could contribute to enhanced neuronal growth and/or differentiation [243, 245, 248, 249].

As HME has been reported in patients with various syndromes [e.g., Proteus syndrome, neurofibromatosis, hypomelanosis of Ito, Klippel–Weber–Trenauany syndrome, TSC, linear sebaceous nevus syndromes (for reviews see [233, 238] and [239])], one longstanding question is whether syndromic HME is distinct from the sporadic forms or reflects a spectrum of hemispheric brain malformations, sharing common mechanism(s) of pathogenesis.

Recent studies point to the role of 2 converging cell signaling pathways (Wnt/ β -catenin and mTOR) in the pathogenesis of HME [245, 249–251]. The identification of mTOR signaling overactivation in HME (as in TSC and FCD IIb) suggests a pathogenic link between these malformations, possibly representing a spectrum of disorders of mTOR signaling (so-called “TORopathies”) [118, 252, 253]. Accordingly, Barkovich et al. [5] include HME in the non-neoplastic malformations secondary to cortical dysgenesis with abnormal cell proliferation (together with TSC and co FCD IIb; Table 2; Fig. 2).

It has been suggested that HME could result from a somatic mutations in genes encoding for proteins that regulate the mTOR signaling pathway, occurring in progenitor cells in one hemisphere during the early stages of corticogenesis [252]. A heterozygous deletion in 15q11.2–15q13.1 has been recently detected in the affected hemisphere in a single case of isolated HME [254]. More recently, *de novo* somatic mutations in *PIK3CA*, *AKT3*, and *MTOR* genes, encoding well-known regulators of the mTOR signaling pathway, have been reported [255]. These mutations were identified in 8–40 % of sequenced alleles in various brain regions and have been shown to be associated with the expression of pS6 (marker of mTOR pathway activation; Fig. 10). Thus, on the basis of these recent observations, HEM can be considered a genetically mosaic disease caused by overactivation in phosphatidylinositol 3-kinase–Akt3–mTOR signaling [255].

Epileptogenesis

There is currently little information available concerning the mechanisms of epileptogenesis of HME. The expression of multiple neurotransmitter receptors in surgery and autopsy HME specimens has been investigated using target complementary DNA array analysis and immunocytochemistry [245, 256]. These studies show changes in expression and/or composition of iGluR and mGluR that could play a role in

epileptogenesis in HME. In particular (similarly to FCD IIb), downregulation of several GABA_AR subunits [256] and increased expression of group I mGluRs (mGluR5) [245] has been detected in HME. Deregulation of glutamate transporters may also play a role, as diminished expression of the neuronal glutamate transporter EAAC-1 has been reported [256].

In addition, the presence of activated glial cells in HME [245] may also be related to the epileptogenicity of this pathology through different mechanisms (Fig. 3), including the production of pro-inflammatory/pro-epileptogenic cytokines, such as IL-1 β [71, 72].

Conclusions

Tumors and focal MCD remain common causes of intractable epilepsy in children and adults. Recent developments in molecular genetics have fostered our understanding of mutational mechanisms that may induce formation of these lesions during fetal brain development. Gaps still exist in our knowledge as to how these lesions actually cause recurrent seizures, but recent identification of select cell signaling pathways, that is, *BRAF* and mTOR, provide logical targets for new therapeutic development. Perhaps most exciting, these therapies may, in the future, be applied *in utero* to prevent formation of brain lesions.

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