Tuberous sclerosis: a syndrome of incomplete tumor suppression

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Tuberous sclerosis (TS) is a congenital neurocutaneous syndrome (or phacomatosis) characterized by widespread development of hamartomas in multiple organs. For affected individuals, neurological and psychiatric complications are the most disabling and lethal features. Although the clinical phenotype of TS is complex, only three lesions characterize the neuropathological features of the disease: cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas. The latter is a benign brain tumor of mixed neuronal and glial origin. Tuberous sclerosis is caused by loss-of-function mutations in one of two genes, TSC1 or TSC2. The normal cellular proteins encoded by these genes, hamartin and tuberin, respectively, form a heterodimer that suppresses cell growth in the central nervous system by dampening the phosphatidylinositols 3–kinase signal transduction pathway. The authors review the clinical and neuropathological features of TS as well as recent research into the molecular biology of this disease. Through this work, investigators are beginning to resolve the paradoxical findings that malignant cancers seldom arise in patients with TS, even though the signaling molecules involved are key mediators of cancer cell growth.

Key Words • tuberous sclerosis • hamartoma • giant cell astrocytoma • hamartin • tuberin

OVERVIEW

Tuberous sclerosis is a congenital neurocutaneous syndrome (or phacomatosis) characterized by widespread development of hamartomas in multiple organs. The French neurologist Désiré-Magloire Bourneville coined the term “tuberous sclerosis” in 1880 when he described the brain lesions found on postmortem examination of a 15-year-old patient who had suffered seizures since infancy as well as mental retardation and hemiplegia. Tuberous sclerosis has an incidence of 1 in 6000 to 1 in 10,000 live births, with no ethnic clustering.1,24,40,68 Approximately two thirds of cases are sporadic; that is, affected individuals have no family history of the disease.3,25,68,76 Familial cases show an autosomal-dominant pattern of inheritance. The cloning of two different disease-causing genes (TSC1 and TSC2) has accelerated our understanding of the molecular pathogenesis of TS. Control of cell growth in the central nervous system is markedly perturbed in TS, but malignant brain tumors rarely occur. Nevertheless, this syndrome is a topic of clinical relevance to neurosurgeons because TS-related space-occupying lesions and intractable epilepsy may require timely surgical intervention.

Clinical Pathology of the TSC

The characteristic lesions of TS are hamartomas, which are congenitally misplaced groups of cells that form disorganized, tumor-like masses. Hamartomas occur in the brain (discussed later), kidneys, lung, heart, eyes, and skin.2 Skin hamartomas include facial angiofibromas (also known as adenoma sebaceum), subungual fibromas, and shagreen patches.26,84 The growth rate of visceral hamartomas can accelerate spontaneously to create expanding tumors (SEGAs of the brain, angiomyolipomas of the kidney, lymphangiomyomatosis of the lung, and rhabdomyomas of the heart). On histopathological examination, these tumors are almost always benign. The molecular signals that trigger this transition from quiescent hamartoma to enlarging tumor are not known. Surprisingly, patients with TS rarely present with malignant neoplasms even though they have numerous hamartomas and benign tumors, which are considered premalignant lesions. The most common malignant tumor associated with TS is renal cell carcinoma.1

The clinical presentation of TS is determined by the spe-
cific organs affected. The severity of presenting symptoms is highly variable, ranging from minor skin lesions to intractable epilepsy and debilitating cognitive impairment. The classic symptom triad of adenoma sebaceum, epilepsy, and mental retardation comprised the first diagnostic criteria for TS. In 1998, the National Institutes of Health convened a consensus conference to standardize diagnostic criteria for the TSC. The published set of criteria was composed of clinical and radiographic features, which were divided into major and minor categories (Table 1). A definitive diagnosis of TS requires that a patient present with two of the major criteria shown in Table 1, or one major and two minor criteria. Notably, certain clinical signs that once were regarded as pathognomonic for TS, like mental retardation and epilepsy, are now considered nonspecific. Furthermore, no single criterion, found either clinically or radiographically, is present in all patients.

For affected individuals, neurological and psychiatric symptoms are the most disabling features. In fact, neurological complications are the leading cause of death for patients with TS, followed by renal disease and pulmonary lymphangioleiomyomatosis. The most common neurological symptoms are seizures, mental retardation, autism, hyperactivity, spastic paralysis, involuntary movements, ataxia, dementia, and ophthalmoplegia. More than 75% of patients suffer from seizures, and 68% have mild to severe cognitive impairment. As a general rule, larger and more numerous cortical tubers are associated with earlier seizure onset and more severe mental retardation. The types of seizures found in patients with TS are highly variable and include tonic–clonic, atonic, myoclonic, atypical absence, partial, and partial complex seizures.

Neuropathology of TS: Hamartomas in the Brain

Although the clinical phenotype of TS is complex, only three lesions characterize the neuropathology of the disease: cortical tubers and SENs, both of which are hamartomas, and SEGAs, which are histopathologically benign neoplasms. All three lesions occur predominantly in the brain. Hamartomas in the spinal cord have been reported, but no lesions occur in the peripheral nervous system. The fact that cortical tubers and SEGAs have been reported in spontaneously aborted fetuses indicates that the lesions of TS originate during fetal development. Cortical tubers occur in approximately 80% of patients with TS. Grossly, they appear as hard, wide gyri with smooth, flat tops or as rounded nodules with rough surfaces. Most cortical tubers occur in the frontal and parietal lobes, but some arise in the cerebellum, brainstem, and spinal cord. Microscopically, cortical tubers consist of interlacing fascicles of normal and abnormal neurons, astrocytes, and giant cells (Fig. 1A–C). Subependymal nodules are distributed along the sulcus terminalis throughout both lateral ventricles. Microscopically they resemble cortical tubers, except that SENs have a higher cellular packing density and sometimes contain polygonal and spindle-shaped epithelioid cells and mast cells (Fig. 1D). Giant cells (also known as balloon cells) are the neuropathological hallmarks of TS. They have prominent nuclei and nucleoli and abundant, glassy, eosinophilic cytoplasm (Fig. 1C and D). The origin of giant cells remains uncertain. Immunohistochemical studies have shown that these cells coexpress proteins normally found in neurons (neurofilament protein, Class III β-tubulin) and in astrocytes (glial fibrillary acidic protein, S100 protein) (Fig. 1E and F).

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### TABLE 1
Diagnostic criteria for TS

<table>
<thead>
<tr>
<th>Major Features</th>
<th>Minor Features</th>
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<tr>
<td>facial angiofibromas</td>
<td>multiple pits in dental enamel</td>
</tr>
<tr>
<td>ungual or perungual fibroma</td>
<td>hamartomatous rectal polyps</td>
</tr>
<tr>
<td>hypomelanotic macules</td>
<td>bone cysts</td>
</tr>
<tr>
<td>shagreen patch</td>
<td>“migration tracts”</td>
</tr>
<tr>
<td>cortical tuber</td>
<td>gingival fibromas</td>
</tr>
<tr>
<td>SEN</td>
<td>nonrenal hamartoma</td>
</tr>
<tr>
<td>SEGAs</td>
<td>retinal achromic patch</td>
</tr>
<tr>
<td>multiple retinal nodular hamartomas</td>
<td>“confetti” skin lesions</td>
</tr>
<tr>
<td>cardiac rhabdomyoma</td>
<td>multiple renal cysts</td>
</tr>
<tr>
<td>lymphangiomatomatosis</td>
<td></td>
</tr>
<tr>
<td>renal angiomyolipoma</td>
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Histologically, intracranial calcification on skull x-ray films was the first radiographic sign of TS. This appearance was due to dystrophic calcification in cortical tubers and SENs. On early pneumoencephalograms, SENs could be seen protruding into the lumen of the lateral ventricle, giving the appearance of molten candle wax (“candle gutterings”). Modern computerized tomography scanning detects brain calcification in 50 to 80% of patients (Fig. 2A). Subependymal nodules are usually densely calcified, whereas cortical tubers show variable density, depending on the amount...
of calcium present.\textsuperscript{37,63} On MR imaging, cortical tubers appear hyperintense on T\textsubscript{2}-weighted images (Fig. 2B).\textsuperscript{37} Subependymal nodules appear slightly more intense than deep gray matter on T\textsubscript{2}-weighted images. Their signal intensity on T\textsubscript{1}-weighted MR images varies from patient to patient but is typically hypointense because of the calcification. The appearance of SEGAs on neuroimages closely resembles that of SENs, except that the tumors are larger and they enhance brightly after delivery of intravenous contrast agents (Fig. 2C). In addition, SEGAs are invariably located at the foramen of Monro. Advances in brain imaging have revealed that patients with TS often exhibit developmental anomalies that are not unique to the syndrome, such as agenesis of the corpus callosum, heterotopias, transmantine cortical dysplasia, and schizencephaly.\textsuperscript{19,44,90} Transmantine cortical dysplasia appears on MR images as radial bands of abnormal signal intensity extending from periventricular to subcortical regions of the cerebral hemispheres (Fig. 2D). Radial bands sometimes interconnect cortical tubers and SENs. These lesions are typically T\textsubscript{1} hyperintense and T\textsubscript{2} hypointense in infants and become T\textsubscript{1} hypointense and T\textsubscript{2} hyperintense in older children and adults.\textsuperscript{5} Radial bands are thought to represent a disturbance in the normal migration of neural progenitor cells from the ventricular germinal matrix to the cerebral cortex during brain development.\textsuperscript{5,12}

\textit{The TSC Genes Encode Tumor Suppressors}

An extensive body of evidence indicates that TS is
caused by loss-of-function mutations in one of two genes, TSC1 located on human chromosome 9q34 or TSC2 located on 16p13. The proteins encoded by TSC1 and TSC2 are called hamartin and tuberin, respectively. A detailed review of the molecular genetics of TS, which contains an analysis of mutations compiled from 446 patients, has been published by Cheadle, et al. In familial cases of TS, the mutation frequency for TSC1 and TSC2 is equal (50% for each gene). In sporadic cases, TSC1 mutations are found in approximately 10 to 15% of patients and TSC2 mutations are found in 70%. In sporadic and familial cases combined, mutations in either TSC1 or TSC2 have been found in 75 to 90% of patients with TS. The absence of mutations in the remaining 10 to 25% of patients most likely reflects limitations in the sensitivity of mutation detection rather than the existence of other genes distinct from TSC1 and TSC2.

Several independent studies have shown close similarities between the phenotypic features associated with TSC1 and TSC2 mutations, suggesting that TS is a disease characterized by locus heterogeneity. Locus heterogeneity predicts that these two genes will encode proteins that function together in the same biochemical pathway. Indeed, hamartin and tuberin, the cellular proteins encoded by TSC1 and TSC2, are now known to interact to suppress the PI3K signal transduction pathway, which will be discussed later. The results of other studies suggest that patients with TSC2 mutations have more disabling neurological impairments than those with TSC1 mutations. For example, a genotype–phenotype correlation in 224 patients showed that TSC1 mutations were associated with lower seizure frequency, milder cognitive impairment, fewer SENs and cortical tubers, less severe kidney and skin disease, and the

Fig. 2. Neuroimages showing the features of TS. A: A computerized tomography scan demonstrating calcified SENs. B: Hyperintense multifocal cortical tubers revealed on T2-weighted MR image. C: Gadolinium-enhanced T1-weighted MR image revealing a SEGA obstructing the right foramen of Monro. D: A fluid-attenuated inversion-recovery MR image showing radial bands (arrows) and multiple cortical tubers.
absence of retinal hamartomas. Patients with TSC2 mutations may be more susceptible to aggressive renal tumors.

Several lines of evidence indicate that TSC1 and TSC2 are tumor suppressor genes. Such genes encode proteins that function normally to inhibit cell growth. According to the Knudson two-hit model, an inherited (germline) mutation in one copy (allele) of a tumor suppressor gene predisposes an individual to tumor formation. A somatic mutation (second hit) that inactivates the remaining normal allele is required to initiate tumor formation. In this model, loss of both allelic copies of a tumor suppressor gene results in a physiological constraint to cell growth. The second hit is often a deletion of the chromosome region containing the tumor suppressor gene. A molecular signpost for a chromosome deletion is loss of heterozygosity in tumor DNA compared with an individual’s normal DNA. Frequent loss of heterozygosity in a particular type of tumor indicates that a tumor suppressor gene important in the genesis of that tumor is present on the missing part of the chromosome.

Loss of heterozygosity for TSC1 and TSC2 has been reported in a wide variety of hamartomas and tumors resected in patients with TS, including renal angiomylipomas, cortical tubers, SEGAs, and peripheral angiosarcomas. Approximately 50% of hamartomas have loss of heterozygosity for loci on chromosome 9q34, where TSC2 is located, and 10% have loss of heterozygosity for chromosome 16p13 loci, which are linked to TSC1. The observation that mutations in these genes are usually nonsense, splicing, or frameshift mutations, which encode truncated nonfunctional proteins, is additional evidence that TSC1 and TSC2 are tumor suppressor genes.

Furthermore, an immunohistochemical study of nine SEGAs showed that expression of both tuberin and hamartin was absent or barely detectable in eight cases. Interestingly, the tumor cells obtained in one patient with a TSC2 mutation showed no hamartin but abundant tuberin. Taken together, these observations support the concept that hamartomas and other tumors arise in patients with TS when inactivation of either hamartin or tuberin stimulates the growth of susceptible cells.

Hamartin and Tuberin Integrate Growth Factor and Nutrient Signals in the Cell

The proteins hamartin and tuberin, which are encoded by TSC1 and TSC2, bind to one another inside the cytoplasm to form a molecular complex that serves as a gate to control cell growth signals conveyed through the PI3K signal transduction pathway. As reviewed by Cantley, the PI3K pathway is a vital information system that governs many aspects of cell growth. In a review of the literature, Rowinsky has reported that the pathway is hyperactive in many types of malignant tumors. Detailed reviews focused on the hamartin/tuberin complex in PI3K signaling have been published by Hay and Sonenberg and by Inoki, et al.

One vital function of the PI3K pathway is to transduce cell growth and survival signals conveyed by extracellular growth factors such as IGFs. Salient features of IGF-stimulated PI3K signaling are shown schematically in Fig. 3. When IGFs engage their cognate receptors on the cell surface, the activated tyrosine kinase receptors phosphorylate the cytoplasmic protein IRS-1, thereby creating a molecular docking site for the regulatory subunit of the enzyme PI3K. Consequently, PI3K is activated, bringing along its cognate signaling partners including Akt. Akt phosphorylates tuberin, causing the hamartin/tuberin complex to dissociate. The result is disinhibition of mTOR activity. Activated Akt phosphorylates tuberin, causing the hamartin/tuberin complex to dissociate. The result is disinhibition of mTOR activity. Activated Akt phosphorylates tuberin, causing the hamartin/tuberin complex to dissociate. The result is disinhibition of mTOR activity. Activated Akt phosphorylates tuberin, causing the hamartin/tuberin complex to dissociate. The result is disinhibition of mTOR activity. Activated Akt phosphorylates tuberin, causing the hamartin/tuberin complex to dissociate. The result is disinhibition of mTOR activity.

Mouse Models Elucidate the Low Level of Malignant Transformation in TS

Considering the fact that hamartin and tuberin apply the brakes in a signal transduction pathway that is frequently activated in many types of malignant tumors, it is surprising that lesions in patients with TS rarely become malignant. Mouse models of TS provide an explanation. Mouse embryos in which either the Tsc1 or the Tsc2 gene is completely knocked out fail to develop beyond midgestation because they suffer hypoplasia of the liver and enlargement of the heart. Mice that are heterozygous defective for Tsc1 or Tsc2 develop normally, but they are predisposed to renal adenomas, which progress at low frequency to malignant cancers. These mice also develop hepatic hemangiomomas and peripheral angiosarcomas. Interestingly, brain lesions, which are so common in cases of TS in humans, do not occur in these mouse models.

When Tsc2 is crossed with mice that are heterozygous for the catalytic subunit of PI3K converts the membrane-bound phospholipid PIP, to PIP₂, which recruits the serine/threonine kinase Akt to the plasma membrane, where Akt is phosphorylated and thereby activated catalytically. The tumor suppressor protein PTEN dampens PI3K signaling by dephosphorylating PIP₂, thereby preventing attachment of Akt to the plasma membrane.

A key downstream component of the PI3K pathway is the cellular protein mTOR. The best-described biochemical function of mTOR is its promotion of mRNA translation and hence stimulation of protein synthesis in the cell. Like Akt, mTOR is a serine/threonine kinase that becomes catalytically activated in response to PI3K signaling. Although mTOR is a direct phosphorylation substrate for Akt, evidence is mounting that the principal mechanism whereby Akt activates mTOR is not by direct phosphorylation, but rather by disruption of the hamartin/tuberin complex. In the model shown in Fig. 3, the hamartin/tuberin complex functions normally to suppress mTOR activity. Activated Akt phosphorylates tuberin, causing the hamartin/tuberin complex to dissociate. The result is disinhibition of mTOR and consequent stimulation of mRNA translation, protein synthesis, and cell cycle progression. Although Akt and mTOR are functionally coupled in the PI3K pathway, each of these proteins transduces cell signals through a unique set of downstream effector molecules.

In addition to relaying growth factor signals to the nucleus of the cell, mTOR functions as a nutrient sensor during cell metabolism. Under conditions of nutrient deprivation, intracellular levels of ATP and amino acids fall. In response, mTOR activity declines. This compensatory mechanism makes sense for cells because it enables them to shut down their energy-demanding processes, like protein synthesis, during nutritionally hard times. The biochemical reactions that couple intracellular ATP levels with mTOR activity are not fully understood, but tuberin clearly plays a role. When cells are in low-energy states, the enzyme adenosine monophosphate–activated protein kinase phosphorylates tuberin, and this phosphorylated form of tuberin protects cells from apoptotic death induced by energy deprivation. Thus, hamartin and tuberin, by regulating mTOR, integrate two of the most important signals governing cell growth: growth factors and nutrients.
erozygous defective for the Pten tumor suppressor gene, the resultant compound heterozygotes (Tsc2−/− Pten−/− mice) show an earlier onset and higher incidence of hepatic hemangiomas and peripheral angiosarcomas. Analysis of signaling molecules specifically regulated by Akt and mTOR shows that, in hepatic hemangiomas, signaling downstream of Akt is attenuated in the benign tumors found in Tsc2−/− mice but is enhanced in the more aggressive tumors present in Tsc2−/− Pten−/− mice. This suggests that loss of Tsc2 expression creates an inhibitory feedback loop, in which mTOR or one of its downstream effectors suppresses Akt signaling (Fig. 3). The Pten deficiency can overcome this inhibition by enabling PI3K signaling to increase cellular levels of activated Akt. Extrapolating these findings to TS in humans provides an explanation for the fact that malignant tumors rarely occur, although hamartomas, which result from aberrant cell growth control, are abundant. Tuberin deficiency simultaneously stimulates mTOR-mediated protein synthesis and inhibits Akt-mediated cell survival and proliferation (Fig. 3). The combined effect is to perturb cell growth control just enough to generate hamartomas but not sufficiently to induce malignant transformation.

TREATMENT CONSIDERATIONS: EPILEPSY AND NEUROONCOLOGY

The mainstay of seizure control for patients with TS is...
medical therapy with anticonvulsant drugs and a ketogenic diet. Evidence is accumulating that vigabatrin, an inhibitor of γ-aminobutyric acid transaminase, is the anticonvulsant medication of choice for patients with TS. In a comprehensive literature review, 73 of 77 patients with infantile spasms and TS attained complete resolution of seizures when treated with vigabatrin alone. If anticonvulsant medications and dietary modifications are not effective, then neurosurgical intervention can be considered. When selecting patients who will most likely benefit from surgery, physicians must use carefully conducted preoperative electroencephalographic studies to localize an epileptogenic focus to a discrete cortical lesion. Resection of such electrically localized seizure foci completely eliminates seizures in 25 to 69% of preselected patients and significantly reduces seizure frequency in the remaining ones.

Factors that predict a favorable response to surgery include unifocal seizures and mild degrees of cognitive impairment. The multifocal distribution of brain lesions in patients with TS may render the search for a safe surgical target unfeasible. If a single seizure focus cannot be identified or if the focus localizes to eloquent cortex, then placement of a vagal nerve stimulator may be an effective surgical alternative. In one series, vagal nerve stimulation reduced seizure frequency by 50% in nine of 10 patients.

Another indication for neurosurgical treatment of patients with TS is decompression of a space-occupying lesion, usually a SEGA causing obstructive hydrocephalus at the foramen of Monro. Microsurgical treatment of these tumors is indicated for patients in whom there are no medical comorbidities or psychosocial contraindications. Giant cell astrocytomas are slow-growing, noninvasive tumors, so gross-total resection is curative. In one series of 12 patients, no tumor recurred postsurgically after a mean follow-up duration of 52 months. When planning the surgical approach to the anterior third ventricle in a patient with TS, neurosurgeons must be aware of coexisting developmental anomalies of the brain. For example, agenesis of the corpus callosum, which can be associated with interdigitation of cortical tissue between opposing surfaces of the cerebral hemispheres, can make interhemispheric approaches difficult and hazardous, because of the need for tedious dissection through ill-defined tissue planes and uncertainty about the location of pericallosal and callosomarginal arteries.

Future Strategies: Targeting Akt and mTOR Signaling

The central role of hyperactive PI3K signaling in TS suggests that pharmacological inhibition of the PI3K pathway might be a rational treatment strategy, at least for associated malignant tumors. A logical treatment target is mTOR itself. As detailed in the review by Bjornsti and Houghton, exposure of tumor cells to rapamycin, a macroline antibiotic agent, markedly suppresses growth of tumor cells in culture by interfering with the ability of mTOR to activate mRNA translational mechanisms. Rapamycin was first developed as an antifungal drug, but when it was found to be a potent immunosuppressant, this discovery led to approval by the US Food and Drug Administration for rapamycin use to prevent rejection of transplanted organs.

Rapamycin reduces tumor cell proliferation in the Eker rat, a naturally occurring genetic model of TS resulting from a Tsc2 gene mutation. Rapamycin and several chemical analogs are now being tested in human clinical trials, and evidence is accumulating that they are effective anticancer agents (see literature reviews by Rowinsky and Sawyers). Reported toxic effects have been mild and include cutaneous reactions, transitory myelosuppression, and reversible hepatic dysfunction. A potential problem involving mTOR inhibitors is the inhibitory feedback loop from mTOR to Akt. Blocking mTOR signaling with rapamycin could promote tumor proliferation by removing the physiological constraint to Akt signaling imposed by mTOR. Considering this possibility, it might be necessary to combine rapamycin with an inhibitor of Akt or PI3K to maximize cell growth suppression.

CONCLUSIONS

Tuberous sclerosis is an outstanding example of a complex genetic disorder whose pathogenesis is being elucidated by application of molecular methods to human disease. In the picture that is emerging, mutations in one of two tumor suppressor genes, TSC1 or TSC2, perturb control of cell growth in the central nervous system by activating the PI3K signal transduction pathway. Further research is likely to resolve the paradox that malignant cancers seldom arise in patients with TS, even though the cell signaling molecules involved are key mediators of cancer cell growth.

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