

Tuberous Sclerosis

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Tuberous sclerosis complex (TSC) is a group of multi-system tumor disorders characterized by benign tumors in the brain, kidneys, lungs, heart or skin. When affecting the brain, TSC can be accompanied by seizures, mental retardation and behavior problems. Patients with TSC are often diagnosed in the first few years of life, may undergo surgical removal of tumors, and often require continued management throughout life. The severity of symptoms vary, with some individuals enjoying relatively normal lives, and others bearing more serious complications.

Two genes have been identified that underlie TSC, and only one needs to be affected for the disorder to be present (Leung et al., 2007; Inoki et al., 2005). The TSC1 gene located on chromosome 9q34 codes for the protein hamartin, while TSC2, located on chromosome 16p13 codes for the protein tuberin. Hamartin and tuberin proteins form a complex inside cells that turns out to be a molecular switch for cell growth. Hamartin-tuberin puts the brakes on a key kinase, mammalian Target of Rapamycin (mTOR), which normally activates S6K and drives cell growth (see figure). When either of these genes is defective and the tuberin-hamartin complex malfunctions, the mTOR pathway is constitutively activated and tumors can form.

The assumption has been that the neurobehavioral deficits seen in some patients were directly related to the number of tubers present in the brain, or repeated seizure activity, but resolution of the molecular pathway suggests a third explanation. For years, there were surprising findings that some patients with many brain tubers functioned normally, while others with few tubers had significant cognitive challenges, so tuber load wasn't the clear explanation. The mTOR pathway also controls the neuronal actin cytoskeleton and synaptic contacts, and

defects in these processes might also underlie the cognitive deficits.

Drugs to control the mTOR pathway are already in use and may control TSC. Initially, a mouse model for TSC was useful in understanding the disorder. Mice with an inactivating mutation in *Tsc2* gene show cognitive deficits, and brief treatment with the mTOR inhibitor rapamycin in adult mice rescued the behavioral deficits. Rapamycin is already in use as an immunosuppressant, particularly after kidney transplant, and clinical trials are now studying its effects in controlling aspects of TSC (Bissler et al., 2008). In late 2010, the FDA approved a rapamycin-based drug for TSC patients with subependymal giant cell astrocytoma who cannot be treated with surgery. Initial reports with rapamycin-based drugs have been encouraging, but there is concern that tumors may re-grow when treatment stops.

References

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