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Tuberous sclerosis complex and the mTOR pathway

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Abstract

Tuberous sclerosis complex (TSC) is a neurocutaneous disease characterized by the growth of hamartomas in many tissues and organs. The most prominent neurological manifestation of TSC is epileptic seizures. Two causative genes have been identified: TSC1 at 9q34 and TSC2 at 16p13.3. TSC1 encodes for hamartin and TSC2 encodes for tuberin. Tuberin contains a small region of homology to the GTPase activating protein. Rapamycin (developed as an antifungal agent) has regulatory effects on cell growth and proliferation via its inhibitory action on a key protein mammalian target of rapamycin (mTOR). Hamartin and tuberin are two major regulatory proteins that negatively modulate mTOR via inhibiting GTPase RHEB. Therefore, mutations of either TSC1 or TSC2 genes cause the same disease TSC. Since rapamycin inhibit mTOR pathway, rapamycin and other mTOR inhibitors are thought to be a new treatment for TSC. Recently increasing data are indicating that rapamycin is effective in various hamartomas in TSC patients. mTOR inhibitors may provide new treatment of TSC, and therapeutic outcomes are encouraging so far. Although several clinical trials have been conducted for the efficacy of rapamycin and other mTOR inhibitor everolimus, well designed multicenter trials are necessary in the near future.

INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal-dominantly inherited multisystem disorder characterized by hamartomas involving various organs most notably in the skin, brain, kidneys, heart and eyes. TSC is the second-most-common neurocutaneous disorder with the prevalence estimated to be one in 6000-10,000 general population. The most common neurological manifestations of TSC are epilepsy, mental retardation and autism. Epileptic seizures occur in up to 80–90% of the patients with TSC.

Two causative genes have been identified so far; TSC1 is located at chromosome 9q34 and TSC2 is located at chromosome 16p13.3. Mutation rate is higher in TSC2, and mutations are usually small truncations in TSC1 and large deletions or rearrangements in TSC2; therefore the patients with mutations in TSC2 may show more severe clinical phenotype.[1] TSC1 and TSC2 encode proteins called hamartin and tuberin respectively. Tuberin has GTPase activating protein (GAP) domain. Hamartin and tuberin have interaction sites for each other; they bind together and make a complex to regulate various signaling molecules including proteins in the mTOR pathway.

mTOR PATHWAY

Rapamycin (sirolimus) is a macrolide antibiotics which was discovered as a product of the bacterium *Streptomyces hygroscopicus* in a soil sample from Rapa Nui otherwise called Easter island.[2] Rapamycin was originally developed as an antifungal agent. Recently rapamycin was approved for clinical use for immunosuppressant, since rapamycin has been shown to have regulatory effects on cellular growth and proliferation via its inhibitory effect on a protein, mammalian target of rapamycin (mTOR). The mTOR pathway plays a role as a master switch responding to both intracellular and extracellular signals to maintain cellular homeostasis.[3]

Hamartin-tuberin complex is known to suppress tumor growth by inhibiting S6K activity in the mTOR pathway. Hamartin-tuberin complex has GAP activity to a GTPase called RHEB (Ras homologue enriched in brain) which is a small G protein of Ras family, and hydrolyze active RHEB•GTP converting to inactive GDP bound state. Since active GTP bound RHEB stimulates mTOR-mediated signaling to downstream components, hamartin-tuberin complex regulates mTOR pathway by inhibiting RHEB. If regulatory function of the hamartin-tuberin complex is

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Table 1: Current and completed clinical trials with mTOR inhibitors in TSC patients (Sep 2010, ClinicalTrials.gov)

Drug	Condition	Phase	Status
Rapamycin	LAM	II	Completed
Rapamycin	Skin	I	Recruiting
Sirolimus	AML	II	Ongoing
Sirolimus	LAM	II	Ongoing
Everolimus	SEGA	III	Ongoing
Everolimus	SEGA	I/II	Ongoing
Everolimus	AML LAM	I/II	Ongoing
Everolimus	AML LAM	III	Recruiting
Everolimus	Epilepsy	I/II	Recruiting

LAM: lymphangioleiomyomatosis, AML: angiomyolipoma, SEGA: subependymal giant cell astrocytoma

disrupted, hyperactivation of the downstream mTOR pathway causes increased protein synthesis, cellular growth and proliferation. Mutations of either TSC1 or 2 genes disrupt the tumor-suppressor function of the complex and can cause the same disease.[1]

CLINICAL APPLICATION OF mTOR INHIBITORS

Since rapamycin inhibit mTOR pathway, rapamycin and other mTOR inhibitors are thought to be a new treatment modality for TSC. Data is accumulating that rapamycin is effective in the treatment of hamartomas in the patients with TSC. In 2006, Franz DN *et al* first reported the clinical application of rapamycin in 5 patients with TSC and either subependymal giant cell astrocytomas (SEGA) or a pilocytic astrocytoma. Serial MRI scans showed that all lesions exhibited regression, and although interruption of therapy resulted in regrowth of SEGA in one patient, resumption of therapy resulted in further regression. The authors concluded that oral rapamycin can induce regression of astrocytomas associated with TSC, and rapamycin may offer an alternative therapy to surgical resection of SEGA.[4] Other authors also indicated that rapamycin is effective in various hamartomas associated with TSC. Muncy J *et al* tried rapamycin in a 10 year old girl with TSC for 10 months for seizure control. The authors reported that a dramatic reduction in seizure frequency was achieved during the rapamycin therapy.[5] Currently (Sep 2010) nine clinical trials are registered in ClinicalTrials.gov site which are conducting mTOR inhibitors (sirolimus and everolimus) for various conditions in TSC including epilepsy (Table 1).[6]

mTOR inhibitors provide new hope for treatment of TSC. Therapeutic outcomes are encouraging in various hamartomas with TSC, although clinical trials for epileptic seizures are still under development. Well designed multicenter trials are necessary to document the effect of mTOR inhibitors on epileptic seizures, to ensure risk/benefit profile and to determine the duration of treatment in human.[7]

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