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Review

Phenotypes associated with inherited and developmental somatic mutations in genes encoding mTOR pathway components

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ABSTRACT

Mutations affecting the genes that encode upstream components in the mammalian (or mechanistic) target of rapamycin signalling pathway are associated with a group of rare inherited and developmental disorders that show overlapping clinical features. These include predisposition to a variety of benign or malignant tumours, localized overgrowth, developmental abnormalities of the brain, neurodevelopmental disorders and epilepsy. Many of these features have been linked to hyperactivation of signalling via mammalian target of rapamycin complex 1, suggesting that inhibitors of this complex such as rapamycin and its derivatives may offer new opportunities for therapy. In this review we describe this group of inherited and developmental disorders and discuss recent progress in their treatment via mTORC1 inhibition.

Contents

Abbreviations: mTOR, Mamalian target of rapamycin; PI3K, phosphoinositide 3-kinase related kinase; mTORC1, mTOR complex 1; mTORC2, mTOR complex 2; AMP, Adenosine monophosphate; ATP, Adenosine triphosphate; S6K, ribosomal S6 Kinase; 4E-BP1, eukaryotic initiation factor 4E-binding protein; PTEN, phosphatase and tensin homolog; PDK1, 3-phosphoinositide dependent protein kinase-1; Akt1, v-akt murine thymoma viral oncogene homolog 1; AMPK, AMP-dependent protein kinase; TSC, Tuberous sclerosis complex; GAP, GTPase activating protein; Rheb, Ras homolog enriched in brain; PKB, protein kinase b; LKB1, liver kinase B; STK11, serine/threonine kinase 11; SEGA, subependymal giant cell astrocytoma; LAM, lymphangioleiomyomatosis; AML, angiomyolipomas; TBC1D7, Tre2-Bub2-Cdc16-1 domain family- member 7; HME, Hemimegalencaphaly; PIK3CA, PI-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PMSE, polyhydramnios, megalencephaly & symptomatic epilepsy; STRADA, STE20-related kinase adaptor alpha; mNPCs, mouse neural progenitor cells; DEPDC5, disheveled, Egl-10 and pleckstrin domain containing protein 5; FFEVF, Familial Focal epilepsy with Variable Foci; ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; BECTS, benign epilepsy with centrotemporal spikes; GATOR, Rag GTPase and GTRs; GAP, GTPase activating protein; PHTS, PTEN hamartoma syndrome; CS, Cowden syndrome; LD, Lhermitte-Duclos disease; BRRS, Bannayan-Riley-Ruvalcaba syndrome; PS, PTEN-related Proteus syndrome; PIP3, phosphatidylinositol 3,4,5 trisphosphate; PIP_2, phosphatidylinositol 4,5 bisphosphate; PJS, Peutz-Jeghers syndrome; PRKAG2, Protein kinase, AMP-activated, gamma 2,; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; CLOVES, Congenital Lipomatous Overgrowth with Vascular, Epidermal, and Skeletal anomalies; KTS, Klippel-Trenaunay syndrome; MCAP, Megalencephaly-capillary malformation syndrome; MPPH, Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome; PIK3R2, phosphoinositide-3-kinase, regulatory subunit 2.

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1. Introduction

The mechanistic Target Of Rapamycin (mTOR) pathway (also known as mammalian Target of Rapamcyin) plays a vital role in the ability of cells to sense internal and external conditions and to mount appropriate physiological responses [1]. The mTOR pathway links a network of signalling molecules, integrating the effects of growth factors, energy, nutrient supply and environmental cues to control cell growth, balance catabolic and anabolic processes, determine aspects of neuronal differentiation and migration and modulate memory and learning [2,3].

mTOR is a member of the phosphoinositide 3-kinase (PI3K) related family. In mammalian cells it forms two structurally and functionally distinct complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [4]. mTORC1 is activated by amino acids, growth factors and energy status (AMP/ATP ratio). Well characterized downstream targets of mTORC1 include ribosomal protein S6 Kinase 1 (S6K1) and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1), through which protein synthesis is regulated. Other processes regulated by mTORC1 include lipogenesis, angiogenesis, glycolysis, autophagy and inflammatory responses [5–7]. mTORC2 on the other hand is activated by ribosomal association in the presence of growth factors and regulates cell survival, gluconeogenesis and the cytoskeleton [8].

Key upstream components in the mTOR signalling pathway include phosphoinositide 3-kinase (PI3K), phosphatase and tensin homolog (PTEN), phosphoinositide dependent protein kinase 1 (PDK1), v-akt murine thymoma viral oncogene (AKT) (also known as PKB – protein kinase B), AMP-dependent protein kinase (AMPK), tuberous sclerosis complex 1 (TSC1) and tuberous sclerosis complex 2(TSC2) (Fig. 1). This signalling pathway is dysregulated in diverse disease states including neurodegeneration, diabetes, epilepsy and cancer. Many tumours exhibit activation of mTOR signalling, often as a direct result of acquired somatic mutations affecting the genes encoding pathway components. By contrast, inherited mutations or somatic mutations occurring during organ development cause a spectrum of rare congenital, inherited or developmentally determined conditions. These disorders exhibit highly variable but overlapping clinical features including localized overgrowth, pigmentary abnormalities, tumour predisposition, cerebral cortical dysplasia, epilepsy and neurodevelopmental disorders. The recent elucidation of the mutational basis of these disorders is leading to new approaches to their treatment, notably using the mTORC1 inhibitor rapamycin (sirolimus) and its derivative everolimus.

2. *TSC1*, *TSC2* and tuberous sclerosis

2.1. The TSC1/TSC2 complex and Tuberous Sclerosis

The TSC1–TSC2 protein complex is a major negative regulator of mTORC1 activity. Its function is mediated via TSC2's GAP (GTPase-activating protein) activity for the small G protein Rheb (Fig. 1). The complex acts as a focal point for integration of signalling inputs from growth factors and cellular energy levels via upstream kinases such as PI3K, PDK 1, AKT, PTEN, LKB1 (liver kinase B or serine/threonine kinase 11-STK11) and AMPK (Fig. 1) [9]. Inherited mutations in *TSC1* or *TSC2* cause Tuberous Sclerosis (TSC, also referred to as the tuberous sclerosis complex). TSC has become a paradigm for the diverse clinical consequences of hyper-activated mTORC1 signalling and the opportunities to counter these through mTORC1 inhibition.

TSC is an autosomal dominant disorder affecting ~1 in 10,000 births. It is characterized by hamartomatous tumours in many organs including the skin (e.g. angiofibromas), kidneys (e.g. angiomyolipomas), brain (e.g. sub-ependymal giant cell astrocytoma – SEGA) and, in females, by lung involvement (e.g. with TSC-associated lymphangioleiomyomatosis or LAM). Neurological features include epilepsy, neurocognitive deficits and neurodevelopmental problems such as autism [10].

Somatic "second hit" mutations of *TSC1* or *TSC2* have been demonstrated in many TSC-associated tumours. In these lesions inactivation of both *TSC* alleles leads to aberrant activation of mTORC1 signalling, driving tumour growth. In the brain, the role of "second hit" mutations in determining the in utero development of the characteristic cortical tubers that give the condition its name, is less clear. None the less, evidence of up-regulated mTOR activity has been reported in cortical tubers from both adult [11] and fetal brains [12,13]. Preclinical studies using mouse models suggest that mTOR inhibition may normalize aspects of brain development in the context of TSC deficiency [13].

2.2. mTOR inhibitor therapy in TSC

Recent clinical trials of the mTOR inhibitors sirolimus (rapamycin) and everolimus have demonstrated shrinkage of TSC-associated brain tumours (SEGA) [14] and renal angiomyolipomas (AML) [15]. Treatment with sirolimus is also associated with significant slowing of disease progression of TSC-associated and sporadic LAM [16]. Everolimus is now a licensed therapeutic option in the management of both renal AML and SEGA. In the most recent consensus guidelines for management of TSC, mTORC1 inhibitor therapy was recommended as first line treatment for patients with renal AML, for use in SEGA and for patients with moderate to severe or rapidly progressing LAM [17]. However, the beneficial effects of mTORC1 inhibition are reversible and tumour re-growth and further progression of LAM have been observed upon drug withdrawal.

The considerable success of mTORC1 inhibitor therapy for tumour-associated manifestations of TSC and reversal of seizures and learning deficits in mouse models of TSC treated with these agents [18,19] has led to interest in their potential for treatment of epilepsy, neurodevelopmental and neurocognitive problems in TSC patients. A significant reduction in seizure frequency was achieved