Mosaic Disorders of the PI3K/PTEN/AKT/TSC/mTORC1 Signaling Pathway

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KEYWORDS

• Mosaicism • mTORC1 • PIK3CA-related overgrowth spectrum • Proteus syndrome • Tuberous sclerosis complex • PTEN hamartoma tumor syndrome • Next-generation sequencing • Sirolimus

KEY POINTS

- Mosaicism may be considered in sporadic cases; there should be a negative history in ancestral generations or siblings but offspring may be affected through gonadal mosaicism.
- A patchy distribution of cutaneous features and tissue overgrowth or disseminated disease that is mild should raise suspicion for mosaicism.
- Next-generation sequencing, or other methods for detecting low frequency alleles, of affected tissue is frequently necessary to identify the genetic basis of mosaic conditions.
- Drugs that target proteins along the PI3K/PTEN/AKT/TSC/mTORC1 signaling pathway have shown promise in the treatment of these disorders.

INTRODUCTION

Mosaicism may occur as a somatic mutation occurring during embryogenesis, resulting in an organism composed of 2 (or more) genetically distinct cell lineages.[1] The resulting phenotype depends on the numbers and organization of abnormal cells in relation to normal cells and how the mutation affects cellular function.[2,3] When the mutation affects cell signaling pathways regulating cell growth, apoptosis, or migration, dramatic regional alterations in the appearance of the skin can occur sometimes with regional overgrowth or tumor susceptibility. Dermatologists are frequent observers of these mosaic conditions and play important roles in diagnosis and management.

Somatic mutations in any of the genes in the PI3K/PTEN/AKT/TSC/mTORC1 signaling pathway (**Fig. 1**) may result in a spectrum of abnormal growth, ranging from an isolated small skin lesion

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Abbreviations and acronyms

BRRS	Bannayan-Riley-Ruvalcaba Syndrome
KTS	Klippel-Trenaunay syndrome
mTORC1	Mechanistic target of rapamycin complex 1
PHTS	PTEN hamartoma tumor syndrome
PI3K	Phosphoinositide-3-kinase
PIP2	Phosphatidylinositol (4,5)-bisphosphate
PIP3	Phosphatidylinositol (3,4,5)-trisphosphate
PROS	PIK3CA-related overgrowth spectrum
Rheb	Ras homolog enriched in brain
TSC	Tuberous sclerosis complex

with minimal or no overgrowth to extensive skin involvement with striking extremity enlargement and tumor susceptibility.[4–7] Proteus syndrome, caused by mutations in *AKT1*, and the *PIK3CA*-related overgrowth spectrum (PROS) may be considered archetypal mosaic disorders, given the patchy distribution of disease features.[8,9] Tuberous sclerosis complex (TSC), caused by mutations in either *TSC1* or *TSC2*, and *PTEN* hamartoma tumor syndrome (PHTS) are most frequently associated with germline mutations, but mosaic forms also appear as isolated (simplex or sporadic) occurrences.[10–12] This article primarily focuses on these entities, chosen for their shared abnormalities in a signaling pathway and analogous or overlapping phenotypes.

PI3K/PTEN/AKT/TSC/MTORC1 SIGNALING PATHWAY AND OVERGROWTH

Cell growth is mediated by extracellular cues and may occur via increasing cell mass or cell division

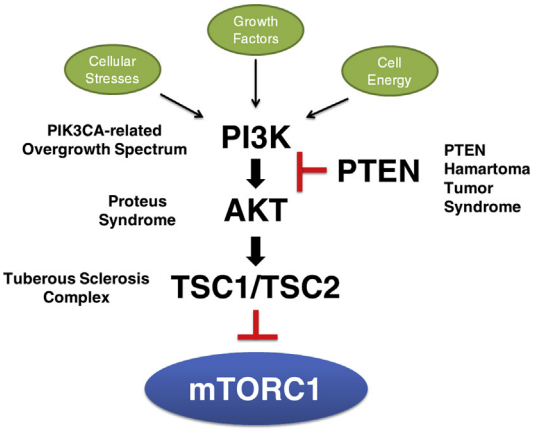

Fig. 1. Disorders of the mTORC1 signaling pathway.

or by suppression of apoptosis. Mechanistic target of rapamycin (mTOR) complex 1 (mTORC1) is a central regulator of cell growth[13] that is disrupted in many human disorders of cell proliferation, including cancers.[4,5,13–15] Under normal conditions, mTORC1 is sensitive to inputs from diverse cellular and environmental cues (see **Fig. 1**), including the phosphoinositide-3-kinase (PI3K) pathway. In short, growth factors stimulate PI3K, which then converts phosphatidylinositol (4,5)-bisphosphate (PIP2) to phosphatidylinositol (3,4,5)-trisphosphate (PIP3) and permits activation of AKT. PTEN dephosphorylates PIP3 to PIP2, thereby exerting inhibitory control on AKT.[16] AKT phosphorylates several proteins, including the TSC1-TSC2 complex, and thus alleviates negative control on mTOR to promote cell growth (see **Fig. 1**).

PTEN, *TSC1*, and *TSC2* are tumor suppressors. For each of these genes, a germline mutation causes a loss of function allele, leading to a syndrome with susceptibility to multiple tumors. Tumorigenesis involves inactivation of the second allele, typically via a second-hit somatic mutation in the wild-type allele.[6,16] Loss of function of *PTEN* results in increased levels of PIP3 and alleviates inhibitory control on AKT to cause tumor formation in PHTS.[17] Biallelic mutations in *TSC1* or *TSC2* result in increased Ras homolog enriched in brain (Rheb)-GTP, which activates signaling through mTORC1, causing tumor formation in TSC.[18] Although the PHTS and TSC are typically caused by germline mutations, both can have mosaic presentations, often with mild disease or later onset than inherited disease.[11,19–23]

PIK3CA, a gene encoding the catalytic subunit of PI3K, and *AKT1* are oncogenes and thus a gain of function, or activating mutation in only one copy of the allele is the mechanism of disease.[24,25] Strongly activating mutations in these genes may only be seen in patients through mosaicism.[26,27] Point mutations activating *PIK3CA* have been documented in a variety of mosaic disorders captured under the umbrella term PROS.[9,27] The mosaic presence of an activating mutation in *AKT1* results in Proteus syndrome.[26,28]

PHENOTYPE OF DISORDERS OF THE PI3K/PTEN/AKT/TSC/MTORC1 SIGNALING PATHWAY

Mosaic-Only Oncogenes

It is widely regarded that strongly activating germline mutations in *AKT1* and *PIK3CA* are lethal, with few reported exceptions.[9,26,29] Mutations in these genes result in distinctive segmental, or asymmetric overgrowth syndromes that can involve