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Invited review article

Mammalian target of rapamycin and tuberous sclerosis complex

Mari Wataya-Kaneda *

Department of Dermatology, Course of Integrated Medicine, Graduate School of Medicine, Osaka University, Osaka, Japan

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ABSTRACT

Mammalian target of rapamycin (mTOR) is an evolutionarily conserved serine/threonine kinase that is a member of the phosphoinositide 3-kinase (PI3K)-related kinase (PIKK) family. mTOR forms two distinct complexes, mTORC1 and mTORC2. mTORC1 has emerged as a central regulator of cellular metabolism, cell proliferation, cellular differentiation, autophagy and immune response regulation. In contrast to mTORC1, mTORC2, which is not well understood, participates in cell survival and the regulation of actin and cytokeratin organization. In addition, mTORC1 has been implicated in many diseases, including cancer, metabolic diseases, neurological disease, genetic diseases and longevity/aging.

One of the diseases resulting from dysfunction of mTORC1 is tuberous sclerosis complex (TSC), which reflects all the symptoms that arise in response to mTORC1 dysfunction. TSC is a multiple hamartomas syndrome with epilepsy, autism, mental retardation and hypopigmented macules that are caused by the constitutive activation of mTORC1 resulting from genetic mutation of *TSC1* or *TSC2*. Inhibitors of mTORC1, such as rapamycin, effectively suppress the symptoms of TSC.

This article summarizes the current knowledge on mTOR and the efficacy of mTORC1 inhibitors in the treatment of TSC.

Contents

1. Introduction

Mammalian target of rapamycin (mTOR) is an evolutionally conserved protein kinase and is an essential regulator of a wide range of functions. The pathway is involved in cell viability, growth, autophagy, cellular senescence and immune reactions. Therefore, deregulation of the mTOR pathways has been

* Correspondence to: Department of Dermatology, Course of Integrated Medicine, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan. Tel.: +81 668 79 3031; fax: +81 668 79 3039.
E-mail address: mkaneda@derma.med.osaka-u.ac.jp

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implicated in many diseases or disorders, such as cancers, neurodegenerative diseases, metabolic diseases, genetic disorders, and immune diseases. Over the past two decades, significant progress has been made in elucidating the regulatory mechanisms and functions of mTOR. This review article summarizes the current knowledge on mTOR and human diseases affected by the mTOR pathway, and refers to the topics of tuberous sclerosis complex (TSC), a representative genetic disease that results from mTORC1 hyperactivity.

2. History of mammalian target of rapamycin (mTOR)

Target of rapamycin (TOR) is a large (300 kDa) conserved serine/threonine kinase that is part of the PI3K-related kinase family. Over the past two decades, significant progress has been made in elucidating the regulation and function of TOR.

TOR was discovered in yeast by genetic selection for mutants that confer rapamycin resistance [1]. In 1994, TOR was shown to be conserved in mammalian cells. Therefore, the mammalian homolog of TOR is called mammalian target of rapamycin (mTOR). In 2002, TOR was discovered to form two distinct kinases complexes, target of rapamycin complex 1 (TORC1) and target of rapamycin complex 2 (TORC2). TORC1 and TORC2 are structurally and functionally distinct kinases, each of which phosphorylates its own substrates to control different cellular processes. Similar to TOR, the two TOR complexes (TORC1 and TORC2) are conserved from yeast to human.

3. Structures of mTORC1 and mTORC2

The two mTORCs, mTORC1 and mTORC2, are multiprotein complexes. Mammalian target of rapamycin complex 1 (mTORC1) is composed of mTOR, regulatory-associated protein of mTOR (Raptor), the DEP domain-containing mTOR-interacting protein (Deptor), mammalian lethal with SEC13 protein 8/G-protein b-subunit-like protein (mLST8/GβL), and protein-rich Akt substrate of 40-kDa (PRAS40) [2,3]. Mammalian target of rapamycin complex 2 (mTORC2) is composed of mTOR, rapamycin-insensitive companion of mTOR (Rictor), mLST8 and mSin1 (mammalian stress-activated protein kinase-interacting protein 1). Recently, two new mTORC related proteins, Tel2-interacting protein 1 (Tti1) and telomere maintenance 2 (Tel2), were identified that anchor mLST8 and Raptor/Rictor to mTOR in mTORC1 and mTORC2, respectively [4] (Fig. 1).

mTOR is a large multi-domain protein. The N-terminal portion of mTOR contains huntingtin, elongation factor 3, A subunit of PP2A, TOR1 (HEAT) repeats. These HEAT repeats form a large helical secondary structure that provides a protein interaction surface for Raptor and Rictor. The C-terminal portion of mTOR contains several important domains. FRAP-ATM-TRRAP (FAT) domains and FAT-C-terminal (FATC) domains are conserved domains among PIKK family members and are necessary for mTOR catalytic function. The FKBP12–rapamycin complex binds to the FKBP12–rapamycin complex binding (FRB) domain, which is adjacent to the FAT domain. The FRB domain is also involved in the

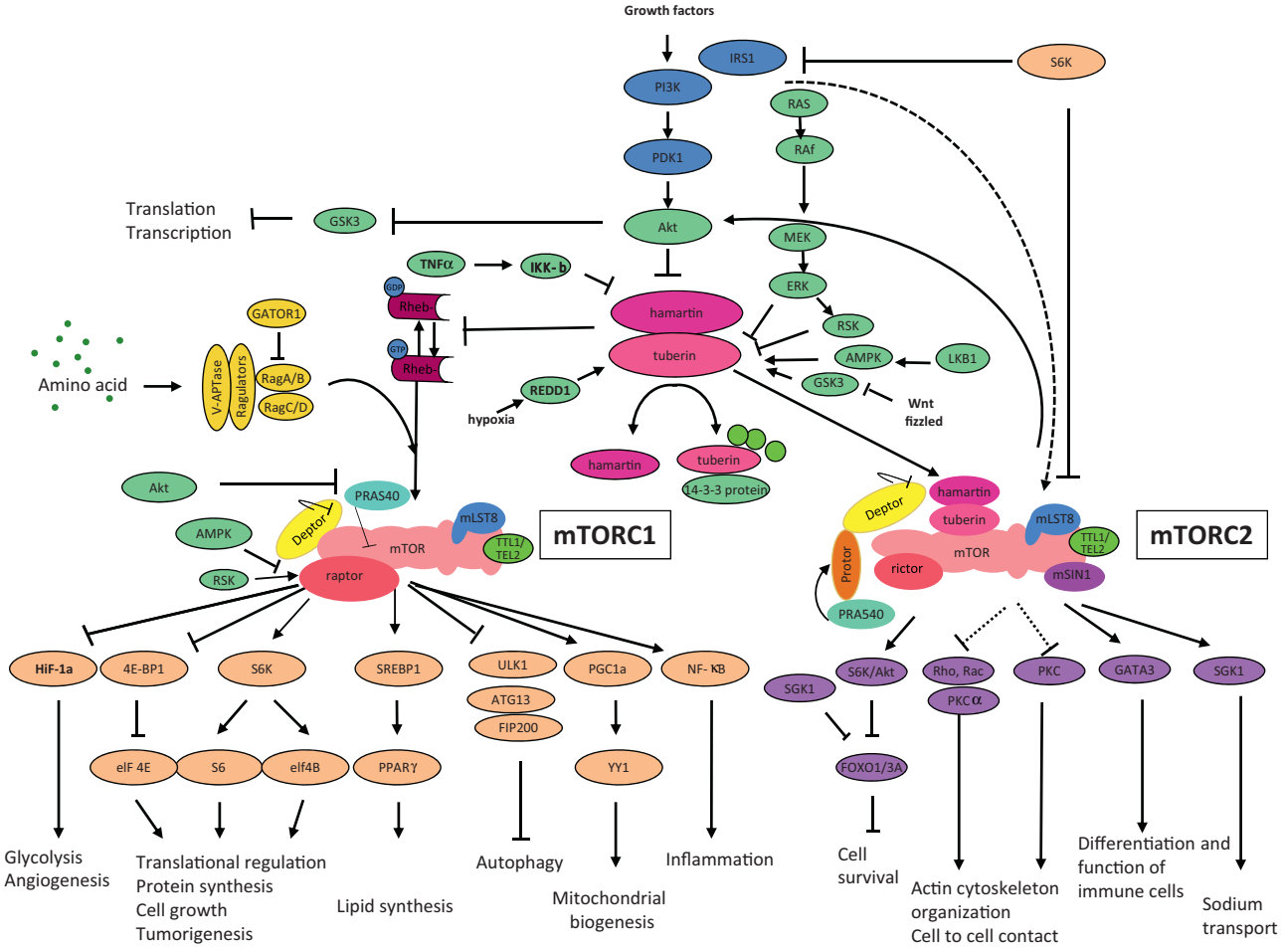

Fig. 1. Overview of mTOR signaling pathway. Critical inputs regulating mTORC1 and mTORC2 and the key outputs of the mTOR1 and mTORC2 pathways are summarized. mTORC1 controls large amount of biological processes and regulates protein synthesis, lipogenesis energy metabolism/mitochondrial biogenesis, autophagy and immunity. mTORC2 regulates survival/metabolism and cytoskeleton organization.