DOCUMENT SUMMARY

This review article by Schmelzle and Hall posits that the **target of rapamycin (TOR)** kinase is a central controller of cell growth. The paper summarizes evidence showing that **TOR** integrates signals from nutrients and growth factors to regulate a diverse set of processes essential for increasing cell mass, including translation, transcription, ribosome biogenesis, and protein degradation. By controlling these fundamental cellular activities, **TOR** plays a crucial, conserved role in coordinating cell growth with cell proliferation.

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FORMATTED CONTENT

Schmelzle_&_Hall_2000_TOR_a_Central_Controller_of_Cell_Growth

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Summary

Cell growth (increase in cell mass) and **cell proliferation** (increase in cell number) are distinct yet coupled processes that go hand-in-hand to give rise to an organ, organism, or tumor. Cyclin-dependent kinase(s) is the central regulator of **cell proliferation**. Is there an equivalent regulator for **cell growth**? Recent findings reveal that the **target of rapamycin (TOR)** controls an unusually abundant and diverse set of readouts all of which are important for **cell growth**, suggesting that this conserved kinase is such a central regulator.

Background

In the late 1960s, **Lee Hartwell** isolated approximately 400 temperature-sensitive yeast mutants which he then characterized for macromolecular synthesis (protein and RNA synthesis), cell division, and cell morphology (Hartwell, 1967). He subsequently chose to focus on the mutants that displayed defects in cell division, the now famous cdc mutants. Importantly, Hartwell made a distinction between **cell proliferation** and **cell growth**. **Proliferation** is cell division which leads to an increase in cell number, whereas **growth** is macromolecular synthesis which leads to an increase in cell mass or size. A fortunate consequence of Hartwell's decision to focus on cell division was that we now have a relatively sophisticated understanding of the mechanisms that control the cell cycle. An inadvertent and unfortunate fallout from this decision, however, was that the study of **cell growth**, and in particular the mechanisms that control it, have been largely neglected. To make matters worse and confusing, the distinction between **growth** and **proliferation** has also been lost; it is common to find in the literature the terms "growth" and "proliferation" incorrectly used interchangeably. **Cell growth** and **cell proliferation** are indeed separable and thus distinct processes, as revealed by Hartwell's mutants and others' studies (Hartwell, 1967; Mitchison, 1971; Thomas and Hall, 1997; Neufeld and Edgar, 1998; Conlon and Raff, 1999).

Growth is not simply an accumulation of mass. It is a carefully orchestrated accumulation of mass, occurring only at specific times and places. In the case of Hartwell's unicellular yeast, **growth** occurs only when nutrients are available and only at a discrete site on the cell surface (hence the name budding yeast). In neurons, **growth** in response to synaptic activity occurs specifically at the synapse. In metazoans, the problem of **growth** is compounded by the need to adhere to an overall body plan during development. For example, the different organs of the body need to grow to a specific size to maintain body proportions. To achieve an appropriate cell, organ, or organism size, **cell growth** must be coordinately controlled with **cell proliferation** and, in the case of metazoans, cell death. How is **cell growth** controlled, and how is this control integrated with that of **cell proliferation** and death?

In recent years, interest in **cell growth** has been rekindled as it has become apparent that elaborate mechanisms actively control **cell growth** in response to favorable conditions. **Cell growth** is not passively controlled simply by the availability of nutrients (building blocks), as was widely thought 30 years ago when Hartwell decided to focus on his cell division mutants, but by signaling pathways that impinge on general cell physiology to elicit balanced macromolecular synthesis. There is growing evidence that the **TOR kinase** plays a central role in controlling these pathways and thus the various readouts that determine **cell growth**.

The TOR Protein

TOR (target of rapamycin) was originally identified genetically by mutations in yeast, **TOR1-1** and **TOR2-1**, that confer resistance to the growth-inhibitory properties of the immunophilin-immunosuppressant complex **FKBP (FK506 binding protein)-rapamycin** (Heitman et al., 1991). The **TOR1** and **TOR2** genes encode the two large

(molecular weight ~280 kDa) and highly homologous (70% identical) **TOR1** and **TOR2** proteins (Kunz et al., 1993; Helliwell et al., 1994). The structurally and functionally conserved mammalian counterpart **mTOR** (also known as FRAP, RAFT, or RAPT) was subsequently discovered biochemically based on its **FKBP-rapamycin** binding properties (Brown et al., 1994; Chiu et al., 1994; Sabatini et al., 1994; Sabers et al., 1995). More recently, single **TOR** homologs have been found encoded in the fly and worm genomes.

The **TORs** contain a C-terminal region with strong homology to the catalytic domain of **phosphatidylinositol 3-kinase (PI3K)** and phosphatidylinositol 4-kinase (Kunz et al., 1993; Keith and Schreiber, 1995) (Figure 1). Studies in yeast, flies, and mammals have revealed a **TOR**-related family of proteins which includes MEC1, TEL1, RAD3, MEI-41, DNA-PK, ATM, ATR, and TRRAP. All these proteins contain a characteristic C-terminal **phosphatidylinositol (PI) kinase homology domain** and have thus been termed **PI kinase (PIK)-related kinases**. The different **PIK-related kinases** are involved in diverse cellular functions, such as control of **cell growth**, cell cycle and DNA damage checkpoints, recombination and maintenance of telomere length. Accordingly, dysfunction of the **PIK-related kinases** results in a wide spectrum of severe diseases, ranging from cancer to immunodeficiency (Keith and Schreiber, 1995). Despite the homology to lipid kinases, none of the **PIK-related kinases** has been demonstrated to have lipid kinase activity, and both yeast and mammalian **TOR**, if not all the **PIK-related kinases**, are Ser/Thr protein kinases.

TOR Readouts

The immunosuppressant and antibiotic **rapamycin** potently inhibits growth in several evolutionarily diverse cells, suggesting that **TOR** has a conserved role in controlling **cell growth**. What are the growth-related readouts controlled by **TOR**? Early findings, as reviewed below, indicated that **TOR** is dedicated to activating translation initiation in response to nutrients. Within the last few years, yeast and mammalian **TOR** has been demonstrated to control several additional readouts, all of which are related to **cell growth**. These readouts include organization of the actin cytoskeleton, membrane traffic and protein degradation, PKC signaling, ribosome biogenesis, transcription, and, although more a consequence than a readout, cancer (Figure 2).

Translation Initiation

mTOR, in response to amino acids and growth factors, controls the mammalian translation machinery via activation of the **p70s6k** protein kinase and via inhibition of the eIF4E inhibitor **4E-BP1** (also known as PHAS-I) (see Thomas and Hall, 1997; Hara et al., 1998) (Figure 3). Activation of **p70s6k** and resulting phosphorylation of the 40S ribosomal protein S6 ultimately drives translation of **5' TOP (terminal oligopyrimidine tract) mRNAs** (Jefferies et al., 1997). These mRNAs constitute a small family of abundant transcripts (up to 20% of cellular mRNA) that encode primarily ribosomal proteins and components of the translational apparatus (Meyuhas et al., 1996).

Actin Organization

In yeast, **TOR2** (but not TOR1) additionally controls cell cycle-dependent polarization of the actin cytoskeleton. This **TOR2**-unique function is rapamycin-insensitive and mediates the polarized growth characteristic of budding yeast cells (Zheng et al., 1995; Schmidt et al., 1996).

Membrane Traffic and Protein Degradation

Delivery of nutrient transporters to the cell surface and uptake of nutrients are essential for **cell growth** and viability. These events are adapted to environmental conditions to optimize nutrient flow and **cell growth**. As part of the above mentioned starvation response occurring upon **TOR** inactivation, **rapamycin** also causes a severe decrease in amino acid import in yeast (Schmidt et al., 1998; Beck et al., 1999). **Autophagy** is the process by which cytoplasmic components are delivered in bulk to the lysosome/vacuole for degradation. Inactivation of **TOR** in yeast or mammalian cells leads to induction of **autophagy**, even in nutrient-rich medium, indicating that **TOR** negatively controls starvation-induced **autophagy** (Blommaart et al., 1995; Noda and Ohsumi, 1998).

Protein Kinase C Signaling

Protein Kinase C (PKC) family members play central regulatory roles in a multitude of cellular processes, including **cell growth** and **proliferation**, apoptosis and survival, and cytoskeletal remodeling. Recently, the phosphorylation of the conserved C-terminal hydrophobic site in classical PKCα and in novel PKC has been shown to be positively controlled by **TOR**.

Ribosome Biogenesis and tRNA Synthesis

Ribosome synthesis, a major consumer of the cell's resources, is the classic growth-related readout. In mammalian cells, the **mTOR-p70s6k** signaling pathway induces synthesis of ribosomal proteins by stimulating translation of **5' TOP mRNAs**, as discussed above. **TOR** also regulates ribosome biogenesis in yeast.

Transcription

Upon nutrient limitation, yeast cells enter a quiescent (stationary) phase characterized not only by a reduction in protein synthesis and many other distinctive phenotypes, but also by an altered transcription pattern. **TOR**, in addition to positively controlling PolII-mediated transcription of ribosomal protein genes, also negatively controls PolII-mediated transcription specific to starved cells (Barbet et al., 1996; Beck and Hall, 1999; Cardenas et al., 1999; Hardwick et al., 1999).

Cancer

Several lines of evidence have implicated **mTOR** in cancer. First, although an oncogenic version of **mTOR** has yet to be found, many of the proteins linked to **TOR** signaling, such as **PI3K**, **PKB**, and **eIF4E**, have been identified in oncogenic versions or demonstrated to have transforming potential (see Thomas and Hall, 1997). Second, **mTOR** controls translation of **c-Myc**, a transcription factor often deregulated in tumors.

The involvement of **mTOR** signaling in cancer further illustrates the link between **cell growth** and **proliferation**.

TOR Effectors and Signaling Mechanisms

The **TOR** effectors and signaling mechanisms mediating the growth-related readouts described above are known in some, but not all cases. **mTOR** signals to the translation initiation machinery via **p70s6k** and **4E-BP1**, as described above. In yeast, **TOR** signals to the translation machinery via **TAP42**, an essential protein homologous to the murine a4 phosphoprotein.

Growth Control in Metazoans

All the studies reviewed above pertain to growth control in single cells, yeast and cultured mammalian cells. However, control of **cell growth** is also important in determining overall organ and body size in multicellular systems. Animals attain characteristic body size and proportions via the coordinate regulation of **cell growth**, **cell proliferation**, and cell death (Conlon and Raff, 1999).

Recent results from the fruit fly *Drosophila* have begun to answer this question and have, albeit so far only indirectly, implicated **TOR**. Manipulation of members of the **PI3K** signaling pathway in *Drosophila* alters organ and organism size, indicating that this pathway controls cell size (growth) and/or number (proliferation and death) (reviewed in Edgar, 1999 and in Weinkove and Leevers, 2000).

Concluding Remarks

> The multitude and diversity of growth-related readouts controlled by **TOR** indicate that this conserved kinase may not be simply part of a single, linear, growth-controlling pathway. Indeed, as suggested by the findings described above, **TOR** may act radially on several different pathways. **TOR** may even be viewed primarily as a "cross-talker" that broadly integrates cell physiology to elicit balanced growth. Thus, **TOR** can be regarded as a central controller of **cell growth**.

Figures

- **Figure 1. Architecture of a Generic TOR Protein:** This figure shows the domain structure of a typical **TOR** protein, including HEAT repeats, a FAT domain, the FRB (FKBP-rapamycin binding) domain, a kinase domain, and a FATC domain.
- **Figure 2. TOR Controls a Large and Diverse Set of Growth-Related Readouts:** This diagram illustrates the central role of **TOR**, showing it activating translation, transcription, tRNA and ribosome biogenesis, and PKC signaling, while repressing nutrient transporter turnover and autophagy. It also shows a connection to actin organization.
- **Figure 3. Model of mTOR Effectors and Signaling Pathways in Mammalian Cells:** This figure depicts the signaling cascade where growth factors and amino

acids activate **mTOR**, which in turn regulates translation via **p70s6k** and **4E-BP1**. It also shows upstream inputs from the **PI3K/PKB** pathway.
- **Figure 4. Model of TOR Effectors and Signaling Pathways in Yeast:** This figure illustrates how nutrients activate **TOR** in yeast, which then signals through effectors like **TAP42** and **ROM2** to control translation, transcription, and actin organization.

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