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Target of rapamycin (TOR) signaling coordinates tRNA and 5S rRNA gene transcription with growth rate in yeast

Review Article

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Summary

Transcriptional regulation of genes encoding ribosomal proteins, translation factors, ribosomal RNAs, and the tRNAs plays a critical role in cellular physiology by modulating the availability of key components of the protein synthetic machinery according to the need for cell growth. Recent work in yeast and mammalian systems has revealed that the target of rapamycin (TOR) signaling pathway functions in setting the translational output of the cell in response to nutrient/growth factor availability. The central components of the TOR pathway are the TOR kinases, which are inhibited by the macrolide antibiotic rapamycin. Using yeast as a model system we have tested if the control of translation by the TOR kinases includes an effect on transcription of two components of the translational apparatus, 5S rRNA and the tRNAs. Biochemical studies reveal that polymerase (pol) III transcription of the 5S rRNA and the tRNA genes is regulated by TOR signaling in yeast. Interference with TOR signaling inhibits the activity of RNA pol III and likely TFIIIB, core components of the pol III transcriptional machinery. The mechanism of inhibition involves an effect that is independent of the repression of translation that results when TOR signaling is impaired. We propose that the TOR kinases are components of a signaling network that ensures appropriate expression of the protein synthetic machinery under different growth conditions. Considering the conservation of the TOR pathway and the pol III transcription machinery between yeast and human, this regulatory mechanism is likely to be conserved in eukaryotes.

I. A signaling network problem

An important determinant of the cell's capacity to synthesize protein is the availability of components of the translational apparatus, particularly the ribosomal (r) RNAs, tRNAs, and the r proteins. How does the cell ensure that the availability of these components is matched to the demand for protein synthesis? Studies performed over the last 20 years using conventional genetic and biochemical techniques have demonstrated that transcription of the genes encoding the rRNAs, tRNAs and r proteins is under growth control in eukaryotes from yeast to human (Warner, 1989; Mager and Planta, 1991; Denis et al., 1993; Clarke et al., 1996; DeRisi et al., 1997; Wang et al., 1997; White, 1997; Grummt, 1999; Reeder, 1999). Measurement of relative transcription rates by DNA microarray and serial analysis of gene expression technologies has further shown that many genes encoding translation factors are growth regulated at the level of mRNA abundance in yeast (DeRisi et al., 1997) and that translation factors and r proteins account for almost half the genes induced in colorectal epithelium cancers as compared to normal colon cells encode either (Zhang et al., 1997). Hence the transcription of genes encoding key components of the translational apparatus, including non-coding RNAs, varies according to cell growth rate.

Three mechanisms, alone or in combination, could account for the coordinated transcriptional regulation of these genes (**Figure 1**; for simplicity this model excludes effects on protein turnover). If signaling directly regulates translation according to growth factor or nutrient availability, then effects on transcriptional machineries could indirectly result from changes in the rate of translation of a limiting and labile transcription factor (pathway A). Similarly if signaling directly regulates transcription of a polymerase (pol) II gene

encoding a limiting and labile component of the pol I and pol III transcriptional machineries, then effects on rRNA and tRNA synthesis could be indirect as well (pathway B). On the other hand the three nuclear transcriptional machineries might be directly regulated in response to nutrient/growth factor signals (pathway C). The challenge is to characterize the network of signaling pathways that coordinately regulates transcription by mechanisms that might involve all effector mechanisms outlined above.

II. Transcriptional regulation of RNA components of the translational apparatus

A. The yeast model

Studies of model systems will likely identify conserved elements of the regulatory network that coordinates transcription of the eukaryotic rRNA, tRNA and r protein genes. The budding yeast *Saccharomyces cerevisiae* is expected to be a useful model because growth control of transcription of these genes is well documented in this organism (Warner, 1989; Sethy et al., 1995; Clarke et al., 1996; DeRisi et al., 1997) and sophisticated biochemical and genetic approaches can be brought to bear on the problem. Studies focusing on the tRNA and 5S rRNA genes transcribed by RNA pol III might prove particularly instructive since components of the pol III transcription machinery are highly conserved between yeast and human (**Table 1**). The yeast pol III transcription machinery, at its most fundamental level, is comprised of the polymerase (14 subunits), TFIIIB (3 subunits) and TFIIIC (6 subunits). The fundamental steps of the pol III transcription cycle are specific binding of TFIIIC to promoter elements, recruitment of TFIIIB to the promoter by virtue of its interaction with TFIIIC, and finally, recruitment of the polymerase. TFIIIB and the polymerase are highly conserved in structure and function between yeast and human (Wang and Roeder, 1998) and the growth control of transcription acts partly at the level of TFIIIB in yeast and metazoans. Our work has therefore concerned the role that protein kinases, as potential components of signaling pathways that impinge on the pol III machinery, play in transcription of the tRNA and 5S rRNA genes of yeast. The following discussion focuses on the role of signaling by the target of rapamycin (TOR) kinases in the regulation of pol III transcription.

B. TOR signaling and the cellular response to nutrient availability

The target of rapamycin (TOR) protein kinases that define TOR signaling pathways were originally identified by virtue of their sensitivity to the antibiotic rapamycin. Rapamycin, in complex with a cellular protein of the FK-506 binding protein (FKBP) class, binds to and inhibits TOR phosphotransferase activity. The TORs are conserved between yeast and human and belong to the MEC/ATM family of protein kinases (Hunter and Plowman, 1997; Dennis et al., 1999). Budding yeast has two TOR kinases, Tor1p and Tor2p, whereas only one TOR has been identified in mammalian cells. Literature pertaining to TOR signaling in yeast and higher eukaryotes has been reviewed extensively in recent years, principally with regard to TOR regulation of cytoplasmic functions (for example: Sigal and Dumont, 1992; Cardenas et al., 1994; Kay, 1996; Brown and Schreiber, 1996; Thomas and Hall, 1997; Conlon and Raff, 1999; Dennis et al., 1999; Polymenis and Schmidt, 1999). Here I focus on those features of the pathway in yeast that are most relevant to control of events in the nucleus, particularly the regulation of transcription. The only protein kinases presently known to be downstream of the TORs in yeast are protein kinase C (PKC) and components of the MAP kinase (MAPK) cascade involved in signaling to the actin cytoskeleton (Helliwell et al., 1998b). It is not yet clear if PKC/MAPK signaling is involved in TOR regulation of transcription (see Section II E.).

TOR function in transcriptional regulation in yeast is critically important in the cell's global response cell to nutrient limitation. Yeast cells respond to nutrient limitation by entering a metabolically inert state called G0 or stationary phase (reviewed in Werner-Washburne et al., 1993, 1996). Entry into G0 involves biochemical reprogramming events that have two major outcomes at the cellular level: 1) lowered energy consumption, and 2) increased stress resistance. Energy consumption declines as a consequence of the repression of translation in G0, which occurs in concert with repression of transcription of the genes encoding many components of the translational apparatus, including the rRNAs, tRNAs and r proteins. The repression of rRNA, tRNA and r protein transcription is particularly important from an energetic viewpoint because the production of these RNAs accounts for most RNA synthesis in the nucleus (Nierras and Warner, 1999). Cells also improve their chance of surviving in G0 by inducing a number of stress response genes (for example heat shock proteins). Transcriptional induction of these genes is a further hallmark of the yeast response to starvation.

Recent evidence suggests that the TOR pathway in yeast sets the transcriptional output of the genes encoding the G0-specific proteins in response to nutrient availability. In a landmark paper in the field, Barbet et al. (1996) showed that interference with TOR signaling by treatment of yeast cells with rapamycin causes a rapid and global repression of translation as well as transcriptional induction of several G0-specific pol II genes. Similar results were obtained using cells that conditionally express functional Tor2p (in a *tor1*Δ background). More generally Barbet et al. showed that Tor1p and Tor2p function redundantly to control many aspects of the cellular response to starvation, including cell cycle arrest with 1n DNA content, failure to reach START, enlargement of the vacuole, accumulation of glycogen, and acquisition of thermotolerance.

Since transcriptional repression of genes encoding the RNA components of the translational apparatus is an integral component of the starvation response of yeast, it is an attractive possibility that the TOR pathway also regulates pol I and pol III transcription according to nutrient availability. We tested this possibility by biochemical methods.

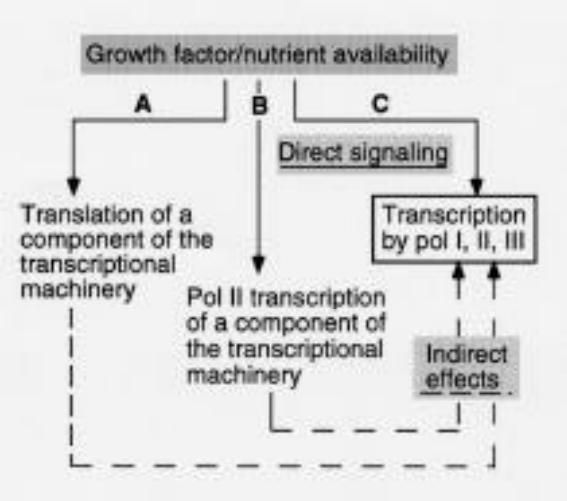

Figure 1: Control mechanisms whose interplay might regulate transcription of key components of the translational apparatus (box) according to nutrient supply or the availability of growth factors.

Transcriptional machinery

Yeast	Function	References	Related human protein	References
Pol III				
Rpo31p (Rpc160)	160 kDa subunit pol III	YPD*/MIPS†	hRPC155 (pol III largest subunit)	Sepehri and Hernandez, 1997
Rpc82p	82 kDa subunit pol III	"	hRPC62	Wang and Roeder, 1997
Rpc53p	47 kDa subunit pol III	"	BN51 (BHK21) temperature sensitivity complementing	Ittmann et al., 1993
Rpc40p	40 kDa subunit pol III	"	pol I subunit RPA40	YPD
Rpc34p	34 kDa subunit pol III	"	hRPC39	Wang and Roeder, 1997
Rpc31p	31 kDa subunit pol III	"	hRPC32	Wang and Roeder, 1997
Rpb6p# (Rpo26)	18 kDa subunit pol I/II/III	"	pol II 14.4 kDa polypeptide	YPD
Rpc128p (Ret1)	130 kDa subunit pol III	"	Unknown	
Rpb5p	25 kDa subunit pol I/II/III	"	Unknown	
Rpc25p	25 kDa subunit pol III	"	Unknown	
Rpc12p (Rpc10)	7.7 kDa subunit pol I/II/III	"	Unknown	
Rpc19p#	16 kDa subunit pol I/III	"	Unknown	
Rpb8p	16 kDa subunit pol I/II/III	"	Unknown	
Rpb10p	8.3 kDa subunit pol I/II/III	"	Unknown	
TFIIIB				
Spt15p	TATA binding protein (TBP)	Willis, 1993	TBP	White et al., 1992
Brf1p (Pcf4p)	70 kDa subunit, related to TFIIB	Willis, 1993	TFIIIB90 (TAF3C)	Wang and Roeder, 1995
Tfc5p	90 kDa subunit	Kassavetis et al., 1995	Unknown	

Table 1: Conservation between yeast and human of the core components of the pol III transcriptional machinery. Only selected references from the text are cited in this table. *Yeast protein database: http://www.proteome.com/databases/YPD/index.html. †Munich Information Center for Protein Sequences: http://www.mips.biochem.mpg.de/proj/yeast/catalogues/funcat/fc04_03_01.html. #Known to exist as phosphoproteins in yeast (Thuriaux and Sentenac, 1992).

C. TOR regulation of rRNA and tRNA transcription

Rapamycin was used to analyze the role of TOR signaling in the regulation of pol I and pol III transcription (Zaragoza et al., 1998). Rapamycin treatment of cells was shown to significantly repress specific transcription by pol I and pol III in crude extracts from wild type strains. Since rapamycin treatment did not repress pol III transcription in extracts from a mutant lacking Fpr1p, the protein to which rapamycin must bind in order to perturb previously defined TOR functions related to the starvation response, we concluded that signals conveyed by the TOR pathway regulate rRNA and tRNA transcription in yeast. In this way the TOR pathway is thought to ensure that production of the RNA components of the translational apparatus is coordinated with the availability of amino acids for protein synthesis.

At least three mechanisms could account for the regulation of transcription by pol I and pol III according to nutrient availability (**Figure 1**). Importantly, because interference with TOR signaling results in a rapid global repression of translation in yeast (Barbet et al., 1996), the effect of rapamycin on pol I/III transcription could be a secondary consequence of a decreased rate of protein synthesis (pathway A in **Figure 1**). This notion is supported by the observation that cycloheximide treatment also represses pol III transcription in some strain backgrounds (Dieci et al., 1995). These results however do not exclude the possibility that translation-independent effects of TOR signaling impinge on the pol III transcriptional machinery (pathway C in **Figure 1**). Indeed, using extracts from wild type cells and a *tor2* temperature sensitive mutant in temperature shift experiments we demonstrated that interference with TOR function in vitro represses pol III transcription independently of translation (Zaragoza et al., 1998). Whether or not this translation-independent mechanism accounts fully for the repression of pol III transcription seen when cells are treated with rapamycin remains to be determined. None the less we are at a point now where we can begin to identify direct target/s of the TOR signaling pathway from among the components of the pol III transcriptional machinery.

Transcription complementation experiments have been used to identify, as biochemical fractions, the components of the pol III machinery that are inactivated when TOR signaling is perturbed. Add-back of TFIIIB purified from control cells significantly restores activity to rapamycin-treated extracts, suggesting that TFIIIB is a target of TOR signaling. Because TFIIIB does not fully restore the activity of rapamycin-treated extracts, another component of the transcriptional machinery is expected to be limiting in this circumstance. That other component is the polymerase, which has lower elongation (bulk) activity in rapamycin-treated as compared to control extracts, and which in partially purified form (from control extract) is able to stimulate transcription in rapamycin-treated extract supplemented with a saturating amount of TFIIIB. The polymerase is therefore a target of a TOR pathway. The TOR-responsive subunits of TFIIIB and pol III remain to be identified, as does the mechanism of their regulation by TOR signaling.

In view of previous reports that TFIIIB activity is regulated according to nutrient/growth factor availability it was not surprising to discover that TFIIIB is sensitive to TOR signaling in yeast. Regulation of the pol III enzyme however has not been described in any organism. On the other hand the activity of pol III is known to be sensitive to misregulation of an enzyme involved in signaling. Thus van Zyl et al. (1992) reported that the pol III enzyme is repressed in yeast cells lacking the Tpd3p regulatory subunit of protein phosphatase 2A (PP2A). Since PP2A is a component of the TOR pathway that regulates translation according to nutrient availability in yeast (Di Como and Arndt, 1996; Jiang and Broach, 1999), the results obtained to date may reflect the existence of pathways for the direct regulation of translation and pol III transcription that share (not unexpectedly) more signaling components than just the TOR kinases.

D. TOR regulation of pol II transcription in yeast: implications for the regulation of pol III subunit transcription

Because TOR signaling regulates many aspects of the cellular response to nutrient limitation it is interesting to consider our data on pol III transcription and TOR signaling in the context of what is known about genome wide-changes in pol II transcription that occur as yeast cells enter G0. Global changes in the pattern of gene expression in response to nutrient depletion have been characterized by DeRisi et al. (1997) using DNA microarray methodology. This data is available on the world wide web at the yeast protein database (http://www.proteome.com/databases/YPD/index.html).

I queried this database with respect to the genes encoding the known core components of the pol III transcriptional machinery. An interesting pattern emerged from this analysis (**Figure 2**). From among the 21 genes for which data are available, 9 show a significant change in expression level (mRNA abundance) between the actively growing and nutrient-limited states. All genes whose expression levels change are repressed upon nutrient depletion. Intriguingly from the viewpoint of our results, all repressed genes are subunits of RNA pol III. This suggests a working model in which the repression of pol III enzyme activity observed when cells are treated with rapamycin is due to decreased transcription of pol III subunit genes and ultimately decreased abundance of the enzyme. In other words, the results are consistent with the hypothesis that TOR signaling regulates specific pol III transcription in part by regulating transcription of pol III enzyme subunits. This indirect mechanism of regulation of tRNA/5S rRNA transcription is represented as pathway B in **Figure 1**.

From the available data we propose that two components of the pol III transcriptional machinery, TFIIIB and the polymerase, are regulated by TOR signaling. TOR signaling acts on the transcriptional machinery by a direct mechanism and perhaps an indirect mechanism involving an effect on

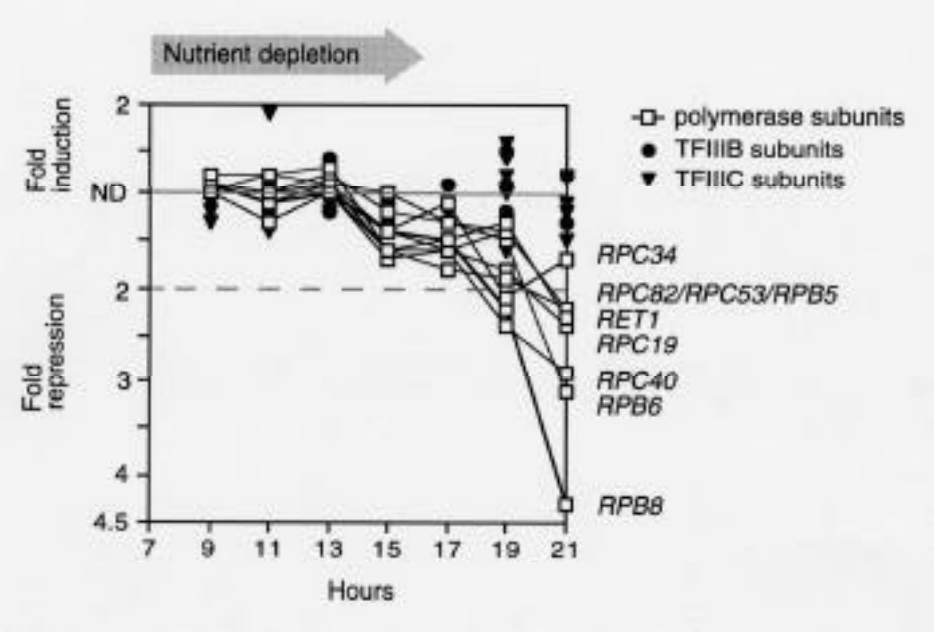

Figure 2: Transcriptional regulation of components of the core pol III transcriptional machinery upon nutrient depletion in yeast (data from DeRisi et al., 1997). The solid gray line indicates no difference (ND) between the starting level of transcript abundance and the level of transcript abundance at the indicated time points of culture. The dashed gray line indicates the cutoff below which repression is considered to be significant in this type of analysis. For simplicity the gene names are not given for the subunits of TFIIIB and TFIIIC.

transcription of the subunits of the polymerase. We do not rule out direct regulation of pol III activity, especially since pol III is a phosphoprotein in yeast (reviewed in Thuriaux and Sentenac, 1992; **Table 1**).

Many pol II genes required for translation, in addition to the subunits of RNA pol III, are regulated at the transcriptional level according to nutrient availability (DeRisi et al., 1997). From among these it has been clearly demonstrated that transcription of several r protein genes is regulated by TOR signaling (Powers and Walter, 1999). Powers and Walter (1999) make the reasonable argument that one or more of the transcriptional activators previously implicated in the regulation of r protein genes is likely to be under TOR control. An interesting candidate from the viewpoint of possible TOR control of pol III subunit transcription is Abf1p, which regulates expression of the Rpc40p subunit of pol III (Della Seta et al., 1990) and many r protein genes. A simple relationship between TOR signaling and transcriptional regulation by Abf1p however is not likely, since Rpo31p, another pol III subunit under Abf1p control (Della Seta et al., 1990), is not down-regulated in G0 (expression data from DeRisi et al., 1997). Since r protein genes with the same pattern of regulation in G0 do not all have the same (potential) regulatory elements in their upstream regions, it may be that the common effector of changes in transcriptional activity is a chromatin remodeling machine that can be recruited to promoters by different DNA-binding transcription factors.

E. Genetic interactions of components of the TOR signaling machinery that may be relevant to pol III transcriptional regulation

As outlined above the biochemical data obtained by rapamycin treatment of yeast establish a link between pol III transcription and TOR signaling that is also suggested by evidence that the Tpd3p regulatory subunit of PP2A is involved in TOR signaling and in the regulation of pol III transcription. There are additional genetic data supporting a link between TOR signaling and pol III transcription (**Figure 3**).

Alleles of the *SSD1* gene have been recovered in screens for suppressors of polymerase mutations and mutations in various signaling molecules. Thus, conditional alleles of a number of pol III subunits are suppressed by *SSD1-v* (Stettler et al., 1993), which also suppresses deletion of the TOR pathway component *sit4* (Sutton et al., 1991a, b). Other genetic interactions of *SSD1* are intriguing in terms of the TOR signaling pathway that impinges upon the pol III transcriptional machinery. *SSD1* suppresses mutants in the PKC/MAPK cascade of yeast (Costigan et al., 1992; Lee et al., 1993) and PKC has been placed downstream of the TORs in a MAPK signaling pathway that regulates cell wall biogenesis and probably other cellular functions (Helliwell et al., 1998a, b). These genetic interactions suggest a functional link between the TORs, PKC and pol III transcription, although direct evidence of this link has not been provided. Indeed, the role of PKC/MAPK signaling in the regulation of

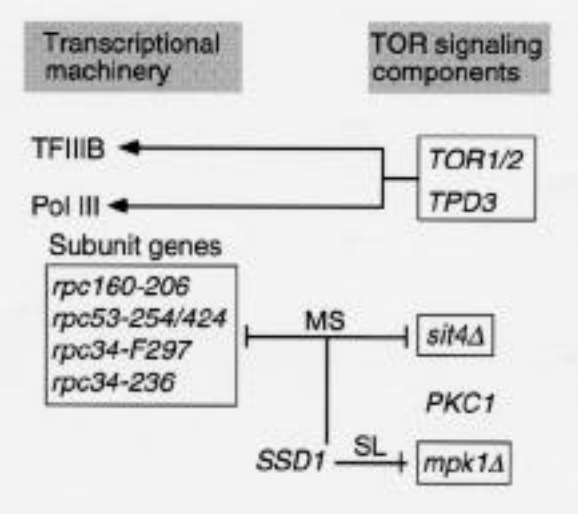

Figure 3: Interactions of TOR signaling components with the pol III transcriptional machinery. Arrows denote effects of TOR signaling on pol III transcription inferred from genetic or pharmacological manipulation of the indicated TOR pathway component. MS and SL respectively indicate multicopy suppression and synthetic lethality with the nominated (boxed) mutant alleles.

pol III transcription may relate to a plasma membrane stress response rather than to the nutrient response. Among other events (Heinisch et al., 1999) the PKC/MAPK pathway of yeast regulates pol I transcription in reaction to cell membrane stretch (Nierras and Warner, 1999). Given the coregulation of pol I and pol III transcription during the yeast life cycle, the genetic evidence indicating a functional relationship between pol III transcription and the PKC/MAPK cascade possibly reflects signaling events that coordinate transcription with cell membrane synthesis required for growth and division. In this respect it is intriguing to note that in some strain backgrounds a *HIS3* disruption allele of *rpc53* confers a cell lysis defect at 38˚C (Mann et al., 1992) that is reminiscent of the lysis phenotype of *pkc1* mutants (Watanabe et al., 1994).

Besides TOR-dependent signaling events the cellular response to nutrient availability involves Ras/protein kinase A (PKA) signaling (see Powers and Walter [1999] for a recent discussion of the literature). Although the relationship between pol III transcription and signaling through the TORs and PKA remains to be fully characterized, it is known that *SSD1* suppresses a mutation in the regulatory subunit (Bcy1p) of PKA that causes misregulation of the enzyme (Wilson et al., 1991), as well as various mutations in the transcriptional and TOR signaling machineries (**Figure 3**).

These relationships may reflect the existence of a PKA/TOR signaling network that sets the rate of pol III transcription according to the physiological state of the cell. Considering the further connections between PKC/MAPK and Ras/PKA signaling (reviewed in Heinisch et al., 1999), it is possible that the regulatory network that governs the rate of pol III transcription in yeast involves three-way cross-talk between TOR, PKA and PKC signaling pathways (**Figure 4**).

F. Related unresolved questions in yeast

TOR signaling is likely to regulate pol III transcription by direct effects on the transcriptional machinery, and by indirect effects at the level of translation and pol II transcription of genes encoding the various components of the pol III transcriptional machinery. The indirect effects ultimately control steady-state protein abundance. Nutrient-dependent changes in the abundance of proteins involved in pol III transcription have not been comprehensively analyzed in yeast. However it is clear that TBP protein levels decline dramatically in G0 (Walker et al., 1997) and that Brf1p (TFIIIB70), which is limiting for TFIIIB activity in extracts from early G0 cells (Sethy et al., 1995), is rapidly depleted when cells are treated with cycloheximide (Dieci et al., 1995). In the long term studies aimed at characterizing indirect mechanisms of TOR action on the pol III transcriptional machinery should take these observations into account, especially in view of evidence that autophagy and the turnover of a number of proteins are under TOR control in yeast (Berset et al., 1998; Noda and Ohsumi, 1998; Schmidt et al., 1998).

III. Comparing yeast with higher eukaryotes

Considering the conservation of the TOR kinases and the signaling molecules that interact with the TORs (**Table 2**) it is not surprising that TOR signaling contributes to the regulation of pol I transcription in mammalian cells (Mahajan, 1994) as in yeast (Zaragoza et al., 1998; Powers and Walter, 1999). The notion that TOR signaling also regulates pol III transcription in mammalian cells is intriguing and is encouraged by the evident conservation, between yeast and human, of the transcriptional machinery and the fundamental steps of the transcription cycle (Section II A.). While the yeast results provide a framework in which to study TOR regulation of pol III transcription in mammalian cells such an analysis will be complicated by two facts, 1) that rapamycin inhibits progression through G1 in various mammalians cell types (Cardenas et al., 1994), and 2) that pol III transcription is repressed in G1 (White et al., 1995). The challenge will be to uncover TOR effects on the transcriptional machinery that are independent of TOR-dependent regulation of the cell cycle.

In view of the available data it is apparent that a conserved function of the TORs is to regulate the overall protein synthetic capacity of the cell. The TORs effect this control in yeast partly by regulating production of the principal non-coding RNAs required for translation (the tRNAs and rRNAs) as well as transcription of genes encoding r proteins. In mammalian cells TOR signaling regulates the translational machinery partly at the level of rRNA (pol I)

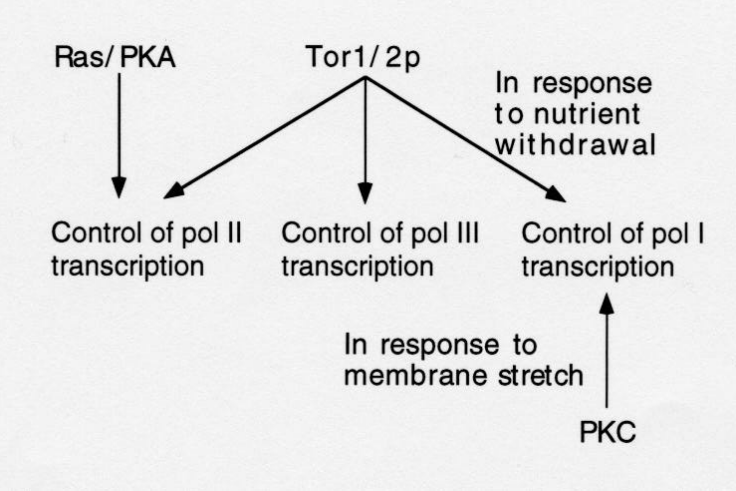

Figure 4: Protein kinases in yeast implicated in the control of transcription in response to nutrient availability and membrane stretch (references in text). No kinases besides those indicated have been directly implicated in the regulatory events depicted.

Signaling molecules

Yeast	Function	References	Related human protein	References
Tor1p	Protein kinase	Thomas and Hall, 1997; Dennis et al., 1999	mTOR (FRAP1/RAFT)	Thomas and Hall, 1997; Dennis et al., 1999
Tor2p	Protein kinase	"	"	As above
Pph21/22p	Redundant protein phosphatase 2A (PP2A) catalytic subunits	Sneddon et al., 1990	Protein phosphatase 2 (formerly 2A), catalytic subunit, β isoform (PPP2CB)	Peterson et al., 1999; YPD*
Tpd3p	Regulatory subunit of PP2A	van Zyl et al., 1992	Protein phosphatase 2 (formerly 2A), regulatory subunit A (PR 65), β isoform (PPP2R1B)	YPD
Cdc55p	Regulatory subunit of PP2A	Healy et al., 1991	Protein phosphatase 2 regulatory subunit B α isoform (PPP2R2A)	YPD
Sit4p	Phosphatase 2A-like catalytic subunit	Sutton et al., 1991	Serine/threonine protein phosphatase 6 (PPP6C)	YPD
Tap42p	Binding partner of Sit4p and Pph21/22p	Di Como and Arndt, 1996	α4	Murata et al., 1997
Pkc1p	Protein kinase C	Levin and Errede, 1995; Herskowitz, 1995; Helliwell et al., 1998	PKC isoforms α, β and γ (phospho-lipids, diacylglycerol, Ca^{2+} cofactors)	YPD
Mpk1p (Slt2)	A MAP kinase	"	BMK1 β kinase (ERK5)	YPD

Table 2: Conservation between yeast and human of TOR signaling components possibly involved in the regulation of pol III transcription. For human proteins specific references are given only when the nominated protein has been experimentally implicated in TOR signaling. Other related human proteins are as given in the yeast protein database (*http://www.proteome.com/databases/YPD/index.html).

transcription, and, through regulation of the translation of specific mRNAs, also at the level of production of r proteins and other protein components of the translational machinery (reviewed in Dennis et al., 1999). Considering the shared functions of the TORs it is likely that yeast will continue to be a valuable tool for characterizing the TOR signaling network involved in the regulation of pol I and pol III transcription in eukaryotes.

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