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Exploiting the yeast stress-activated signaling network to inform on stress biology and disease signaling

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Abstract

Healthy cells utilize intricate systems to monitor their environment and mount robust responses in the event of cellular stress. Whether stress arises from external insults or defects due to mutation and disease, cells must be able to respond precisely to mount the appropriate defenses. Multi-faceted stress responses are generally coupled with arrest of growth and cell-cycle progression, which both limits the transmission of damaged materials and serves to reallocate limited cellular resources toward defense. Therefore, stress defense versus rapid growth represent competing interests in the cell. How eukaryotic cells set the balance between defense versus proliferation, and in particular knowledge of the regulatory networks that control this decision, are poorly understood. In this perspective, we expand upon our recent work inferring the stress-activated signaling network in budding yeast, which captures pathways controlling stress defense and regulators of growth and cell-cycle progression. We highlight similarities between the yeast and mammalian stress responses and explore how stress-activated signaling networks in yeast can inform on signaling defects in human cancers.

Keywords

Stress response; Growth control; Transcription; Signal transduction

Introduction

All cells must allocate resources to balance conflicting physiological demands. From free-living microbes to multicellular animals, actively growing cells funnel resources to biosynthesis needed for division. A key consumer of cellular resources is translation, since production of ribosomes and translation itself require substantial amounts of energy (Warner 1999; Thomas 2000). The drive for proliferation often comes at the cost of stress tolerance (Fig. 1). For example, rapidly growing yeast cells are the most sensitive to environmental insults (Zakrzewska et al. 2011), whereas slow-growing clones are extremely resistant to adversity (Elliott and Futcher 1993; Lu et al. 2009; Levy et al. 2012). The same relationship exists in higher organisms, most notably in rapidly dividing cancer cells that are often the most susceptible to chemotherapy drugs and treatments (Jones and Thompson 2009).

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Understanding how cells allocate cellular resources toward proliferation versus stress defense is therefore critically important for understanding stress defense and, in turn, human disease.

The balance between cellular growth and stress defense can be modulated in response to stressful situations, and thus the mobilization of defense strategies is often coordinated with arrest of growth and cell-cycle progression (Lopez-Maury et al. 2008). At the same time, defense responses include orchestrated changes to transcription, translation, and post-translational protein modifications that mediate changes in protein abundance, localization, and function. Although much is known about the signaling pathways that control individual physiological responses to stress, how signaling is integrated into a single cellular network that coordinates a multi-faceted response is only beginning to emerge. To address this question, we recently developed an experimental and computational pipeline in budding yeast *Saccharomyces cerevisiae*. The approach integrates stress-activated transcriptome alterations, phospho-proteomic changes, and gene-fitness contributions with large-scale protein interaction data, to implicate a single network coordinating the response to, in this case, salt stress (Chasman et al. 2014). The resulting network identified known and novel salt-regulated signaling proteins, uncovered previously unrecognized cross-connections between signaling pathways, and implicated important decision points in the growth-versus-defense decision. Importantly, the network is enriched with statistical significance for genes whose human orthologs cause cancer when mutated in somatic tissues.

In this perspective, we first provide a broad overview of signaling pathways that control proliferation versus stress defense in yeast and mammalian cells. We then highlight opportunities for using the stress-activated signaling network in yeast to understand the growth-versus-defense decision points in eukaryotic cells.

The environmental stress response: a common yeast response to diverse stresses

Actively growing microbial cells maintain high translational capacity to support division, in part by promoting ribosome biogenesis. Supporting high translational capacity therefore consumes a significant amount of the cell's resources. Under optimal conditions, cells produce ~2000 ribosomes per minute (Warner 1999). The high demand for ribosomes requires active transcription of the rDNA locus; nearly 60 % of cellular transcription is devoted to rRNA production by RNA polymerase (Pol) I. Furthermore, over half the activity of Pol II transcription occurs at genes encoding ribosomal proteins (RPs), while Pol III is dedicated to transcribing 5S rRNA and tRNAs (Warner 1999; Rudra and Warner 2004). A significant fraction of Pol II is also dedicated to transcribing genes encoding ribosome assembly factors (commonly called the RiBi regulon) (Jorgensen et al. 2004). In addition to consuming transcriptional capacity, transcripts emerging from RP and RiBi genes are highly translated and thus monopolize a large fraction of the cell's ribosomes (90 % of which are actively involved in translation during rapid growth) (Arava et al. 2003; von der Haar 2008). Thus, significant resources support ribosome biogenesis and translational capacity in cells actively growing under optimal conditions.

Upon a sudden shift to stressful conditions, cells must rapidly adjust resource allocation to mount cellular defense strategies (Fig. 1). Much has been gleaned from studying

transcriptome changes in response to stress. Stressed yeast cells activate condition-specific transcript changes at specialized genes that specifically address the particular stress condition. Concurrently, cells activate the environmental stress response (ESR) (Gasch et al. 2000; Causton et al. 2001), a common response to diverse types of stress. The ESR includes ~300 induced ESR (iESR) genes that are broadly involved in stress defense and ~600 repressed (rESR) genes that encode RPs and RiBi factors (Gasch et al. 2000; Gasch 2002). The expression patterns of the iESR and rESR genes are strikingly anti-correlated across diverse types of stress, indicating that they are likely regulated by the same upstream signaling systems (Gasch 2002).

The ESR is postulated to relate to stress defense, given the functions of the encoded proteins. But surprisingly, activation of the ESR—and of stress-activated transcript changes in general—is not required to survive the initial stress treatment, at least in yeast (Berry and Gasch 2008; Westfall et al. 2008; Mitchell et al. 2009; Berry et al. 2011). Instead, transcript changes are critical for surviving subsequent stressful insults, through a phenomenon known as acquired stress resistance (Berry and Gasch 2008). Induction of iESR transcripts correlates with increased abundance of the encoded proteins, which most likely serve to defend against stress (Berry and Gasch 2008; Lee et al. 2011; Vogel et al. 2011). However, the role of the rESR transcript changes has remained somewhat elusive. Previous observations found that the abundance of RP and RiBi transcripts correlates with growth rate upon nutrient restriction (Jorgensen et al. 2002, 2004; Regenberg et al. 2006; Castrillo et al. 2007; Brauer et al. 2008), leading to the suggestion that rESR gene repression underlies growth and translational arrest during stress. However, we later showed that stress-dependent repression of RP and RiBi genes is not required for translational arrest or growth reduction, at least during salt stress (Lee et al. 2011). Instead, we proposed that rESR transcript reduction serves to release engaged ribosomes, thereby redirecting limited translational capacity to newly made mRNAs (Lee et al. 2011). More recent work from our lab also implies that reduced transcription of rESR genes is required to reallocate RNA Pol II to iESR and other defense genes (Chasman et al. 2014). Thus, the anti-correlation between rESR and iESR gene expression is at least partly explained by competition of these gene modules for limited resources.

Regulation of the growth-versus-defense decision in yeast

Two central signaling pathways regulating ribosome biogenesis are the target of rapamycin (TOR) and the RAS/cAMP/Protein Kinase A (PKA) signaling pathways, which respond to nitrogen and carbon availability, respectively (Neuman-Silberberg et al. 1995; Wang et al. 2004; Xiao and Grove 2009; Broach 2012). Both pathways are largely conserved from yeast to mammals. The TOR complex 1 (TORC1) directly binds the rDNA locus under optimal conditions (Li et al. 2006) and promotes rDNA transcription, by promoting activity of the rDNA transcription factor Rrn3 and, indirectly, by inhibiting the Pol III repressor Maf1 (Claypool et al. 2004; Lee et al. 2009; Philippi et al. 2010). Maf1 is also directly regulated by PKA, which suppresses the inhibitory activity of Maf1 during rapid growth (Moir et al. 2006; Willis and Moir 2007). Both TORC1 and PKA pathways have been implicated in regulating the RP genes and RiBi regulon, by modulating transcriptional activators (Fhl1/Crf1/Ifh1, Rap1, Sfp1) and repressors (Dot6/Tod6) (Klein and Struhl 1994; Jorgensen et al.

2004; Marion et al. 2004; Martin et al. 2004; Lippman and Broach 2009; Huber et al. 2011). The TOR and RAS/PKA pathways are clearly interconnected, even though the precise relationships in regulating ribosomal biogenesis are still controversial. Although some studies have suggested PKA as a downstream effector of the TOR pathway, possibly via the TORC1 downstream target Sch9 (Martin et al. 2004; Schmelzle et al. 2004; Soulard et al. 2010), other evidence has indicated that PKA and TOR are two parallel pathways activating RP gene expression (Zurita-Martinez and Cardenas 2005; Ramachandran and Herman 2011).

Along with promoting biogenesis of ribosomes and translational machinery, PKA and TOR act in parallel to antagonize ESR activation, in part by suppressing Msn2 and Msn4, the so-called ‘general stress’ transcription factors (Görner et al. 1998; Smith et al. 1998; Beck and Hall 1999). Thus, under stressful conditions TOR and PKA pathways must be suppressed—although the mechanisms remain poorly understood—while stress-activated signaling pathways are mobilized. For example, the MAP kinase Hog1 (orthologous to human kinase p38) is activated by osmotic shock and related stresses to coordinate myriad responses, including induction and repression of ~2000 transcripts (including iESR and rESR genes) (O’Rourke and Herskowitz 2004; Chasman et al. 2014), reallocation of RNA Pol II distribution (Cook and O’Shea 2012; Nadal-Ribelles et al. 2012; Chasman et al. 2014), alterations in translational capacity (Teige et al. 2001; Uesono and Toh-E 2002; Nagiec and Dohlman 2012), altered metabolism including osmolyte production (Albertyn et al. 1994; Proft and Struhl 2004), and transient cell-cycle arrest (Bellí et al. 2001; Escoté et al. 2004; Clotet et al. 2006; Yaakov et al. 2009). Alternate signaling pathways are specifically activated by other stresses (such as PKC in the case of cell wall stress (Heinisch et al. 1999), ATM/ATR in response to DNA damage (Abraham 2001), and the AMPK ortholog Snf1 during starvation (Conrad et al. 2014)). How activation of these stress-regulated pathways is coordinated with suppression of the TOR and PKA pathways remains unclear. Nonetheless, coordination and integration of signaling pathways is likely to be key for precise allocation of limited resources and adaptation to a new environment.

Stress responsive signaling in mammalian cells

There are many similarities in the molecular responses to stress in yeast and mammalian systems, despite the added complexities of multi-celled organisms. Studying cellular stress responses in the organismal context is particularly challenging, and thus much of the knowledge comes from culturing immortalized lines or primary cells responding to external stresses. A variety of environmental stresses have been studied extensively in mammalian systems, with the greatest focus on stresses linked to infection and disease, including DNA damaging agents, oxidants, elevated temperature, chemotherapy and other drugs, and hypoxic conditions that mimic the inter-tumor environment. Like yeast, cells must decide between maintaining proliferation or mediating cell-cycle arrest and stress defense. In addition, cells in a multicellular context have a third option in apoptosis, to clear cells that simply cannot recover from the insult. Thus, during adversity, mammalian cells face a multi-pronged decision point directing cells toward proliferation, defense, or death. Although there are many specific aspects of stress responses that are critically influenced by tissue type,

developmental phase, and stress identity, several themes can be generalized from research in this area.

As in yeast, high ribosome biogenesis and translational activity are maintained in actively growing mammalian cells, promoted via signaling through mTORC1 and RAS to the ERK MAP kinase (Hannan et al. 2011). MTORC1 supports ribosome biogenesis through rRNA production, by stimulating transcription of rDNA genes as well as genes encoding rRNA processing factors (Mayer et al. 2004; Mayer and Grummt 2006; Kantidakis et al. 2010; Chauvin et al. 2014). mTORC signaling also promotes ribosome production by favoring translation of so-called 5-TOP transcripts that encode RPs and translation factors (Meyuhas and Dreazen 2009). mTOR also broadly enables cap-dependent translation by suppressing the eIF4e inhibitory binding protein 4E-BP1 (Gingras et al. 1998) and by activating the S6K kinase (orthologous to yeast Sch9), which further stimulates translation initiation and elongation (Magnuson et al. 2012; Roux and Topisirovic 2012). Mitogen-activated RAS/ERK signaling also provides a dual boost to translational activity: ERK signaling stabilizes the growth-enhancing transcription factor Myc, which induces Pol I, II, and III-dependent transcription of ribosome components, and phosphorylates rDNA transcription factors Tif1-A (orthologous to Rrn3 in yeast) and UBF to stimulate rDNA transcription (Hannan et al. 2011; Kusnadi et al. 2015). At the same time, ERK phosphorylation activates downstream kinases that promote cap-dependent translation initiation and elongation (Roux and Blenis 2004; Roux and Topisirovic 2012). As in yeast, there are multiple points of cross-talk between the RAS and mTORC pathways that are thought to produce precisely tuned growth behavior (Mendoza et al. 2011).

In response to stressful situations, many cell types mount a response that shares hallmarks with the yeast ESR. Murray et al. (2004) was one of the first to compare and contrast stress-activated transcriptome changes in primary and immortalized human cells: at least under the conditions and time frames studied, there were relatively few commonly induced or repressed genes upon diverse stress treatments (that included heat, oxidants, ER stress, and crowding). However, more recent studies have identified common responses to different stresses within a given cell type, albeit with smaller magnitude transcript changes than seen in yeast. Nayak et al. (2014) leveraged statistical power in a large study of B cell responses to ER stress and ionizing radiation, finding substantial overlap in response to the two stresses. Several studies interrogating p53 activity (see below) identified a common response that persists across several cell lines and conditions: induced genes are related to stress defense and regulation of cell cycle or apoptosis and repressed genes are linked to rDNA transcription, ribosome biogenesis, translation and cell cycle/apoptotic factors that work antagonistically to induced genes (Cairns and White 1998; Budde and Grummt 1999; Zhai and Comai 2000; Wei et al. 2006; Menendez et al. 2009; Nikulenkov et al. 2012; Schlereth et al. 2013). The coordinated induction of defense genes with repression of rDNA/protein synthesis genes is reminiscent of the coordinated expression changes of the induced and repressed gene modules of the yeast ESR.

Beyond the level of gene expression, other aspects of the stress response are conserved from yeast to humans. Upon stressful insults, transcription of rDNA is generally sharply decreased and coupled to an overall drop in cap-dependent translation (Spriggs et al. 2010;

Liu and Qian 2014; Kusnadi et al. 2015). These responses are mediated by abrogated signaling through the mTOR/S6K and RAS/ERK pathways, and via activation of the stress-activated protein kinases (SAPKs) JNK and p38. p38 isoforms, including the broadly expressed p38α and β along with more tissue-specific γ and δ isoforms, vary in their responsiveness according to tissue type and developmental stage, but they generally respond to diverse types of cellular stress, cytokines and cell–cell contact as well as mitogens and cellular development (Zarubin and Han 2005; Ashwell 2006). The broad responsiveness of p38 isoforms distinguishes them from the yeast ortholog, Hog1, which responds primarily to osmotic and related stresses (Saito and Posas 2012). Both JNK and p38 are activated by a number of upstream kinases, some that have overlapping affinity for both SAPKs and others with specificity for only one of the kinases (Roux and Blenis 2004). Both SAPKs in turn activate a slew of downstream kinases and a host of transcription factors that mediate many aspects of the stress response.

Among the most famous of the SAPK targets is the transcription factor p53, which lies at the crux of the growth/defense/apoptosis decision (Beckerman and Prives 2010). Recent transcriptomic experiments have identified at least 280 common p53 targets activated by diverse stresses and in multiple tissues, with perhaps hundreds of additional targets identified by studies looking at different tissue and stress types (Mirza et al. 2003; Wei et al. 2006; Menendez et al. 2009; Huarte et al. 2010; Nikulenkov et al. 2012; Gambino et al. 2013; Schlereth et al. 2013; Leveille et al. 2015). Upon activation and translocation from the cytosol to nucleus, p53 can function both as an inducer and as a repressor (working directly and indirectly via its transcriptional targets); the genes regulated by p53 can vary in a given tissue depending on severity of the stress (see below) (Vousden and Lu 2002; Menendez et al. 2009; Levav-Cohen et al. 2014). Commonly induced genes include those linked to stress defense, regulators of cell-cycle arrest, and pro- or anti-apoptotic factors (Wei et al. 2006; Menendez et al. 2009; Nikulenkov et al. 2012; Schlereth et al. 2013), while repressed genes include genes that promote cell-cycle progression and proliferation and genes inked to ribosome biogenesis and translation. In fact, p53 can repress activity of all three RNA polymerases, and in the case of Pol I and Pol III, it does so by interfering with proper assembly of general transcriptional machinery (Cairns and White 1998; Budde and Grummt 1999; Zhai and Comai 2000; Becker-man and Prives 2010). Interestingly, the severity and duration of p53 activation are thought to influence whether cells arrest the cell cycle or sacrifice themselves through apoptosis (Vousden and Lu 2002). p53 binding elements upstream of pro-arrest and anti-apoptosis genes have higher affinity for p53 and lower dependence on cooperative binding, while promoters of pro-apoptosis factors are more likely to harbor degenerate p53 elements that require cooperative tetrameric association (Schlereth et al. 2013). This has led to the model that weak p53 activation (producing transient or incomplete nuclear localization) may promote cell survival, while strong or prolonged activation directs cells toward death (Beckerman and Prives 2010).

Signaling crosstalk and the role of the growth-defense-death decision in human cancers

The correct balance between growth versus stress defense or apoptosis is fundamental for proper organismal function. Improper balance leading to unchecked growth is thought to be a critical driver in diseases such as cancer (Jones and Thompson 2009). Regulators

promoting RAS/ERK and mTORC signaling harbor gain-of-function mutations in many human cancers (Shaw and Cantley 2006; Fernández-Medarde and Santos 2011), underscoring the importance of these pathways in promoting growth. Furthermore, many cancerous cells show aberrantly high ribosome production and altered translation regulation (consistent with the oncogene status of eIF4e (Mamane et al. 2004)). Thus, elevated flux toward growth and cell division is a driving force in cancer emergence.

But mutations in stress-activated regulators can also contribute to cancer. For example, 5–10 % of diverse cancers harbor mutations in the SAPK-activating kinase MEK4, which is also associated with poor prognosis in several cancer types (Taylor et al. 2008), while a striking 50 % of human cancers have inactivating alleles of p53 (Vousden and Lu 2002). Several stress-activated signaling pathways play dual roles in suppressing cancer, by triggering apoptosis and by inhibiting signaling through the growth-promoting pathways. Thus, their mutation both prevents cells death and results in unchecked proliferation signaling. For example, p53 suppresses tumorogenesis not only by activating arrest or apoptosis, but also by suppressing mTORC and ERK via up-regulating expression of their inhibitors, at least in certain tissues (Matthew et al. 2009; Feng and Levine 2010; Hasty et al. 2013; Drosten et al. 2014; Akeno et al. 2015). There are other examples of stress-activated pathways directly repressing proliferation signals: upon nutrient limitation in mouse embryonic fibroblasts, stress-activated AMPK and p38β suppress mTORC activity through at least three independent routes (Zheng et al. 2011). Thus, it is clear that stress-activated pathways work at several levels to shift the balance away from proliferation and toward a productive stress response.

Stress-activated networks in yeast: a model for understanding design principles

The design principles of stress-activated signal integration remain poorly understood in both yeast and higher mammals. One strategy to investigate signaling organization is through systems-biology approaches to infer signaling networks. Several recent studies have conducted computational inference of the stress-activated signaling networks, most commonly based on transcriptome data (Friedman 2004; Schadt et al. 2005; Gat-Viks and Shamir 2007; Gitter et al. 2013; Wu et al. 2013). In our recent work, we integrated disparate high-throughput yeast datasets using an integer linear programming approach to infer the salt-activated signaling network (Chasman et al. 2014). The resulting network of ~400 proteins captured known and novel salt-activated pathways as well as key regulators in the growth-promoting TORC1, RAS, and cAMP/PKA pathways, which are suppressed upon salt treatment. It also uncovered previously unrecognized cross-connections between what are generally studied as discrete pathways. We defined pathways based on the literature and scored the number of cross-pathway connections between them. Among those with the greatest connections to other pathways were the TORC1, RAS, and cAMP/PKA pathways. The consequences of this inter-pathway connectivity remain to be tested, but we hypothesize that it reflects an intricate level of control exerted by stress-activated pathways on growth-promoting signaling.

Many of the regulatory connections in the yeast salt-responsive signaling network are orthologous to known signaling connections in mammals. But even more striking is the link

to disease: the salt-activated signaling network we inferred is significantly enriched (p = 8e–4) for proteins whose human orthologous cause cancer when mutated in somatic tissues, according to the latest release of the COSMIC database (Forbes et al. 2015). Using a stringent method of identifying orthologs (Deluca et al. 2006), we found 11 of 49 orthologs from the COSMIC database in the salt-activated network: nearly half were chromatin regulators or transcription factors (including the ortholog of Sfp1 which regulates RP genes), two were involved in RNA metabolism, and one was the Hog1 activator Pbs2 (which is assigned orthologous to the ERK-activating MKK2 kinase). Remarkably, the network is also enriched nearly 3.5-fold for orthologs of p53 interacting proteins captured in the Biogrid database (p = 1e–5 (Chatr-Aryamontri et al. 2015))—even though budding yeast lacks a p53 ortholog. The group of yeast genes orthologous to p53 interactors is enriched for kinases (p = 1.5e–7) and cell-cycle regulators (p = 4e–5). These results indicate that the salt-activated signaling network in yeast shares key features with cancer-related signaling in humans, suggesting that the networks represent modern-day renditions of an ancient signaling system.

Much remains to be dissected about how diverse signals are integrated into a single signaling network, and how cells set the balance between growth-versus-stress defense. It is in this light that yeast research can contribute fundamental insights. Yeast provides an excellent test bed for systems-biology approaches to this question, since detailed follow-up studies can test predictions from network science. Despite the differences in complexity between yeast and mammalian systems, we believe that continued exploration of stress-activated yeast signaling networks in the context of disease-causing orthologs could provide a new perspective on such signaling decisions. Understanding how these fundamental decision are made and disseminated in cells will expand our understanding of stress biology and foster our eventual ability to modulate it.

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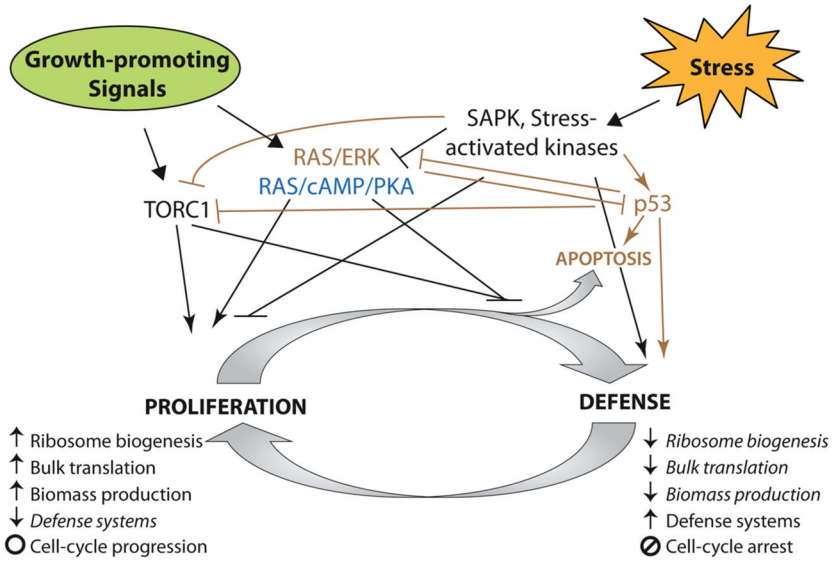

Fig. 1.

Proliferation and stress defense compete for limited resources in the cell. A simplified view of the signaling processes that occur in yeast and/or mammalian cells responding to growth-promoting signals versus cellular stress signals. Signaling molecules relevant in yeast are shown in *blue* and those unique to mammalian cells are shown in *brown*. See text for details