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# cAMP-PKA signal transduction specificity in *Saccharomyces cerevisiae*

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## Abstract

Living cells have developed a set of complex signaling responses, which allow them to withstand different environmental challenges. Signaling pathways enable the cell to monitor external and internal states and to articulate the appropriate physiological responses. Cellular signal transmission requires the dynamic formation of spatiotemporal controlled molecular interactions. One of the most important signaling circuits in *Saccharomyces cerevisiae* is the one controlled by cAMP-Protein Kinase A (PKA). In budding yeast, extracellular glucose and a plethora of signals related with growth and stress conditions regulate the intracellular cAMP levels that modulate PKA activity which in turn regulates a broad range of cellular processes. The cAMP-PKA signaling output requires a controlled specificity of the PKA responses. In this review we discuss the molecular mechanisms that are involved in the establishment of the specificity in the cAMP-PKA signaling pathway in *S. cerevisiae*.

**Keywords** cAMP-PKA · Specificity · Signal transduction · Anchoring proteins · Bcy1 · TPK · Transcription-P-bodies · Stress granules · *Saccharomyces cerevisiae*

## Introduction

Cells sense extracellular stimuli to adjust intracellular processes appropriately to changes in the environment and to maintain cellular homeostasis. Therefore, the key is to ensure that the signals must be specific and subjected to strict control of the regulatory response (Li and Qian 2003; Hynes et al. 2013; Lee and Yaffe 2016). In most cases, cells respond to the environmental changes by signaling through the action of enzyme cascades. Spatial and temporal control of signal transduction is frequently achieved by compartmentalization of intracellular effectors through adaptors or anchoring proteins (Pawson and Scott 2010).

In many cases, the signal recognized by a receptor triggers the synthesis of a second messenger which in turn controls the activity of kinases. These kinases phosphorylate their downstream substrates. A widely known example of a

second messenger is cAMP, which activates cAMP-dependent protein kinase (PKA) (Taylor et al. 2005, 2013).

PKA in *Saccharomyces cerevisiae* is a tetramer composed of two regulatory subunits and two catalytic subunits. The cAMP binding regulatory subunit is encoded by a single gene *BCY1*, while the catalytic subunits are encoded by the *TPK1*, *TPK2* and *TPK3* genes (Toda et al. 1987). In the absence of cAMP, the Bcy1 dimer binds two catalytic subunits (Tpk) and the enzyme is in the inactive state. The cAMP-PKA signaling in *S. cerevisiae* (Thevelein et al. 2008; Conrad et al. 2014) controls a variety of essential cellular processes associated with fermentative growth, the entrance into stationary phase, stress responses and developmental pathways (Palecek et al. 2002; Santangelo 2006; Gancedo 2008). Two major stimuli induce cAMP synthesis in yeast: extracellular fermentable sugars and intracellular acidification. (Thevelein and Winde 1999). The increase of cAMP levels mediates the consequent PKA activation (Fig. 1).

Considering the pleiotropic role of the cAMP-PKA signaling pathway in *S. cerevisiae* a major question is how specificity is attained and how the cell ensures the phosphorylation of the right substrate in response to different stimuli that trigger the production of cAMP as single second messenger. Although the three Tpk isoforms demonstrated to be functionally redundant for cell viability, specific

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functions have been described for each one (Robertson and Fink 1998; Robertson et al. 2000; Pan and Heitman 2002; Chevtzoff et al. 2005; Palomino et al. 2006). The substrate specificity for Tpk1, Tpk2 and Tpk3 does not seem to rely on sequence determinants around the phosphorylation site nor on a difference in the turnover number (*K<sub>cat</sub>*) for each isoform although the substrate has an important role in the activation of the holoenzyme (Galello et al. 2010; Mok et al. 2010). Therefore, other cellular strategies must contribute to the specificity of PKA-signaling in *S. cerevisiae*. This review will focus on discussing these strategies, and although we will center around the current knowledge in yeast as model organism, whenever pertinent we will refer to the mammalian counterparts for comparison.

### PKA tethering through Bcy1 interacting proteins

The regulatory subunit (R) is a modular protein with two highly conserved cAMP binding domains at the C-terminus and a more variable N-terminus domain involved in dimerization and docking (DD) (Taylor et al. 2012). In mammals, there are two forms of the PKA holoenzyme, PKAI and PKAII, which contain RI or RII subunit isoforms (subclassified in RI $\alpha$ , RI $\beta$ , RII $\alpha$ , and RII $\beta$ , subtypes) (Brandon et al. 1997; Taylor et al. 2004; Zhang et al. 2015). The R subunits target the holoenzyme to defined subcellular compartments through interaction of their DD domain with AKAPs (A Kinase Anchoring Proteins) (Calejo and Taskén 2015; Torres-Quesada et al. 2017). Mammalian AKAPs bind with high affinity to a hydrophobic surface of a helix bundle on the dimeric DD domains through an amphipathic  $\alpha$ -helix (14–18 residues) (Gold et al. 2006; Kinderman et al. 2006). AKAPs are normally subdivided into three classes: RI-, RII- or dual-specific (Jarnaess et al. 2008). AKAPs were first described to bind to the RII subunit (Carr et al. 1991) and although PKAI holoenzymes are usually in the soluble fraction of the cell, however, they may be bound to RI-AKAPs or AKAPs with dual specificity. More detailed accounts on the mechanisms involved to spatially and temporally restrict PKA phosphorylation events in mammals can be found in excellent reviews (Calejo and Taskén 2015; Gold 2019; Torres-Quesada et al. 2017).

The mechanism of PKA localization in *S. cerevisiae* seems to be different to the one described for mammals. In contrast to mammalian PKA, the localization of Bcy1, is dynamic and responsive to environmental nutritional conditions (Griffioen et al. 2000; Tudisca et al. 2010). Recently it has been reported that Bcy1 exists as a homotetrameric R subunit, an oligomeric state that has never been reported before in other organisms (González Bardeci et al. 2016). However, the N-terminus of Bcy1 exhibits the classical helix-turn-helix motif and the key residues for dimerization present in a canonical RII $\alpha$ -like DD domain are conserved.

(Griffioen and Thevelein 2002; González Bardeci et al. 2016).

Several Bcy1 N-terminal dependent interacting proteins have been described. The first reported was Zds1, identified in a yeast two-hybrid screen, using the N-terminal domain of Bcy1 as bait. It was shown that Zds1 regulates the cytoplasmic localization of Bcy1 (Griffioen et al. 2001). The phosphorylation of two clusters of serine residues located at the N-terminal region of Bcy1 has been reported to be required for its cytoplasmic localization when cells are deprived of glucose (Griffioen et al. 2001). In fact, the phosphorylation of serines cluster II increased the affinity of the Bcy1-Zds1 interaction, resulting in the retention of Bcy1 in the cytoplasm (Griffioen et al. 2001).

Subsequently, Eno2 (enolase II), Hsp60 (mitochondrial chaperonin), and Ira2 (RAS GTPase-activating protein) were identified as Bcy1-interacting proteins using a mass spectrometry-based proteomic analysis and a bioinformatic approach (Galello et al. 2014). The physiological relevance of Ira 2 and Hsp60 interactions with Bcy1 were demonstrated. Ira2 mediates tethering of PKA to the Ras complex, known to regulate cAMP levels in yeast (Thevelein 1994) while the chaperone Hsp60 facilitates localization of PKA to the mitochondria and provides stability to the catalytic subunits (Galello et al. 2014) (Fig. 1A). The interaction domain in Bcy1 binding proteins was predicted using bioinformatic analysis and. Peptides designed from the predictions showed to bind Bcy1 and display different molecular characteristics than canonical AKAP domain. In a classical DD-AKAP interaction hydrophobic residues are essential (Newlon et al. 2001; Gold et al. 2006; Kinderman et al. 2006; Sarma et al. 2010). However, in the interaction peptide Ira2-Bcy1 only positively charged amino acids were required (Galello et al. 2014). The structural analysis of the tetrameric DD domain diffracting crystals from Bcy1 provides not only insights into the determinants of oligomerization of these subunits but also allow to infer which negatively charged residues on the surface of Bcy1 could participate of its interaction with Ira2 peptide (Gonzalez Bardeci N., personal communication).

### Subcellular localization of the Tpk1, Tpk2 and Tpk3 catalytic isoforms

The human genome encodes three different catalytic subunits (C),  $\alpha$ ,  $\beta$  and  $\gamma$  isoforms that are differentially expressed in different organs and tissues. In addition to subcellular localization of C by interaction with anchored RI or RII (via AKAPs), targeting of C subunits to various specific binding proteins at the cell membrane, nucleus and cytosol, named C-KAP (Catalytic Kinase Anchoring Proteins) have also been described (Søberg and Skålhegg 2018). In the classical view, the PKA holoenzyme is size-excluded from the nucleus and when cAMP levels increase, the free

C subunit is then able to move to the nucleus by passive diffusion (Harootunian et al. 1993). However, contrary to this dogma, the existence of a resident pool of nuclear PKA holoenzyme has been demonstrated (Sample et al. 2012; Haj Slimane et al. 2014; Clister et al. 2019).

In *S. cerevisiae*, both Bcy1 and Tpk2 are mainly localized to the nucleus in actively growing cells in the presence of glucose, whereas Tpk1 and Tpk3 show a nuclear-cytoplasmic localization (Tudisca et al. 2010). However, during exponential growth on glycerol or in stationary phase after glucose has been consumed, both Bcy1 and all three Tpk subunits display mostly cytoplasmic localization (Tudisca et al. 2010). Significant progress has been made in understanding the mechanisms involved in the localization of yeast PKA subunits. Under exponential growth on glucose, a different  $\beta$ -karyopherin facilitates the nuclear import of Tpk1, Tpk2 and Bcy1 (Baccarini et al. 2015). In silico analysis of PKA subunits protein sequences did not unveil a nuclear localization signal (NLS) (Marfori et al. 2011), thus the reason that allows their nuclear transport had to be established experimentally. Nuclear Bcy1 determine Tpk1 localization, indicating inactive holoenzyme can be found inside the nucleus (Fig. 1A). When cAMP levels increase, Tpk1-Bcy1 holoenzyme dissociates and Tpk1 translocates to the cytoplasm (Griffioen et al. 2000). In addition, several post translational modifications on Tpk1 have been described affecting its nuclear-cytoplasmic localization (Haesendonckx et al. 2012; Solari et al. 2014). The mechanism of Tpk3 nucleus-cytoplasmic localization has not been widely studied due to the low levels of Tpk3 protein expression.

The Tpk3s show a subcellular localization that is also isoform specific during several stress conditions, including glucose starvation, heat shock, osmotic stress, and quiescent arrest. In response to osmotic stress, Tpk1 accumulates in the nucleus, while Tpk2 and Bcy1 show no changes in their localization (Baccarini et al. 2015). However, during glucose starvation, heat stress and quiescent arrest, Tpk1 and Bcy1 remain diffusely distributed throughout the cytoplasm and, while Tpk2 and Tpk3 condensate to stress induced mRNPs like PBs (P-bodies) and SGs (Stress Granules) (Tudisca et al. 2010, 2012; Shah et al. 2013, 2014; Barraza et al. 2017). Although the precise mechanism that controls the differential Tpk2 and Tpk3 localization on cytoplasmic foci is not fully understood there are studies that have demonstrated that the catalytic domains and an intrinsically disordered region of Tpk2 play a role in this process. Kinase dead mutant of Tpk2 localizes into PBs under glucose starvation conditions, but remains diffusely distributed throughout the cytoplasm in cells exposed to thermal stress (Tudisca et al. 2012; Barraza et al. 2017). A prion like domain, exclusively present in the N-terminus of Tpk2, is involved in the targeting of this subunit to PBs and SGs in response to glucose

starvation, heat stress and after quiescent arrest (Barraza, C to be published elsewhere). Tpk3 kinase activity is required for its condensation into PBs induced by glucose starvation whereas this activity is not required for Tpk3 localization on SGs evoked by heat stress (Tudisca et al. 2012; Barraza et al. 2017).

The cause-effect relationship between isoform specificity and subcellular localization has been probed in response to stress. During osmotic stress, the gene expression response is dependent on the proper nuclear localization of PKA subunits and their physical interaction with chromatin. Both Tpk1 and Tpk2 subunits are recruited to the coding regions of osmoinducible genes while only Tpk2 is recruited to the promoter regions of ribosomal protein genes (Pokholok et al. 2006; Baccarini et al. 2015). Tpk2 localization into PB and SG positively regulates their condensation but reduces *PDC1*, *ENO2* and *TIF1* mRNA upon glucose starvation. Tpk2 promotes PBs formation that correlates with the long-term cell survival of quiescent cells (Barraza, C to be published elsewhere). Altogether, the evidence supports a model in which, in response to changes in the environment, specific subcellular localization allows the interaction of each catalytic isoform of PKA with a complex network of distinct protein and potential substrates (Fig. 1B).

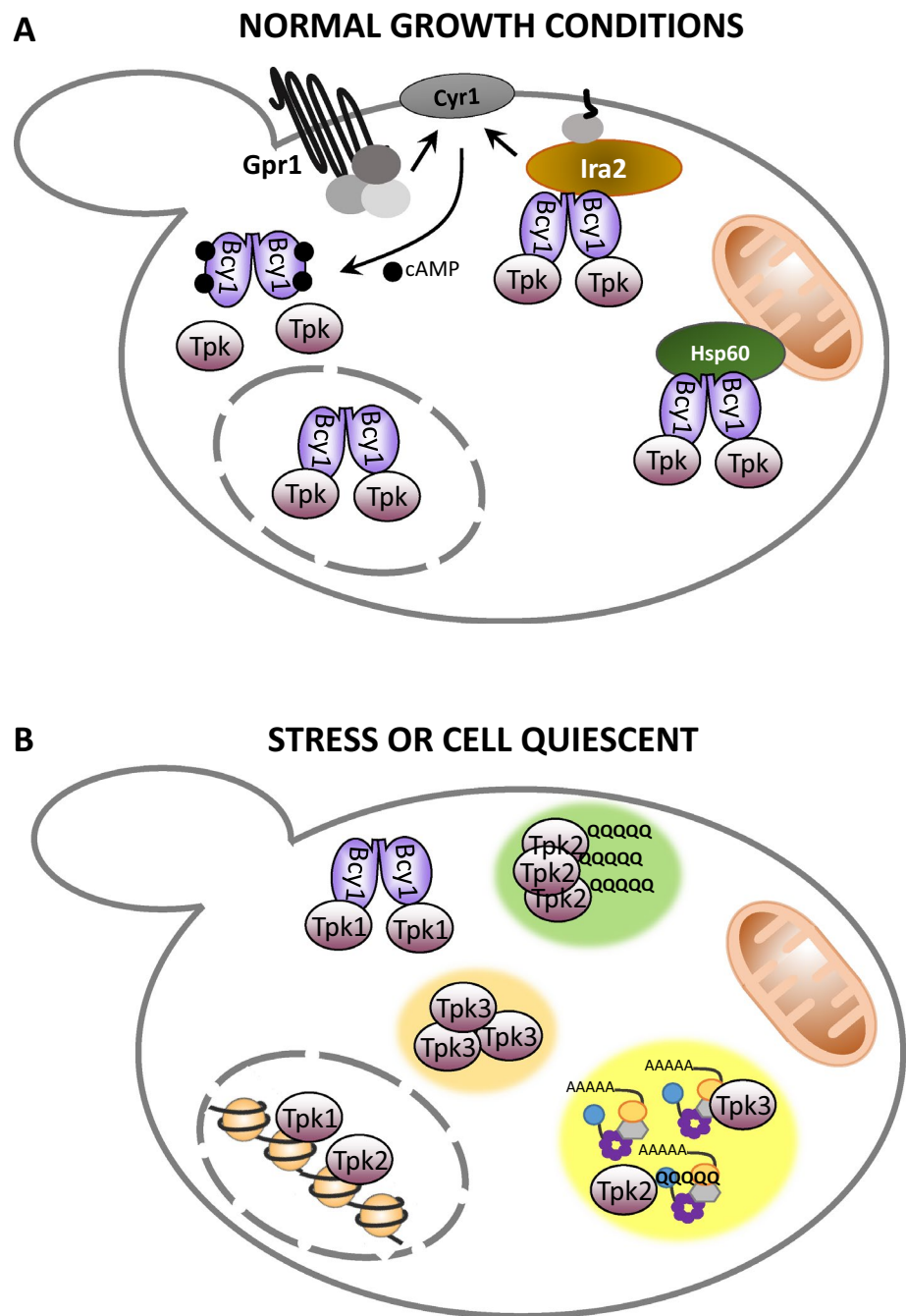
### Transcriptional regulation of the protein kinase A subunits in *Saccharomyces cerevisiae*

In mammals, the expression levels of R and C subunits are regulated by hormones and mitogenic signals acting through G-protein coupled receptor (Oyen et al. 1988; Landmark et al. 1993) or tyrosine kinases associated receptors (Skålhegg et al. 1994). It has been demonstrated that C $\alpha$ , C $\beta$ , RI $\alpha$ , RI $\beta$ , RII $\alpha$ , and RII $\beta$  isoforms have tissue specific, developmental and differentiation stages expression patterns. (Oyen et al. 1988; Cadd and Mcknight 1989; Cummings et al. 1996; Reinton et al. 1998). Several studies demonstrated that cAMP has transcriptional and post-transcriptional effect on mRNA as well as on the isoforms protein stability after dissociation of the holoenzyme (Houge et al. 1990; Knutsen et al. 1991; Tasken et al. 1993; Dahle et al. 2001).

In *S. cerevisiae*, it is well established that *TPK1*, *TPK2*, *TPK3* and *BCY1* gene expression is upregulated in response to heat shock and saline stress, with evidence coming mostly from high throughput transcriptomic studies (Rep et al. 2000; Posas et al. 2000; Gasch et al. 2000; Causton et al. 2001; Yale and Bohnert 2001; Castells-Roca et al. 2011). High PKA activity in yeast is associated with several phenotypes, one of them being low stress resistance due to the repression of genes under the control of stress response element (STRE) (Estruch 2000). Apparently, there is a contradiction since transcription of PKA subunits is stimulated in response to stress, but higher PKA activity leads to a lower



**Fig. 1** Subcellular localization of the PKA in *Saccharomyces cerevisiae*. **A.** In exponential growing cells on glucose as carbon source, PKA holoenzyme (Bcy1-Tpk) shows nuclear-cytoplasmic localization. Bcy1 and Tpk2 are mainly localized into the nucleus while Tpk1 and Tpk3 show a nuclear-cytoplasmic localization (to simplify the figure, all the possible localization of the Tpk isoform were not depicted, see the text for details). In cytoplasm, Ira2 mediates tethering of PKA to Ras complex. In response to glucose, Ras complex and heterotrimeric G protein-coupled to Gpr1 receptor regulate the adenylate cyclase (Cyr1) activity and the production of cAMP. In the presence of cAMP, PKA dissociates into Bcy1 dimer and two Tpk subunits which are free to phosphorylate the substrates. Other interaction of Bcy1 is with Hsp60 which facilitates the localization of PKA to the mitochondria. **B.** Under stress or quiescent, Tpk2 and Tpk3 accumulate into cytoplasmic foci and localize with PBs and/or SGs. Prion like domain present in the N-terminal of Tpk2 (Q-rich domain) is involved in its localization into PB. Tpk1 and Bcy1 show a diffuse cytoplasmic localization. Inside the nucleus, Tpk1 and Tpk2 interact with stress-responsive genes like *TPK1* promoter



stress resistance. This suggests a complex mechanism regulating the expression of PKA subunits.

Recently published evidence supports the differential expression of PKA subunits during different conditions as growth in the presence of glucose or glycerol as carbon sources (Galello et al. 2017). Protein expression levels of each Tpk is different and changes from low levels under fermentative metabolism to higher levels during the switch to non-fermentative metabolism associated with stationary phase (Tudisca et al. 2010).

Pautasso et al. have demonstrated that the promoters of all genes coding for PKA subunits, *TPK1*, *TPK2*, *TPK3* and *BCY1* are negatively regulated by PKA activity in a mechanism isoform dependent. Each catalytic subunits have negative effect on the activity of all the subunit promoters. However, Tpk2 is the isoform with higher inhibitory effect on *TPK1* and *TPK3* promoters but lacks inhibition towards its own promoter (Pautasso and Rossi 2014).

During stress conditions, heat shock and osmotic stress, the *TPK1* promoter is the only one of the PKA subunit promoters that is upregulated. This promoter presents three

positioned nucleosomes that are evicted upon heat stress or osmostress, in correlation with promoter activation and upregulation of *TPK1* mRNA levels (Pautasso and Rossi 2014; Reca et al. 2020). It was demonstrated that the kinase Rim15 and the transcription factors Msn2/4, Gis1, and Sok2 are involved in *TPK1* upregulation during heat shock (Pautasso and Rossi 2014). The remodelers RSC and INO80 are necessary for nucleosome positioning, contributing to repression of *TPK1* under normal growth conditions while SWI/SNF plays a role in the eviction of nucleosomes and activation after heat stress (Reca et al. 2020). The recruitment of SWI/SNF complex upon heat shock is Msn2/4-dependent. Interestingly, the recruitment of Tpk1 and Tpk2 subunits to the *TPK1* promoter was also unveiled in this study, and they were recruited in opposite temporal patterns upon heat shock (Reca et al. 2020). Furthermore, while Tpk1 catalytic activity is necessary for chromatin remodeling on the *TPK1* promoter, Tpk2 (and Tpk3) activities maintained a repressive chromatin conformation inhibiting promoter activity (Reca et al. 2020). The results of this study revealed an intricate mechanism of feedback regulation of the different Tpk subunits on the *TPK1* promoter (Fig. 1B).

## Summary

Specificity in cAMP-PKA signaling is key for the accurate response to a determined stimulus. The recognition of one specific substrate is achieved through the dynamic, concerted, and cooperative interrelation of different levels of control. In yeast, one cellular strategy is to restrict the localization of each Tpk subunit in subcellular compartments defined by their interaction with the Bcy1, which in turn interacts with tethering proteins. Although this mechanism resembles the one described for mammalian R subunits, the yeast tethering proteins are different from canonical AKAPs. Another strategy relates to Tpk localization in different subcellular compartments through the interaction with specific protein complexes independently of Bcy1. This is the case for the association of different catalytic isoforms with PBs and SGs in response to nutrient availability, quiescent stages and stress. Finally, regulation of the expression of each PKA subunit proved to be differential during growth phases, in fermentative *versus* respiratory growth conditions and during stress conditions as heat shock or saline stress. We have just started to unveil the molecular details on how the combined effect of each of these levels of control, operating simultaneously, provide fine-tuning and specificity to the response of the cAMP–PKA signaling.

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