



Figure 6 The limited process description displays all posttranslational modifications and their catalysts, but excludes complex formation. Each specific internal state is represented as a distinct node, although some intermediate phosphorylation states have been excluded. Phosphorylations are indicated with red arrows (ATP as co-substrate and ADP as co-product), GEF reactions as orange arrows ($- \text{GTP} + \text{GDP}$), and dephosphorylation or GAP reactions as blue arrows ($+ \text{P}$). Only a fraction of the catalytic modifications have a known catalyst for both forward and reverse reactions, and the required state of the catalyst known is in even fewer cases. Therefore, even this highly simplified process description includes uncertainty in the required states of both catalysts and substrates. In this visualisation, this uncertainty has been shown by using a single catalysis arrow from a box including all potentially active state of the catalyst to the basic state of the substrate (completely unphosphorylated for kinase reactions, or completely phosphorylated for phosphatase reactions). While these simplifications are unsupported, including additional catalytic arrows would be equally arbitrary with the added drawback of making the figure more complex (see Supplementary Figure S2). Despite the need for implicit assumptions, the process description is useful as it is very explicit and intuitive to read.

individually in the reaction and contingency lists in the 'PubMedIdentifier(s)' column with their PMID number.

(Ai *et al.*, 2002; Alepuz *et al.*, 2003; Alepuz *et al.*, 2001; Andrews and Herskowitz, 1989; Andrews and Moore, 1992; Apanovitch *et al.*, 1998; Baetz and Andrews, 1999; Baetz *et al.*, 2001; Ballon *et al.*, 2006; Bao *et al.*, 2004; Bao *et al.*, 2010; Bar *et al.*, 2003; Bardwell *et al.*, 1996; Bardwell *et al.*, 1998a; Bardwell *et al.*, 1998b; Bender and Sprague, 1986; Bilsland-Marchesan *et al.*, 2000; Blumer *et al.*, 1988; Breitreutz *et al.*, 2001; Bruckner *et al.*, 2004; Butty *et al.*, 1998; Chou *et al.*, 2004; Chou *et al.*, 2006; Cismowski *et al.*, 2001; Clark *et al.*, 1993; Collister *et al.*, 2002; Cook *et al.*, 1996; Crosby *et al.*, 2000; Cullen *et al.*, 2004; Davenport *et al.*, 1999; de Nadal *et al.*, 2003; Dodou and Treisman, 1997; Doi *et al.*, 1994; Dolan *et al.*, 1989; Dowell *et al.*, 1998; Drogen *et al.*, 2000; Elion *et al.*, 1993; Errede *et al.*, 1993; Escote *et al.*, 2004; Feng *et al.*, 1998; Fitch *et al.*, 2004; Flandez *et al.*, 2004; Flotho *et al.*, 2004; Friant *et al.*, 2001; Garcia-Gimeno and Struhl, 2000; Garrison *et al.*, 1999; Gartner *et al.*, 1998; Gartner *et al.*, 1992; Good *et al.*, 2009; Green *et al.*, 2003; Guo *et al.*, 2009; Hagen *et al.*, 1986; Hagen *et al.*, 1991; Hahn and Thiele, 2002; Heenan *et al.*, 2009; Heise *et al.*, 2010; Ho *et al.*, 2002; Horie *et al.*, 2008; Inagaki *et al.*, 1999; Inouye *et al.*, 1997a; Inouye *et al.*, 1997b; Irie *et al.*, 1993; Jacoby *et al.*, 1997; Jung *et al.*, 2002; Kamada *et al.*, 1995; Kamada *et al.*, 1996; Ketela *et al.*, 1999; Kim *et al.*, 2010; Kim *et al.*, 2008; Kranz *et al.*, 1994; Kusari *et al.*, 2004; Lamson *et al.*, 2002; Lee and Levin, 1992; Leeuw *et al.*, 1995; Leeuw *et al.*, 1998; Li *et al.*, 1998; Liu *et al.*, 2005; MacKay *et al.*, 1991; MacKay *et al.*, 1988; Madden *et al.*, 1997; Madhani and Fink, 1997; Madhani *et al.*, 1997; Maeda *et al.*, 1995; Maeda *et al.*, 1994; Maleri *et al.*, 2004; Mapes and Ota, 2004; Martin *et al.*, 2000;

Mattison and Ota, 2000; Mattison *et al.*, 1999; Medici *et al.*, 1997; Melcher and Thorner, 1996; Metodiev *et al.*, 2002; Miyajima *et al.*, 1987; Murakami *et al.*, 2008; Nasmyth and Dirick, 1991; Nehlin *et al.*, 1992; Neiman and Herskowitz, 1994; Nern and Arkowitz, 1998; Nern and Arkowitz, 1999; Nonaka *et al.*, 1995; Olson *et al.*, 2000; Ostrander and Gorman, 1999; Ozaki *et al.*, 1996; Paravicini and Friedli, 1996; Parnell *et al.*, 2005; Pascual-Ahuir *et al.*, 2001; Peter *et al.*, 1996; Peterson *et al.*, 1994; Philip and Levin, 2001; Posas and Saito, 1997; Posas and Saito, 1998; Posas *et al.*, 1998; Posas *et al.*, 1996; Proft *et al.*, 2005; Proft *et al.*, 2001; Proft and Serrano, 1999; Proft and Struhl, 2002; Raicu *et al.*, 2005; Raitt *et al.*, 2000; Rajavel *et al.*, 1999; Reiser *et al.*, 2000; Remenyi *et al.*, 2005; Rep *et al.*, 2000; Rep *et al.*, 1999; Roberts and Fink, 1994; Schmelzle *et al.*, 2002; Schmidt *et al.*, 1997; Schmidt *et al.*, 2002; Schmitz *et al.*, 2002; Shi *et al.*, 2005; Shimada *et al.*, 2004; Sidorova and Breeden, 1993; Siegmund and Nasmyth, 1996; Siekhaus and Drubin, 2003; Simon *et al.*, 1995; Skowyra *et al.*, 1997; Smith *et al.*, 2002; Soler *et al.*, 1995; Song *et al.*, 1996; Taba *et al.*, 1991; Takahashi and Pryciak, 2007; Tao *et al.*, 2002; Tarassov *et al.*, 2008; Tatebayashi *et al.*, 2003; Tatebayashi *et al.*, 2007; Tatebayashi *et al.*, 2006; Tedford *et al.*, 1997; Truckses *et al.*, 2006; Truman *et al.*, 2009; Vadaie *et al.*, 2008; Valtz *et al.*, 1995; Varanasi *et al.*, 1996; Verna *et al.*, 1997; Vilella *et al.*, 2005; Wang and Konopka, 2009; Wang *et al.*, 2005; Warmka *et al.*, 2001; Wassmann and Ammerer, 1997; Watanabe *et al.*, 1994; Watanabe *et al.*, 1995; Watanabe *et al.*, 1997; Winters and Pryciak, 2005; Wu *et al.*, 2006; Wu *et al.*, 1999; Wu *et al.*, 1995; Wu *et al.*, 2004; Wurgle-Murphy *et al.*, 1997; Yablonski *et al.*, 1996; Yamamoto *et al.*, 2010; Yesilaltay and Jenness, 2000; Young *et al.*, 2002; Yuan and Fields, 1991; Zarrinpar *et al.*, 2004;

Zarrinpar *et al*, 2003; Zarzov *et al*, 1996; Zeitlinger *et al*, 2003; Zhan *et al*, 1997; Zhan and Guan, 1999; Zhao *et al*, 1995; Zheng and Guan, 1994; Zheng *et al*, 1994; Zhou *et al*, 1993).

The methods used are an integral part of the results and are outlined in that section. For additional details, please see Supplementary information.

Supplementary information

Supplementary information is available at the *Molecular Systems Biology* website (www.nature.com/msb).

Conflict of interest

The authors declare that they have no conflict of interest.

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References

- Ai W, Bertram PG, Tsang CK, Chan TF, Zheng XF (2002) Regulation of subtelomeric silencing during stress response. *Mol Cell* **10**: 1295–1305
- Alepuz PM, de Nadal E, Zapater M, Ammerer G, Posas F (2003) Osmostress-induced transcription by Hot1 depends on a Hog1-mediated recruitment of the RNA Pol II. *EMBO J* **22**: 2433–2442
- Alepuz PM, Jovanovic A, Reiser V, Ammerer G (2001) Stress-induced map kinase Hog1 is part of transcription activation complexes. *Mol Cell* **7**: 767–777
- Andrews BJ, Herskowitz I (1989) Identification of a DNA binding factor involved in cell-cycle control of the yeast HO gene. *Cell* **57**: 21–29
- Andrews BJ, Moore LA (1992) Interaction of the yeast Swi4 and Swi6 cell cycle regulatory proteins in vitro. *Proc Natl Acad Sci USA* **89**: 11852–11856
- Apanovitch DM, Slep KC, Sigler PB, Dohlman HG (1998) Sst2 is a GTPase-activating protein for Gpa1: purification and characterization of a cognate RGS-Galpha protein pair in yeast. *Biochemistry* **37**: 4815–4822

- Aranda B, Achuthan P, Alam-Faruque Y, Armean I, Bridge A, Derow C, Feuermann M, Ghanbarian AT, Kerrien S, Khadake J, Kerssemakers J, Leroy C, Menden M, Michaut M, Montecchi-Palazzi L, Neuhauser SN, Orchard S, Perreau V, Roechert B, van Eijk K *et al* (2010) The IntAct molecular interaction database in 2010. *Nucleic Acids Res* **38**: D525–D531
- Baetz K, Andrews B (1999) Regulation of cell cycle transcription factor Swi4 through auto-inhibition of DNA binding. *Mol Cell Biol* **19**: 6729–6741
- Baetz K, Moffat J, Haynes J, Chang M, Andrews B (2001) Transcriptional coregulation by the cell integrity mitogen-activated protein kinase Sit2 and the cell cycle regulator Swi4. *Mol Cell Biol* **21**: 6515–6528
- Ballon DR, Flanary PL, Gladue DP, Konopka JB, Dohlman HG, Thorner J (2006) DEP-domain-mediated regulation of GPCR signaling responses. *Cell* **126**: 1079–1093
- Bao MZ, Schwartz MA, Cantin GT, Yates JR3rd, Madhani HD (2004) Pheromone-dependent destruction of the Tec1 transcription factor is required for MAP kinase signaling specificity in yeast. *Cell* **119**: 991–1000
- Bao MZ, Shock TR, Madhani HD (2010) Multisite phosphorylation of the Saccharomyces cerevisiae filamentous growth regulator Tec1 is required for its recognition by the E3 ubiquitin ligase adaptor Cdc4 and its subsequent destruction in vivo. *Eukaryot Cell* **9**: 31–36
- Bar EE, Ellicott AT, Stone DE (2003) Gbetagamma recruits Rho1 to the site of polarized growth during mating in budding yeast. *J Biol Chem* **278**: 21798–21804
- Bardwell L, Cook JG, Chang EC, Cairns BR, Thorner J (1996) Signaling in the yeast pheromone response pathway: specific and high-affinity interaction of the mitogen-activated protein (MAP) kinases Kss1 and Fus3 with the upstream MAP kinase Ste7. *Mol Cell Biol* **16**: 3637–3650
- Bardwell L, Cook JG, Voora D, Baggott DM, Martinez AR, Thorner J (1998a) Repression of yeast Ste12 transcription factor by direct binding of unphosphorylated Kss1 MAPK and its regulation by the Ste7 MEK. *Genes Dev* **12**: 2887–2898
- Bardwell L, Cook JG, Zhu-Shimoni JX, Voora D, Thorner J (1998b) Differential regulation of transcription: repression by unactivated mitogen-activated protein kinase Kss1 requires the Dig1 and Dig2 proteins. *Proc Natl Acad Sci USA* **95**: 15400–15405
- Bender A, Sprague GJr. (1986) Yeast peptide pheromones, a-factor and alpha-factor, activate a common response mechanism in their target cells. *Cell* **47**: 929–937
- Bilsland-Marchesan E, Arino J, Saito H, Sunnerhagen P, Posas F (2000) Rck2 kinase is a substrate for the osmotic stress-activated mitogen-activated protein kinase Hog1. *Mol Cell Biol* **20**: 3887–3895
- Biographer <http://code.google.com/p/biographer/>
- Blinov ML, Faeder JR, Goldstein B, Hlavacek WS (2004) BioNetGen: software for rule-based modeling of signal transduction based on the interactions of molecular domains. *Bioinformatics (Oxford, England)* **20**: 3289–3291
- Blinov ML, Yang J, Faeder JR, Hlavacek WS (2006) Depicting signaling cascades. *Nature Biotechnology* **24**: 137–138author reply 138
- Blumer KJ, Reneke JE, Thorner J (1988) The STE2 gene product is the ligand-binding component of the alpha-factor receptor of Saccharomyces cerevisiae. *J Biol Chem* **263**: 10836–10842
- Borisov NM, Chistopolsky AS, Faeder JR, Kholodenko BN (2008) Domain-oriented reduction of rule-based network models. *IET Syst Biol* **2**: 342–351
- Breitkreutz A, Boucher L, Tyers M (2001) MAPK specificity in the yeast pheromone response independent of transcriptional activation. *Curr Biol* **11**: 1266–1271
- Breitkreutz A, Choi H, Sharom JR, Boucher L, Neduva V, Larsen B, Lin ZY, Breitkreutz BJ, Stark C, Liu G, Ahn J, Dewar-Darch D, Reguly T, Tang X, Almeida R, Qin ZS, Pawson T, Gingras AC, Nesvizhskii AI, Tyers M (2010) A global protein kinase and phosphatase interaction network in yeast. *Science (New York, NY)* **328**: 1043–1046
- Bruckner S, Kohler T, Braus GH, Heise B, Bolte M, Mosch HU (2004) Differential regulation of Tec1 by Fus3 and Kss1 confers signaling specificity in yeast development. *Curr Genet* **46**: 331–342

- Butty AC, Pryciak PM, Huang LS, Herskowitz I, Peter M (1998) The role of Far1p in linking the heterotrimeric G protein to polarity establishment proteins during yeast mating. *Science* **282**: 1511–1516
- Chautard E, Ballut L, Thierry-Mieg N, Ricard-Blum S (2009) MatrixDB, a database focused on extracellular protein-protein and protein-carbohydrate interactions. *Bioinformatics (Oxford, England)* **25**: 690–691
- Chou S, Huang L, Liu H (2004) Fus3-regulated Tec1 degradation through SCFCdc4 determines MAPK signaling specificity during mating in yeast. *Cell* **119**: 981–990
- Chou S, Lane S, Liu H (2006) Regulation of mating and filamentation genes by two distinct Ste12 complexes in *Saccharomyces cerevisiae*. *Mol Cell Biol* **26**: 4794–4805
- Chylek LA, Hu B, Blinov ML, Emonet T, Faeder JR, Goldstein B, Gutenkunst RN, Haugh JM, Lipniacki T, Posner RG, Yang J, Hlavacek WS (2011) Guidelines for visualizing and annotating rule-based models. *Mol Biol Syst* **7**: 2779–2795
- Cismowski MJ, Metodiev M, Draper E, Stone DE (2001) Biochemical analysis of yeast G(alpha) mutants that enhance adaptation to pheromone. *Biochem Biophys Res Commun* **284**: 247–254
- Clark KL, Dignard D, Thomas DY, Whiteway M (1993) Interactions among the subunits of the G protein involved in *Saccharomyces cerevisiae* mating. *Mol Cell Biol* **13**: 1–8
- Collister M, Didmon MP, MacIsaac F, Stark MJ, MacDonald NQ, Keyse SM (2002) YIL113w encodes a functional dual-specificity protein phosphatase which specifically interacts with and inactivates the Slt2/Mpk1p MAP kinase in *S. cerevisiae*. *FEBS Lett* **527**: 186–192
- Conzelmann H, Fey D, Gilles ED (2008) Exact model reduction of combinatorial reaction networks. *BMC Syst Biol* **2**: 78
- Cook JG, Bardwell L, Kron SJ, Thorner J (1996) Two novel targets of the MAP kinase Kss1 are negative regulators of invasive growth in the yeast *Saccharomyces cerevisiae*. *Genes Dev* **10**: 2831–2848
- Croft D, O’Kelly G, Wu G, Haw R, Gillespie M, Matthews L, Caudy M, Garapati P, Gopinath G, Jassal B, Jupe S, Kataskaya I, Mahajan S, May B, Ndegwa N, Schmidt E, Shamovsky V, Yung C, Birney E, Hermjakob H *et al* (2010) *Reactome: a database of reactions, pathways and biological processes* *Nucleic Acids Res* **39(Database issue)**: D691–D697
- Crosby JA, Konopka JB, Fields S (2000) Constitutive activation of the *Saccharomyces cerevisiae* transcriptional regulator Ste12p by mutations at the amino-terminus. *Yeast* **16**: 1365–1375
- Cullen PJ, Sabbagh WJr., Graham E, Irick MM, van Olden EK, Neal C, Delrow J, Bardwell L, Sprague GFJr. (2004) A signaling mucin at the head of the Cdc42- and MAPK-dependent filamentous growth pathway in yeast. *Genes Dev* **18**: 1695–1708
- Danos V (2007) Rule-based modelling of cellular signalling. *Cell Signal* **17**: 41
- Davenport KD, Williams KE, Ullmann BD, Gustin MC (1999) Activation of the *Saccharomyces cerevisiae* filamentation/invasion pathway by osmotic stress in high-osmolarity glycogen pathway mutants. *Genetics* **153**: 1091–1103
- de Nadal E, Casadome L, Posas F (2003) Targeting the MEF2-like transcription factor Smp1 by the stress-activated Hog1 mitogen-activated protein kinase. *Mol Cell Biol* **23**: 229–237
- Dodou E, Treisman R (1997) The *Saccharomyces cerevisiae* MADS-box transcription factor Rlm1 is a target for the Mpk1 mitogen-activated protein kinase pathway. *Mol Cell Biol* **17**: 1848–1859
- Doi K, Gartner A, Ammerer G, Errede B, Shinkawa H, Sugimoto K, Matsumoto K (1994) MSG5, a novel protein phosphatase promotes adaptation to pheromone response in *S. cerevisiae*. *EMBO J* **13**: 61–70
- Dolan JW, Kirkman C, Fields S (1989) The yeast STE12 protein binds to the DNA sequence mediating pheromone induction. *Proc Natl Acad Sci USA* **86**: 5703–5707
- Dowell SJ, Bishop AL, Dyos SL, Brown AJ, Whiteway MS (1998) Mapping of a yeast G protein betagamma signaling interaction. *Genetics* **150**: 1407–1417
- Drogen F, O’Rourke SM, Stucke VM, Jaquenoud M, Neiman AM, Peter M (2000) Phosphorylation of the MEKK Ste11p by the PAK-like kinase Ste20p is required for MAP kinase signaling in vivo. *Curr Biol* **10**: 630–639
- Elion EA, Satterberg B, Kranz JE (1993) FUS3 phosphorylates multiple components of the mating signal transduction cascade: evidence for STE12 and FAR1. *Mol Biol Cell* **4**: 495–510
- Errede B, Gartner A, Zhou Z, Nasmyth K, Ammerer G (1993) MAP kinase-related FUS3 from *S. cerevisiae* is activated by STE7 in vitro. *Nature* **362**: 261–264
- Escote X, Zapater M, Clotet J, Posas F (2004) Hog1 mediates cell-cycle arrest in G1 phase by the dual targeting of Sic1. *Nat Cell Biol* **6**: 997–1002
- Faeder JR, Blinov ML, Goldstein B, Hlavacek WS (2005) Rule-based modeling of biochemical networks. *Complexity* **10**: 22–41
- Feng Y, Song LY, Kincaid E, Mahanty SK, Elion EA (1998) Functional binding between Gbeta and the LIM domain of Ste5 is required to activate the MEKK Ste11. *Curr Biol* **8**: 267–278
- Fitch PG, Gammie AE, Lee DJ, de Candal VB, Rose MD (2004) Lrg1p Is a Rho1 GTPase-activating protein required for efficient cell fusion in yeast. *Genetics* **168**: 733–746
- Flandez M, Cosano IC, Nombela C, Martin H, Molina M (2004) Reciprocal regulation between Slt2 MAPK and isoforms of Msg5 dual-specificity protein phosphatase modulates the yeast cell integrity pathway. *J Biol Chem* **279**: 11027–11034
- Flotho A, Simpson DM, Qi M, Elion EA (2004) Localized feedback phosphorylation of Ste5p scaffold by associated MAPK cascade. *J Biol Chem* **279**: 47391–47401
- Friant S, Lombardi R, Schmelzle T, Hall MN, Riezman H (2001) Sphingoid base signaling via Pkh kinases is required for endocytosis in yeast. *EMBO J* **20**: 6783–6792
- Garcia-Gimeno MA, Struhl K (2000) Aca1 and Aca2, ATF/CREB activators in *Saccharomyces cerevisiae*, are important for carbon source utilization but not the response to stress. *Mol Cell Biol* **20**: 4340–4349
- Garrison TR, Zhang Y, Pausch M, Apanovitch D, Aebersold R, Dohlman HG (1999) Feedback phosphorylation of an RGS protein by MAP kinase in yeast. *J Biol Chem* **274**: 36387–36391
- Gartner A, Jovanovic A, Jeoung DI, Bourlat S, Cross FR, Ammerer G (1998) Pheromone-dependent G1 cell cycle arrest requires Far1 phosphorylation, but may not involve inhibition of Cdc28-Cln2 kinase, in vivo. *Mol Cell Biol* **18**: 3681–3691
- Gartner A, Nasmyth K, Ammerer G (1992) Signal transduction in *Saccharomyces cerevisiae* requires tyrosine and threonine phosphorylation of FUS3 and KSS1. *Genes Dev* **6**: 1280–1292
- Good M, Tang G, Singleton J, Remenyi A, Lim WA (2009) The Ste5 scaffold directs mating signaling by catalytically unlocking the Fus3 MAP kinase for activation. *Cell* **136**: 1085–1097
- Green R, Lesage G, Sdicu AM, Menard P, Bussey H (2003) A synthetic analysis of the *Saccharomyces cerevisiae* stress sensor Mid2p, and identification of a Mid2p-interacting protein, Zeo1p, that modulates the PKC1-MPK1 cell integrity pathway. *Microbiology* **149**: 2487–2499
- Guo S, Shen X, Yan G, Ma D, Bai X, Li S, Jiang Y (2009) A MAP kinase dependent feedback mechanism controls Rho1 GTPase and actin distribution in yeast. *PLoS One* **4**: e6089
- Hagen DC, McCaffrey G, Sprague GFJr. (1986) Evidence the yeast STE3 gene encodes a receptor for the peptide pheromone a factor: gene sequence and implications for the structure of the presumed receptor. *Proc Natl Acad Sci USA* **83**: 1418–1422
- Hagen DC, McCaffrey G, Sprague GFJr. (1991) Pheromone response elements are necessary and sufficient for basal and pheromone-induced transcription of the FUS1 gene of *Saccharomyces cerevisiae*. *Mol Cell Biol* **11**: 2952–2961
- Hahn JS, Thiele DJ (2002) Regulation of the *Saccharomyces cerevisiae* Slt2 kinase pathway by the stress-inducible Sdp1 dual specificity phosphatase. *J Biol Chem* **277**: 21278–21284
- Heenan EJ, Vanhooke JL, Temple BR, Betts L, Sondek JE, Dohlman HG (2009) Structure and function of Vps15 in the endosomal G protein signaling pathway. *Biochemistry* **48**: 6390–6401

- Heise B, van der Felden J, Kern S, Malcher M, Bruckner S, Mosch HU (2010) The TEA transcription factor Tec1 confers promoter-specific gene regulation by Ste12-dependent and -independent mechanisms. *Eukaryot Cell* **9**: 514–531
- Hlavacek WS, Faeder JR, Blinov ML, Perelson AS, Goldstein B (2003) The complexity of complexes in signal transduction. *Biotechnol Bioeng* **84**: 783–794
- Ho Y, Gruhler A, Heilbut A, Bader GD, Moore L, Adams SL, Millar A, Taylor P, Bennett K, Boutillier K, Yang L, Wolting C, Donaldson I, Schandorff S, Shewnarane J, Vo M, Taggart J, Goudreault M, Muskat B, Alfarano C *et al* (2002) Systematic identification of protein complexes in *Saccharomyces cerevisiae* by mass spectrometry. *Nature* **415**: 180–183
- Horie T, Tatebayashi K, Yamada R, Saito H (2008) Phosphorylated Ssk1 prevents unphosphorylated Ssk1 from activating the Ssk2 mitogen-activated protein kinase kinase in the yeast high-osmolarity glycerol osmoregulatory pathway. *Mol Cell Biol* **28**: 5172–5183
- Hucka M, Finney A, Sauro HM, Bolouri H, Doyle JC, Kitano H, Arkin AP, Bornstein BJ, Bray D, Cornish-Bowden A, Cuellar AA, Dronov S, Gilles ED, Ginkel M, Gor V, Goryanin II, Hedley WJ, Hodgman TC, Hofmeyr JH, Hunter PJ *et al* (2003) The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models. *Bioinformatics (Oxford, England)* **19**: 524–531
- Inagaki M, Schmelzle T, Yamaguchi K, Irie K, Hall MN, Matsumoto K (1999) PDK1 homologs activate the Pkc1-mitogen-activated protein kinase pathway in yeast. *Mol Cell Biol* **19**: 8344–8352
- Inouye C, Dhillon N, Durfee T, Zambryski PC, Thorner J (1997a) Mutational analysis of STE5 in the yeast *Saccharomyces cerevisiae*: application of a differential interaction trap assay for examining protein-protein interactions. *Genetics* **147**: 479–492
- Inouye C, Dhillon N, Thorner J (1997b) Ste5 RING-H2 domain: role in Ste4-promoted oligomerization for yeast pheromone signaling. *Science* **278**: 103–106
- Irie K, Takase M, Lee KS, Levin DE, Araki H, Matsumoto K, Oshima Y (1993) MKK1 and MKK2, which encode *Saccharomyces cerevisiae* mitogen-activated protein kinase-kinase homologs, function in the pathway mediated by protein kinase C. *Mol Cell Biol* **13**: 3076–3083
- Jacoby T, Flanagan H, Faykin A, Seto AG, Mattison C, Ota I (1997) Two protein-tyrosine phosphatases inactivate the osmotic stress response pathway in yeast by targeting the mitogen-activated protein kinase, Hog1. *J Biol Chem* **272**: 17749–17755
- Jung US, Sobering AK, Romeo MJ, Levin DE (2002) Regulation of the yeast Rlm1 transcription factor by the Mpk1 cell wall integrity MAP kinase. *Mol Microbiol* **46**: 781–789
- Kaizu K, Ghosh S, Matsuoka Y, Moriya H, Shimizu-Yoshida Y, Kitano H (2010) A comprehensive molecular interaction map of the budding yeast cell cycle. *Mol Syst Biol* **6**: 415
- Kaltenbach H-M, Constantinescu S, Feigelman J, Stelling J (2011) *Graph-Based Decomposition of Biochemical Reaction Networks Into Monotone Subsystems Algorithms in Bioinformatics*, Przytycka T, Sagot M-F (eds) Vol. 6833, pp 139–150 Springer Berlin/Heidelberg
- Kamada Y, Jung US, Piotrowski J, Levin DE (1995) The protein kinase C-activated MAP kinase pathway of *Saccharomyces cerevisiae* mediates a novel aspect of the heat shock response. *Genes Dev* **9**: 1559–1571
- Kamada Y, Qadota H, Python CP, Anraku Y, Ohya Y, Levin DE (1996) Activation of yeast protein kinase C by Rho1 GTPase. *J Biol Chem* **271**: 9193–9196
- Kanehisa M, Goto S, Furumichi M, Tanabe M, Hirakawa M (2010) KEGG for representation and analysis of molecular networks involving diseases and drugs. *Nucleic Acids Res* **38**: D355–D360
- Kanehisa M, Goto S, Hattori M, Aoki-Kinoshita KF, Itoh M, Kawashima S, Katayama T, Araki M, Hirakawa M (2006) From genomics to chemical genomics: new developments in KEGG. *Nucleic Acids Res* **34**: D354–D357
- Ketela T, Green R, Bussey H (1999) *Saccharomyces cerevisiae* mid2p is a potential cell wall stress sensor and upstream activator of the PKC1-MPK1 cell integrity pathway. *J Bacteriol* **181**: 3330–3340
- Kim KY, Truman AW, Caesar S, Schlenstedt G, Levin DE (2010) Yeast Mpk1 cell wall integrity mitogen-activated protein kinase regulates nucleocytoplasmic shuttling of the Swi6 transcriptional regulator. *Mol Biol Cell* **21**: 1609–1619
- Kim KY, Truman AW, Levin DE (2008) Yeast Mpk1 mitogen-activated protein kinase activates transcription through Swi4/Swi6 by a noncatalytic mechanism that requires upstream signal. *Mol Cell Biol* **28**: 2579–2589
- Kiselyov VV, Versteyhe S, Gauguin L, De Meyts P (2009) Harmonic oscillator model of the insulin and IGF1 receptors' allosteric binding and activation. *Mol Syst Biol* **5**: 243
- Kitano H, Funahashi A, Matsuoka Y, Oda K (2005) Using process diagrams for the graphical representation of biological networks. *Nat Biotechnol* **23**: 961–966
- Kohn KW, Aladjem MI, Kim S, Weinstein JN, Pommier Y (2006) Depicting combinatorial complexity with the molecular interaction map notation. *Mol Syst Biol* **2**: 51
- Kranz JE, Satterberg B, Elion EA (1994) The MAP kinase Fus3 associates with and phosphorylates the upstream signaling component Ste5. *Genes Dev* **8**: 313–327
- Kusari AB, Molina DM, Sabbagh WJr., Lau CS, Bardwell L (2004) A conserved protein interaction network involving the yeast MAP kinases Fus3 and Kss1. *J Cell Biol* **164**: 267–277
- Lamson RE, Winters MJ, Pryciak PM (2002) Cdc42 regulation of kinase activity and signaling by the yeast p21-activated kinase Ste20. *Mol Cell Biol* **22**: 2939–2951
- Le Novere N, Hucka M, Mi H, Moodie S, Schreiber F, Sorokin A, Demir E, Wegner K, Aladjem MI, Wimalaratne SM, Bergman FT, Gauges R, Ghazal P, Kawaji H, Li L, Matsuoka Y, Villegier A, Boyd SE, Calzone L, Courtot M *et al* (2009) The systems biology graphical notation. *Nat Biotechnol* **27**: 735–741
- Le Novere N, Demir E, Mi H, Moodie S, Villegier A (2011) Systems biology graphical notation: entity relationship language Level 1 (Version 1.2). Available from Nature Precedings (<http://dx.doi.org/10.1038/npre.2011.5902.1>)
- Lee KS, Levin DE (1992) Dominant mutations in a gene encoding a putative protein kinase (BCK1) bypass the requirement for a *Saccharomyces cerevisiae* protein kinase C homolog. *Mol Cell Biol* **12**: 172–182
- Leeuw T, Fourest-Lieuvin A, Wu C, Chenevert J, Clark K, Whiteway M, Thomas DY, Leberer E (1995) Pheromone response in yeast: association of Bem1p with proteins of the MAP kinase cascade and actin. *Science* **270**: 1210–1213
- Leeuw T, Wu C, Schrag JD, Whiteway M, Thomas DY, Leberer E (1998) Interaction of a G-protein beta-subunit with a conserved sequence in Ste20/PAK family protein kinases. *Nature* **391**: 191–195
- Li E, Cismowski MJ, Stone DE (1998) Phosphorylation of the pheromone-responsive Gbeta protein of *Saccharomyces cerevisiae* does not affect its mating-specific signaling function. *Mol Gen Genet* **258**: 608–618
- Liu K, Zhang X, Lester RL, Dickson RC (2005) The sphingoid long chain base phytosphingosine activates AGC-type protein kinases in *Saccharomyces cerevisiae* including Ypk1, Ypk2, and Sch9. *J Biol Chem* **280**: 22679–22687
- Lok L, Brent R (2005) Automatic generation of cellular reaction networks with MolecuLizer 1.0. *Nat Biotechnol* **23**: 131–136
- MacKay VL, Armstrong J, Yip C, Welch S, Walker K, Osborn S, Sheppard P, Forstrom J (1991) Characterization of the Bar proteinase, an extracellular enzyme from the yeast *Saccharomyces cerevisiae*. *Adv Exp Med Biol* **306**: 161–172
- MacKay VL, Welch SK, Inasley MY, Manney TR, Holly J, Saari GC, Parker ML (1988) The *Saccharomyces cerevisiae* BAR1 gene encodes an exported protein with homology to pepsin. *Proc Natl Acad Sci USA* **85**: 55–59

- Madden K, Sheu YJ, Baetz K, Andrews B, Snyder M (1997) SBF cell cycle regulator as a target of the yeast PKC-MAP kinase pathway. *Science* **275**: 1781–1784
- Madhani HD, Fink GR (1997) Combinatorial control required for the specificity of yeast MAPK signaling. *Science* **275**: 1314–1317
- Madhani HD, Styles CA, Fink GR (1997) MAP kinases with distinct inhibitory functions impart signaling specificity during yeast differentiation. *Cell* **91**: 673–684
- Maeda T, Takekawa M, Saito H (1995) Activation of yeast Pbs2 MAPKK by MAPKKs or by binding of an SH3-containing osmosensor. *Science* **269**: 554–558
- Maeda T, Wurgler-Murphy SM, Saito H (1994) A two-component system that regulates an osmosensing MAP kinase cascade in yeast. *Nature* **369**: 242–245
- Maleri S, Ge Q, Hackett EA, Wang Y, Dohlman HG, Errede B (2004) Persistent activation by constitutive Ste7 promotes Kss1-mediated invasive growth but fails to support Fus3-dependent mating in yeast. *Mol Cell Biol* **24**: 9221–9238
- Mapes J, Ota IM (2004) Nbp2 targets the Ptc1-type 2C Ser/Thr phosphatase to the HOG MAPK pathway. *EMBO J* **23**: 302–311
- Martin H, Rodriguez-Pachon JM, Ruiz C, Nombela C, Molina M (2000) Regulatory mechanisms for modulation of signaling through the cell integrity Slt2-mediated pathway in *Saccharomyces cerevisiae*. *J Biol Chem* **275**: 1511–1519
- Mattison CP, Ota IM (2000) Two protein tyrosine phosphatases, Ptp2 and Ptp3, modulate the subcellular localization of the Hog1 MAP kinase in yeast. *Genes Dev* **14**: 1229–1235
- Mattison CP, Spencer SS, Kresge KA, Lee J, Ota IM (1999) Differential regulation of the cell wall integrity mitogen-activated protein kinase pathway in budding yeast by the protein tyrosine phosphatases Ptp2 and Ptp3. *Mol Cell Biol* **19**: 7651–7660
- Medici R, Bianchi E, Di Segni G, Tocchini-Valentini GP (1997) Efficient signal transduction by a chimeric yeast-mammalian G protein alpha subunit Gpa1-Gsalphal covalently fused to the yeast receptor Ste2. *EMBO J* **16**: 7241–7249
- Melcher ML, Thorner J (1996) Identification and characterization of the CLK1 gene product, a novel CaM kinase-like protein kinase from the yeast *Saccharomyces cerevisiae*. *J Biol Chem* **271**: 29958–29968
- Metodiev MV, Matheos D, Rose MD, Stone DE (2002) Regulation of MAPK function by direct interaction with the mating-specific Galpha in yeast. *Science* **296**: 1483–1486
- Miyajima I, Nakafuku M, Nakayama N, Brenner C, Miyajima A, Kaibuchi K, Arai K, Kaziro Y, Matsumoto K (1987) GPA1, a haploid-specific essential gene, encodes a yeast homolog of mammalian G protein which may be involved in mating factor signal transduction. *Cell* **50**: 1011–1019
- Murakami Y, Tatebayashi K, Saito H (2008) Two adjacent docking sites in the yeast Hog1 mitogen-activated protein (MAP) kinase differentially interact with the Pbs2 MAP kinase kinase and the Ptp2 protein tyrosine phosphatase. *Mol Cell Biol* **28**: 2481–2494
- Nasmyth K, Dirick L (1991) The role of SWI4 and SWI6 in the activity of G1 cyclins in yeast. *Cell* **66**: 995–1013
- Nehlin JO, Carlberg M, Ronne H (1992) Yeast SKO1 gene encodes a bZIP protein that binds to the CRE motif and acts as a repressor of transcription. *Nucleic Acids Res* **20**: 5271–5278
- Neiman AM, Herskowitz I (1994) Reconstitution of a yeast protein kinase cascade in vitro: activation of the yeast MEK homologue STE7 by STE11. *Proc Natl Acad Sci USA* **91**: 3398–3402
- Nern A, Arkowitz RA (1998) A GTP-exchange factor required for cell orientation. *Nature* **391**: 195–198
- Nern A, Arkowitz RA (1999) A Cdc24p-Far1p-Gbetagamma protein complex required for yeast orientation during mating. *J Cell Biol* **144**: 1187–1202
- Nonaka H, Tanaka K, Hirano H, Fujiwara T, Kohno H, Umikawa M, Mino A, Takai Y (1995) A downstream target of RHO1 small GTP-binding protein is PKC1, a homolog of protein kinase C, which leads to activation of the MAP kinase cascade in *Saccharomyces cerevisiae*. *EMBO J* **14**: 5931–5938
- Olson KA, Nelson C, Tai G, Hung W, Yong C, Astell C, Sadowski I (2000) Two regulators of Ste12p inhibit pheromone-responsive transcription by separate mechanisms. *Mol Cell Biol* **20**: 4199–4209
- Ostrander DB, Gorman JA (1999) The extracellular domain of the *Saccharomyces cerevisiae* Sln1p membrane osmolarity sensor is necessary for kinase activity. *J Bacteriol* **181**: 2527–2534
- Overington J (2009) ChEMBL. An interview with John Overington, team leader, chemogenomics at the European Bioinformatics Institute Outstation of the European Molecular Biology Laboratory (EMBL-EBI). Interview by Wendy A. Warr. *J Comput Aided Mol Des* **23**: 195–198
- Ozaki K, Tanaka K, Imamura H, Hihara T, Kameyama T, Nonaka H, Hirano H, Matsuura Y, Takai Y (1996) Rom1p and Rom2p are GDP/GTP exchange proteins (GEPs) for the Rho1p small GTP binding protein in *Saccharomyces cerevisiae*. *EMBO J* **15**: 2196–2207
- Paravicini G, Friedli L (1996) Protein-protein interactions in the yeast PKC1 pathway: Pkc1p interacts with a component of the MAP kinase cascade. *Mol Gen Genet* **251**: 682–691
- Parnell SC, Marotti LA Jr., Kiang L, Torres MP, Borchers CH, Dohlman HG (2005) Phosphorylation of the RGS protein Sst2 by the MAP kinase Fus3 and use of Sst2 as a model to analyze determinants of substrate sequence specificity. *Biochemistry* **44**: 8159–8166
- Pascual-Ahuir A, Posas F, Serrano R, Proft M (2001) Multiple levels of control regulate the yeast cAMP-response element-binding protein repressor Sko1p in response to stress. *J Biol Chem* **276**: 37373–37378
- Peter M, Neiman AM, Park HO, van Lohuizen M, Herskowitz I (1996) Functional analysis of the interaction between the small GTP binding protein Cdc42 and the Ste20 protein kinase in yeast. *EMBO J* **15**: 7046–7059
- Peterson J, Zheng Y, Bender L, Myers A, Cerione R, Bender A (1994) Interactions between the bud emergence proteins Bem1p and Bem2p and Rho-type GTPases in yeast. *J Cell Biol* **127**: 1395–1406
- Philip B, Levin DE (2001) Wsc1 and Mid2 are cell surface sensors for cell wall integrity signaling that act through Rom2, a guanine nucleotide exchange factor for Rho1. *Mol Cell Biol* **21**: 271–280
- Posas F, Saito H (1997) Osmotic activation of the HOG MAPK pathway via Ste11p MAPKKK: scaffold role of Pbs2p MAPKK. *Science* **276**: 1702–1705
- Posas F, Saito H (1998) Activation of the yeast SSK2 MAP kinase kinase by the SSK1 two-component response regulator. *EMBO J* **17**: 1385–1394
- Posas F, Witten EA, Saito H (1998) Requirement of STE50 for osmotic stress-induced activation of the STE11 mitogen-activated protein kinase kinase kinase in the high-osmolarity glycerol response pathway. *Mol Cell Biol* **18**: 5788–5796
- Posas F, Wurgler-Murphy SM, Maeda T, Witten EA, Thai TC, Saito H (1996) Yeast HOG1 MAP kinase cascade is regulated by a multistep phosphorelay mechanism in the SLN1-YPD1-SSK1 'two-component' osmosensor. *Cell* **86**: 865–875
- Proft M, Gibbons FD, Copeland M, Roth FP, Struhl K (2005) Genomewide identification of Sko1 target promoters reveals a regulatory network that operates in response to osmotic stress in *Saccharomyces cerevisiae*. *Eukaryot Cell* **4**: 1343–1352
- Proft M, Pascual-Ahuir A, de Nadal E, Arino J, Serrano R, Posas F (2001) Regulation of the Sko1 transcriptional repressor by the Hog1 MAP kinase in response to osmotic stress. *EMBO J* **20**: 1123–1133
- Proft M, Serrano R (1999) Repressors and upstream repressing sequences of the stress-regulated ENA1 gene in *Saccharomyces cerevisiae*: bZIP protein Sko1p confers HOG-dependent osmotic regulation. *Mol Cell Biol* **19**: 537–546
- Proft M, Struhl K (2002) Hog1 kinase converts the Sko1-Cyc8-Tup1 repressor complex into an activator that recruits SAGA and SWI/SNF in response to osmotic stress. *Mol Cell* **9**: 1307–1317
- PSICQUIC <http://www.ebi.ac.uk/Tools/webservices/psicquic/view/main.xhtml>
- Raicu V, Jansma DB, Miller RJ, Friesen JD (2005) Protein interaction quantified in vivo by spectrally resolved fluorescence resonance energy transfer. *Biochem J* **385**: 265–277

- Raitt DC, Posas F, Saito H (2000) Yeast Cdc42 GTPase and Ste20 PAK-like kinase regulate Sho1-dependent activation of the Hog1 MAPK pathway. *EMBO J* **19**: 4623–4631
- Rajavel M, Philip B, Buehrer BM, Errede B, Levin DE (1999) Mid2 is a putative sensor for cell integrity signaling in *Saccharomyces cerevisiae*. *Mol Cell Biol* **19**: 3969–3976
- Reiser V, Salah SM, Ammerer G (2000) Polarized localization of yeast Pbs2 depends on osmotic stress, the membrane protein Sho1 and Cdc42. *Nat Cell Biol* **2**: 620–627
- Remenyi A, Good MC, Bhattacharyya RP, Lim WA (2005) The role of docking interactions in mediating signaling input, output, and discrimination in the yeast MAPK network. *Mol Cell* **20**: 951–962
- Rep M, Krantz M, Thevelein JM, Hohmann S (2000) The transcriptional response of *Saccharomyces cerevisiae* to osmotic shock. Hot1p and Msn2p/Msn4p are required for the induction of subsets of high osmolarity glycerol pathway-dependent genes. *J Biol Chem* **275**: 8290–8300
- Rep M, Reiser V, Gartner U, Thevelein JM, Hohmann S, Ammerer G, Ruis H (1999) Osmotic stress-induced gene expression in *Saccharomyces cerevisiae* requires Msn1p and the novel nuclear factor Hot1p. *Mol Cell Biol* **19**: 5474–5485
- Roberts RL, Fink GR (1994) Elements of a single MAP kinase cascade in *Saccharomyces cerevisiae* mediate two developmental programs in the same cell type: mating and invasive growth. *Genes Dev* **8**: 2974–2985
- Schmelzle T, Helliwell SB, Hall MN (2002) Yeast protein kinases and the RHO1 exchange factor TUS1 are novel components of the cell integrity pathway in yeast. *Mol Cell Biol* **22**: 1329–1339
- Schmidt A, Bickle M, Beck T, Hall MN (1997) The yeast phosphatidylinositol kinase homolog TOR2 activates RHO1 and RHO2 via the exchange factor ROM2. *Cell* **88**: 531–542
- Schmidt A, Schmelzle T, Hall MN (2002) The RHO1-GAPs SAC7, BEM2 and BAG7 control distinct RHO1 functions in *Saccharomyces cerevisiae*. *Mol Microbiol* **45**: 1433–1441
- Schmitz HP, Lorberg A, Heinisch JJ (2002) Regulation of yeast protein kinase C activity by interaction with the small GTPase Rho1p through its amino-terminal HR1 domain. *Mol Microbiol* **44**: 829–840
- Shi C, Shin YO, Hanson J, Cass B, Loewen MC, Durocher Y (2005) Purification and characterization of a recombinant G-protein-coupled receptor, *Saccharomyces cerevisiae* Ste2p, transiently expressed in HEK293 EBNA1 cells. *Biochemistry* **44**: 15705–15714
- Shimada Y, Wiget P, Gulli MP, Bi E, Peter M (2004) The nucleotide exchange factor Cdc24p may be regulated by auto-inhibition. *EMBO J* **23**: 1051–1062
- Sidorova J, Breeden L (1993) Analysis of the SWI4/SWI6 protein complex, which directs G1/S-specific transcription in *Saccharomyces cerevisiae*. *Mol Cell Biol* **13**: 1069–1077
- Siegmund RE, Nasmyth KA (1996) The *Saccharomyces cerevisiae* Start-specific transcription factor Swi4 interacts through the ankyrin repeats with the mitotic Clb2/Cdc28 kinase and through its conserved carboxy terminus with Swi6. *Mol Cell Biol* **16**: 2647–2655
- Siekhaus DE, Drubin DG (2003) Spontaneous receptor-independent heterotrimeric G-protein signalling in an RGS mutant. *Nat Cell Biol* **5**: 231–235
- Simon MN, De Virgilio C, Souza B, Pringle JR, Abo A, Reed SI (1995) Role for the Rho-family GTPase Cdc42 in yeast mating-pheromone signal pathway. *Nature* **376**: 702–705
- Skowyra D, Craig KL, Tyers M, Elledge SJ, Harper JW (1997) F-box proteins are receptors that recruit phosphorylated substrates to the SCF ubiquitin-ligase complex. *Cell* **91**: 209–219
- Smith GR, Givan SA, Cullen P, Sprague GJ Jr. (2002) GTPase-activating proteins for Cdc42. *Eukaryot Cell* **1**: 469–480
- Sneddon MW, Faeder JR, Emonet T (2011) Efficient modeling, simulation and coarse-graining of biological complexity with NFsim. *Nat Methods* **8**: 177–183
- Soler M, Plovins A, Martin H, Molina M, Nombela C (1995) Characterization of domains in the yeast MAP kinase Slt2 (Mpk1) required for functional activity and in vivo interaction with protein kinases Mkk1 and Mkk2. *Mol Microbiol* **17**: 833–842
- Song J, Hirschman J, Gunn K, Dohlman HG (1996) Regulation of membrane and subunit interactions by N-myristoylation of a G protein alpha subunit in yeast. *J Biol Chem* **271**: 20273–20283
- Stark C, Breitkreutz BJ, Reguly T, Boucher L, Breitkreutz A, Tyers M (2006) BioGRID: a general repository for interaction datasets. *Nucleic Acids Res* **34**: D535–D539
- Taba MR, Muroff I, Lydall D, Tebb G, Nasmyth K (1991) Changes in a SWI4,6-DNA-binding complex occur at the time of HO gene activation in yeast. *Genes Dev* **5**: 2000–2013
- Takahashi S, Pryciak PM (2007) Identification of novel membrane-binding domains in multiple yeast Cdc42 effectors. *Mol Biol Cell* **18**: 4945–4956
- Tao W, Malone CL, Ault AD, Deschenes RJ, Fassler JS (2002) A cytoplasmic coiled-coil domain is required for histidine kinase activity of the yeast osmosensor, SLN1. *Mol Microbiol* **43**: 459–473
- Tarassov K, Messier V, Landry CR, Radinovic S, Serna Molina MM, Shames I, Malitskaya Y, Vogel J, Bussey H, Michnick SW (2008) An in vivo map of the yeast protein interactome. *Science* **320**: 1465–1470
- Tatebayashi K, Takekawa M, Saito H (2003) A docking site determining specificity of Pbs2 MAPKK for Ssk2/Ssk22 MAPKKs in the yeast HOG pathway. *EMBO J* **22**: 3624–3634
- Tatebayashi K, Tanaka K, Yang HY, Yamamoto K, Matsushita Y, Tomida T, Imai M, Saito H (2007) Transmembrane mucins Hkr1 and Msb2 are putative osmosensors in the SHO1 branch of yeast HOG pathway. *EMBO J* **26**: 3521–3533
- Tatebayashi K, Yamamoto K, Tanaka K, Tomida T, Maruoka T, Kasukawa E, Saito H (2006) Adaptor functions of Cdc42, Ste50, and Sho1 in the yeast osmoregulatory HOG MAPK pathway. *EMBO J* **25**: 3033–3044
- Tedford K, Kim S, Sa D, Stevens K, Tyers M (1997) Regulation of the mating pheromone and invasive growth responses in yeast by two MAP kinase substrates. *Curr Biol* **7**: 228–238
- Thorner J, Westfall PJ, Ballon DR (2005) High Osmolarity Glycerol (HOG) pathway in yeast. *Sci. Signal* (Connections Map in the Database of Cell Signaling, as seen 10 January 2011) http://stke.sciencemag.org/cgi/cm/stkecm;CMP_14620
- Trucksas DM, Bloomekatz JE, Thorner J (2006) The RA domain of Ste50 adaptor protein is required for delivery of Ste11 to the plasma membrane in the filamentous growth signaling pathway of the yeast *Saccharomyces cerevisiae*. *Mol Cell Biol* **26**: 912–928
- Truman AW, Kim KY, Levin DE (2009) Mechanism of Mpk1 mitogen-activated protein kinase binding to the Swi4 transcription factor and its regulation by a novel caffeine-induced phosphorylation. *Mol Cell Biol* **29**: 6449–6461
- Vadaie N, Dionne H, Akajagbor DS, Nickerson SR, Krysan DJ, Cullen PJ (2008) Cleavage of the signaling mucin Msb2 by the aspartyl protease Yps1 is required for MAPK activation in yeast. *J Cell Biol* **181**: 1073–1081
- Valtz N, Peter M, Herskowitz I (1995) FAR1 is required for oriented polarization of yeast cells in response to mating pheromones. *J Cell Biol* **131**: 863–873
- Varanasi US, Klis M, Mikesell PB, Trumbly RJ (1996) The Cyc8 (Ssn6)-Tup1 corepressor complex is composed of one Cyc8 and four Tup1 subunits. *Mol Cell Biol* **16**: 6707–6714
- Verna J, Lodder A, Lee K, Vagts A, Ballester R (1997) A family of genes required for maintenance of cell wall integrity and for the stress response in *Saccharomyces cerevisiae*. *Proc Natl Acad Sci USA* **94**: 13804–13809
- Vilella F, Herrero E, Torres J, de la Torre-Ruiz MA (2005) Pkc1 and the upstream elements of the cell integrity pathway in *Saccharomyces cerevisiae*, Rom2 and Mtl1, are required for cellular responses to oxidative stress. *J Biol Chem* **280**: 9149–9159

- Wang HX, Konopka JB (2009) Identification of amino acids at two dimer interface regions of the alpha-factor receptor (Ste2). *Biochemistry* **48**: 7132–7139
- Wang Y, Chen W, Simpson DM, Elion EA (2005) Cdc24 regulates nuclear shuttling and recruitment of the Ste5 scaffold to a heterotrimeric G protein in *Saccharomyces cerevisiae*. *J Biol Chem* **280**: 13084–13096
- Warmka J, Hanneman J, Lee J, Amin D, Ota I (2001) Ptc1, a type 2C Ser/Thr phosphatase, inactivates the HOG pathway by dephosphorylating the mitogen-activated protein kinase Hog1. *Mol Cell Biol* **21**: 51–60
- Wassmann K, Ammerer G (1997) Overexpression of the G1-cyclin gene CLN2 represses the mating pathway in *Saccharomyces cerevisiae* at the level of the MEKK Ste11. *J Biol Chem* **272**: 13180–13188
- Watanabe M, Chen CY, Levin DE (1994) *Saccharomyces cerevisiae* PKC1 encodes a protein kinase C (PKC) homolog with a substrate specificity similar to that of mammalian PKC. *J Biol Chem* **269**: 16829–16836
- Watanabe Y, Irie K, Matsumoto K (1995) Yeast RLM1 encodes a serum response factor-like protein that may function downstream of the Mpk1 (Slt2) mitogen-activated protein kinase pathway. *Mol Cell Biol* **15**: 5740–5749
- Watanabe Y, Takaesu G, Hagiwara M, Irie K, Matsumoto K (1997) Characterization of a serum response factor-like protein in *Saccharomyces cerevisiae*, Rlm1, which has transcriptional activity regulated by the Mpk1 (Slt2) mitogen-activated protein kinase pathway. *Mol Cell Biol* **17**: 2615–2623
- Winters MJ, Pryciak PM (2005) Interaction with the SH3 domain protein Bem1 regulates signaling by the *Saccharomyces cerevisiae* p21-activated kinase Ste20. *Mol Cell Biol* **25**: 2177–2190
- Wu C, Jansen G, Zhang J, Thomas DY, Whiteway M (2006) Adaptor protein Ste50p links the Ste11p MEKK to the HOG pathway through plasma membrane association. *Genes Dev* **20**: 734–746
- Wu C, Leberer E, Thomas DY, Whiteway M (1999) Functional characterization of the interaction of Ste50p with Ste11p MAPKKK in *Saccharomyces cerevisiae*. *Mol Biol Cell* **10**: 2425–2440
- Wu C, Whiteway M, Thomas DY, Leberer E (1995) Molecular characterization of Ste20p, a potential mitogen-activated protein or extracellular signal-regulated kinase kinase (MEK) kinase from *Saccharomyces cerevisiae*. *J Biol Chem* **270**: 15984–15992
- Wu YL, Hooks SB, Harden TK, Dohlman HG (2004) Dominant-negative inhibition of pheromone receptor signaling by a single point mutation in the G protein alpha subunit. *J Biol Chem* **279**: 35287–35297
- Wurgler-Murphy SM, Maeda T, Witten EA, Saito H (1997) Regulation of the *Saccharomyces cerevisiae* HOG1 mitogen-activated protein kinase by the PTP2 and PTP3 protein tyrosine phosphatases. *Mol Cell Biol* **17**: 1289–1297
- Xenarios I, Salwinski L, Duan XJ, Higney P, Kim SM, Eisenberg D (2002) DIP, the Database of Interacting Proteins: a research tool for studying cellular networks of protein interactions. *Nucleic Acids Res* **30**: 303–305
- Yablonski D, Marbach I, Levitzki A (1996) Dimerization of Ste5, a mitogen-activated protein kinase cascade scaffold protein, is required for signal transduction. *Proc Natl Acad Sci USA* **93**: 13864–13869
- Yamamoto K, Tatebayashi K, Tanaka K, Saito H (2010) Dynamic control of yeast MAP kinase network by induced association and dissociation between the Ste50 scaffold and the Opy2 membrane anchor. *Mol Cell* **40**: 87–98
- Yang J, Meng X, Hlavacek WS (2010) *Rule-based Modeling and Simulation of Biochemical Systems with Molecular Finite Automata* **23** yeastpheromonemodel.org
- Yesilaltay A, Jenness DD (2000) Homo-oligomeric complexes of the yeast alpha-factor pheromone receptor are functional units of endocytosis. *Mol Biol Cell* **11**: 2873–2884
- Young C, Mapes J, Hanneman J, Al-Zarban S, Ota I (2002) Role of Ptc2 type 2C Ser/Thr phosphatase in yeast high-osmolarity glycerol pathway inactivation. *Eukaryot Cell* **1**: 1032–1040
- Yuan YL, Fields S (1991) Properties of the DNA-binding domain of the *Saccharomyces cerevisiae* STE12 protein. *Mol Cell Biol* **11**: 5910–5918
- Zarrinpar A, Bhattacharyya RP, Nittler MP, Lim WA (2004) Sho1 and Pbs2 act as coscaffolds linking components in the yeast high osmolarity MAP kinase pathway. *Mol Cell* **14**: 825–832
- Zarrinpar A, Park SH, Lim WA (2003) Optimization of specificity in a cellular protein interaction network by negative selection. *Nature* **426**: 676–680
- Zarrov P, Mazzoni C, Mann C (1996) The SLT2(MPK1) MAP kinase is activated during periods of polarized cell growth in yeast. *EMBO J* **15**: 83–91
- Zeitlinger J, Simon I, Harbison CT, Hannett NM, Volkert TL, Fink GR, Young RA (2003) Program-specific distribution of a transcription factor dependent on partner transcription factor and MAPK signaling. *Cell* **113**: 395–404
- Zhan XL, Deschenes RJ, Guan KL (1997) Differential regulation of FUS3 MAP kinase by tyrosine-specific phosphatases PTP2/PTP3 and dual-specificity phosphatase MSG5 in *Saccharomyces cerevisiae*. *Genes Dev* **11**: 1690–1702
- Zhan XL, Guan KL (1999) A specific protein-protein interaction accounts for the in vivo substrate selectivity of Ptp3 towards the Fus3 MAP kinase. *Genes Dev* **13**: 2811–2827
- Zhao ZS, Leung T, Manser E, Lim L (1995) Pheromone signalling in *Saccharomyces cerevisiae* requires the small GTP-binding protein Cdc42p and its activator CDC24. *Mol Cell Biol* **15**: 5246–5257
- Zheng CF, Guan KL (1994) Activation of MEK family kinases requires phosphorylation of two conserved Ser/Thr residues. *EMBO J* **13**: 1123–1131
- Zheng Y, Cerione R, Bender A (1994) Control of the yeast bud-site assembly GTPase Cdc42. Catalysis of guanine nucleotide exchange by Cdc24 and stimulation of GTPase activity by Bem3. *J Biol Chem* **269**: 2369–2372
- Zhou Z, Gartner A, Cade R, Ammerer G, Errede B (1993) Pheromone-induced signal transduction in *Saccharomyces cerevisiae* requires the sequential function of three protein kinases. *Mol Cell Biol* **13**: 2069–2080



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